Review Article

Prediction and Diagnosis of Poor Ovarian Response: The Dilemma

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Abstract

Failure to respond adequately to standard protocols and to recruit adequate follicles is called 'poor response'. This results in decreased oocyte production, cycle cancellation and, overall, is associated with a significantly diminished probability of pregnancy. It has been shown that ovarian reserve tests, such as basal FSH, antimullarian hormone (AMH), inhibin B, basal estradiol, antral follicular count (AFC), ovarian volume, ovarian vascular flow, ovarian biopsy and multivariate prediction models, have little clinical value in the prediction of a poor response. Although recent evidence points that AMH and AFC may be better than other testsbut they still continue to be used and form the basis for the exclusion of women from fertility treatments. Despite the rigorous efforts made in this regard, a test that could reliably predict poor ovarian response in all clients that undergo IVF is currently lacking.

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Introduction

Failure to respond adequately to standard protocols and to recruit adequate follicles is called 'poor ovarian response'. This results in decreased oocyte production, cycle cancellation and, overall, it is associated with a significantly diminished probability of pregnancy (1, 2).

What is meant by poor ovarian response? Controlled ovarian hyperstimulation (COH) has contributed to the success of assisted reproduction techniques (ART), in vitro fertilization (IVF) and embryo transfer (ET). The efficacy of these techniques seems to depend on a personalized protocol of COH for each patient. The response to ovarian stimulation protocols is not always as expected or the same in many patients.

A poor responder was first described in 1983 as one who, on a standard stimulation regimen (150 *IU* human menopausal gonadotrophin), had a peak estradiol concentration of <300 *pg/mL* and who had poor follicle production leading to a smaller number of eggs retrieved and, therefore, a smaller number of embryos transferred.

Recently, the European Society of Human Reproduction and Embryology (ESHRE) working group reported that in order to define a poor response in IVF, at least two of the following three features must be present: (i) advanced maternal age or any other risk factor for poor ovarian response (POR); (ii) a previous POR; and (iii) an abnormal ovarian reserve test (ORT). Two episodes of POR after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT. By definition, the term POR refers to the ovarian response and, therefore, one stimulated cycle is considered essential for the diagnosis of POR. However, patients of advanced age with an abnormal ORT may be classified as poor responders since both advanced age and an abnormal ORT may indicate reduced ovarian reserve and act as a surrogate for ovarian stimulation cycle outcome. In this case, the patients should be more properly defined as an 'expected poor responder' (3).

Is this problem frequent? The occurrence of poor response to ovarian stimulation is not infrequent; the prevalence of poor responders varies in the literature between 9 and 24% (2). This range is wide as it depends on the definition of a poor

responder that individual IVF centers employ. Data from the ASRM[1]/SART[2] registry showed that 14.1% of initial cycles were cancelled; at least 50% of these were poor responders (4).

Who are poor responders? There is no universal definition for "poor responders", although numerous criteria have been proposed by researchers to describe this situation (5). The number of developed follicles and the number of oocytes retrieved after a standard stimulation protocol are the most important criteria. The proposed quantity varies among authors and ranges from less than three to less than five dominant follicles on the day of hCG administration noted on ultrasound and/or less than three to less than five retrieved oocytes (6–11).

Another correlative criterion that has been proposed is the peak E2 level. A peak E2 level of <300 to <500 *pg/mL* or a level <100 *pg/mL* has been reported as crucial for defining poor response (8, 9, 12). Others have proposed the total gonadotropin dose used and/or the daily stimulation dose along with the duration of stimulation to be a defining criterion for poor responders. Shaker et al. reported an increased number of hMG or FSH ampoules used (>44), while Toth et al. considered a daily dose >300 *IU/day* to be the criterion for a poor response to the used gonadotropin (13, 14).

An (day 3) elevated basal serum FSH (≥7 to ≥15 *mIU/mL*) is an additional criterion (15–18). In addition, there are other criteria such as calculation of FSH/LH ratio as proposed by Yang et al. and measurement of basal E2 levels proposed by Manzi et al. and Ibrahim et al. A client's advanced age (≥40 years) is sometimes considered the cause (19–22). Some authors use a combination of the aforesaid parameters (12). However, a poor ovarian response can be confirmed only after having had a failed standard ovarian stimulation, and at least one cancelled IVF cycle (23).

Loutradis et al. considered a poor responder as a patient who fulfilled the following criteria: three or fewer recruited follicles or collected oocytes and a serum estradiol concentration lower than 300 *pg/mL* (if one follicle) or 500 *pg/mL* (if 2 or 3 follicles) at the time of hCG administration (9). Sallam et al. defined poor responders as patients undergoing treatment with ICSI, IVF, or TESE/ICSI from whom fewer than 5, 6, or 8 oocytes are retrieved, respectively (24). Kailasam et al. considered poor responders to be those patients who fail to develop more than three preovulatory follicles after using more than 300 *IU* of daily FSH or when it requires more than 3000 *IU* FSH to recruit less than four follicles (25). Yarali et al. considered poor responders as those patients who have a day 3 FSH >10 *mIU/mL*, day 3 E >60 *pg/mL*, or bilateral antral follicle count <6 or a history of poor ovarian response defined as cycle cancellation, peak E ≤500 *pg/mL*, or retrieval of less than four oocytes upon using the luteal long GnRH-a protocol (26).

Can poor responders be classified? The different definitions proposed for poor ovarian response can be roughly categorized into two subgroups; those in whom poor ovarian response has been observed in previous stimulated cycles (retrospective definition), and those in whom poor ovarian response is expected based on ovarian reserve tests or other factors such as age, ovarian surgery, *etc* (prospective definition) (2).

Some researchers classify poor responders into two subgroups; the first, includes young (age ≤37 years) and slim-bodied (weight ≤70 *kg*) patients who develop less than five follicles following 9 days of ovarian stimulation with 225 *IU/day* and do not reach oocyte retrieval, or those who require >600 *IU* of gonadotropin per retrieved oocyte if they reach that stage. The second, includes patients who are >37 years old and weight >70 *kg* and their cycles have been cancelled due to the production of less than five follicles following 9 days of ovarian stimulation with 300 *IU/day* of gonadotropins (27).

Another classification categorizes patients into the ones with a low response to previous IVF in the presence of normal basal FSH levels, young patients with non-fluctuating high FSH levels and older patients with an abnormal endocrinological profile. However, none of these classifications has any clinical significance, because no significant differences in ovarian response have been observed among different groups (28).

What are the suggested etiologies for poor ovarian response? The etiology of poor response to ovarian stimulation is unknown. Despite being highly correlated with maternal age, the condition is also common in younger women in whom low ovarian reserve represents the most frequent etiological factor (29–31). In addition, low ovarian reserve may be associated with advanced endometriosis, prior ovarian surgery, pelvic adhesions, increased

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body mass index, or smoking (32–37). However, this condition might also occur, unexpectedly, in young women who are non-smoker and have apparently normal ovarian reserves (38).

What is the possible mechanism? Studies have shown that poor ovarian response is the first sign of ovarian aging (early ovarian failure or early menopause) (38–40). This is clinically displayed by a shortened follicular phase which limits the time available to recruit an adequate number of follicles. Suggested mechanisms for poor ovarian response include: decreased number of FSH receptors in granulosa cells, defective signal transduction after FSH receptor binding, an inappropriate local vascular network for the distribution of gonadotropins, the presence of autoantibodies against granulosa cells, an excess of vascular growth factor receptor (VEGFR-1), abnormality in IGF-I and IGF-II levels, and diminished circulating gonadotropin surge-attenuating factor (GnSAF) bioactivity (41–47).

Genetic background of poor responders: Ovarian response to follicle-stimulating hormone (FSH) action differs considerably among women. Recently, new insights have been gained in the investigation of variability in the gene that encodes FSH receptor (FSHR) gene or genes of the estrogen pathway. Several polymorphisms of the FSHR gene have been discovered, but Ser680Asn and Thr307Ala are the two most studied. The Ser680Asn polymorphism of the FSHR gene has been found to influence the ovarian response to FSH stimulation in women undergoing in vitro fertilization (IVF), and in women with the genotype Ser/Ser, in whom the FSHR appears to be more resistant to FSH action. The clinical implications of this finding are highly important; the ultimate goal is to apply genetic markers as routine diagnostic tests before ovarian stimulation to predict ovarian response, determine the required FSH dose, and avoid the possible complications related to FSH stimulation (48).

Can poor ovarian response be predicted? Despite being difficult, it is of extreme importance to predict who will be a poor responder, because stimulation protocols should be individualized according to the conditions of each case. However, several tests have been proposed to predict ovarian reserve, which can give an idea about the ovarian response. These include static and dynamic tests:

Static testes

Biochemical testing of ovarian reserve based on a single measurement of early follicular phase (cycle days 2–4).

1- High levels of serum FSH (>12 or >15 *mIU/mL*) on cycle days 2 or 3 (49–51). In regularly cycling females, only high levels of basal FSH is an accurate prediction of poor response (52). This test is not suitable as a diagnostic test but only as a screening one for counseling purposes in the first IVF attempt.

2- Elevated FSH/luteinizing hormone (LH) on day 3 blood tests (53).

3- Elevated levels of serum estradiol (>30 or 75 *pg/mL*) on cycle days 2 or 3. The clinical applicability for basal estradiol as a test before starting IVF is limited by its very low predictive accuracy for poor response (54).

4- Decreased levels of serum inhibin B (45 *pg/mL*) on cycle days 2 or 3 are considered to be more predictive (55). In regularly cycling women, basal inhibin B is accurate only at a very low threshold level (52).

5- Reduced production and bioactivity of GnSAF (41).

6- Low insulin-like growth factor (IGF-I) in the follicular fluid (56).

7- Decreased serum concentrations of antimullerian hormone (AMH).

In 2002 de Vet et al. published a landmark paper that reported a 38% decline in AMH levels over a mean period of only 2.6 years in a group of young ovulatory women. This large decline in AMH over a relatively short period of time was not accompanied by any significant changes in antral follicle count, serum FSH or inhibin B levels, suggesting that AMH was the most sensitive maker of ovarian reserve. Serum AMH has become an increasingly popular method for the assessment of ovarian reserve; AMH is a glycoprotein produced by the granulosa cells within pre-antral and early antral follicles (55).

Serum AMH levels closely reflect the size of the growing cohort of small follicles which are sensitive to gonadotrophin stimulation, making AMH an ideal predictor of ovarian response during COH. Use of AMH has overcome the intercycle variability observed with other markers. Intercycle variability is a problem as women who may have displayed normal ovarian reserve on a single measurement may, in fact, have poor ovarian reserve if this was measured in a number of different cycles (57–59). On the contrary, AMH can be measured at any time of the menstrual cycle.

(59–60). Since then, several research groups have confirmed that low serum AMH levels are predictive of a poor response to COH. Therefore, use of serum AMH for the assessment of ovarian reserve could enable clinicians to identify women with early diminished ovarian reserves (60–70). Although, AMH is not still in widespread use due to the cost of testing, it is hoped that this state will be changed in the future as it promises to be a better prognostic indicator of ovarian reserve.

Sonographic tests: Different sonographic tests have also been proposed as predictors of ovarian response. These include:

1- Decreased ovarian volume (OVVOL): It is hardly suitable as a routine test for ovarian reserve assessment (52–71). A meta-analysis showed that ovarian volume measurement with a cut-off value of 3 cm^3, had the specificity for the prediction of cycle cancellation and non-pregnancy of 92% and 93%, respectively (72).

2- Decreased antral follicle count (AFC): The accuracy of the AFC for predicting poor response in regularly cycling women is adequate at low threshold levels (73–74). It will not be suitable as a diagnostic test, but it may be used as a screening one directing further diagnostic steps in the first IVF attempt (52, 75). Another meta-analysis showed that women having AFCs less than four were more likely to have cancelled cycles and less likely to get pregnant than women having AFCs of four or more (72).

3- Decreased ovarian stromal blood flow: The clinical value of doppler studies for ovarian stromal blood flow has been unclear (72, 76).

Dynamic tests

1- The clomiphene challenge test (CCT): It performs no better than other tests like the AFC or basal FSH, especially because of a loss in specificity (77).

2- The exogenous FSH ovarian reserve test (FSHORT) (78).

3- The GnRH agonist stimulation test (GAST). When used in regularly cycling women, GAST showed a high degree of accuracy in the prediction of poor response that could match that of AFC. However, it can be a candidate for more extensive confirmation research (52, 79).

However, given the present level of evidence, dynamic ovarian tests should be completely abandoned (80).

Unexpectedly, use of multifactor models has shown no definite increase in the predictive capacity compared to other ovarian reserve tests (52). In a systematic review and meta-analysis it has been conclusively shown that ovarian reserve tests, such as basal FSH, AMH, inhibin B, basal estradiol, AFC, ovarian volume, ovarian vascular flow, ovarian biopsy, CCCT, exogenous FSHORT, GAST, and multivariate prediction models, have only little clinical value in the prediction of poor response (52). This was agreed by Maheshwari et al. who stated that available tests for ovarian reserve do not have enough predictive power to justify their routine clinical use. However, recent evidence points that AMH and AFC may be better than other tests, although other tests continue to be used and form the basis for the exclusion of women from fertility treatments (80).

Conclusion

Despite the extensive efforts made, a test that could reliably predict a poor ovarian response in all patients that undergo IVF is currently lacking. Therefore, a consistent identification of a poor-responder would comprise a previously demonstrated poor ovarian response to adequate ovarian stimulation. This means that entering the first cycle of IVF without any prior testing seems to be the most preferable strategy.

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