

Prediction and Diagnosis of Poor Ovarian Response: The Dilemma

Ahmed Badawy *, Alaa Wageah, Mohamed El Gharib, Ezz Eldin Osman

- Department of Obstetrics and Gynecology, Mansoura University, Mansoura, Egypt

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 tests but 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.

Keywords: Controlled ovarian hyperstimulation, Female infertility, Ovarian failure, Poor ovarian response.

To cite this article: Badawy A, Wageah A, El Gharib M, Osman EE. Prediction and Diagnosis of Poor Ovarian Response: The Dilemma. *J Reprod Infertil.* 2011;12(4): 241-248.

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

* Corresponding Author:
Ahmed Badawy,
Department of Obstetrics
and Gynecology,
Mansoura University,
Mansoura, Egypt
E-mail:
ambadawy@yahoo.com

Received: Aug. 20, 2011

Accepted: Nov. 1, 2011

responder that individual IVF centers employ. Data from the ASRM¹/SART² 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

1- American Society for Reproductive Medicine

2- Society for Assisted Reproductive Technology

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 antimüllerian 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 cm³, 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.

References

1. Shanbhag S, Aucott L, Bhattacharya S, Hamilton M A, McTavish AR. Interventions for 'poor responders' to controlled ovarian hyperstimulation (COH) in in-vitro fertilisation (IVF). Cochrane Database Syst Rev. 2007;(1):CD004379.
2. Venetis CA, Kolibianakis EM, Tarlatzi TB, Tarlatzis BC. Evidence-based management of poor ovarian response. Ann N Y Acad Sci. 2010;1205:199-206.
3. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L; ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011;26(7):1616-24.
4. Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 2001 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology registry. Fertil Steril. 2007;87(6):1253-66.

5. Kyrrou D, Kolibianakis EM, Venetis CA, Papanikolaou EG, Bontis J, Tarlatzis BC. How to improve the probability of pregnancy in poor responders undergoing in vitro fertilization: a systematic review and meta-analysis. *Fertil Steril.* 2009;91(3):749-66.
6. Land JA, Yarmolinskaya MI, Dumoulin JC, Evers JL. High-dose human menopausal gonadotropin stimulation in poor responders does not improve in vitro fertilization outcome. *Fertil Steril.* 1996;65(5):961-5.
7. Fridström M, Akerlöf E, Sjöblom P, Hillensjö T. Serum levels of luteinizing and follicle-stimulating hormones in normal and poor-responding patients undergoing ovarian stimulation with urofollitropin after pituitary downregulation. *Gynecol Endocrinol.* 1997;11(1):25-8.
8. Raga F, Bonilla-Musoles F, Casañ EM, Bonilla F. Recombinant follicle stimulating hormone stimulation in poor responders with normal basal concentrations of follicle stimulating hormone and oestradiol: improved reproductive outcome. *Hum Reprod.* 1999;14(6):1431-4.
9. Loutradis D, Drakakis P, Milingos S, Stefanidis K, Michalas S. Alternative approaches in the management of poor response in controlled ovarian hyperstimulation (COH). *Ann N Y Acad Sci.* 2003;997:112-9.
10. Rombauts L, Suikkari AM, MacLachlan V, Trounson AO, Healy DL. Recruitment of follicles by recombinant human follicle-stimulating hormone commencing in the luteal phase of the ovarian cycle. *Fertil Steril.* 1998;69(4):665-9.
11. Surrey ES, Bower J, Hill DM, Ramsey J, Surrey MW. Clinical and endocrine effects of a microdose GnRH agonist flare regimen administered to poor responders who are undergoing in vitro fertilization. *Fertil Steril.* 1998;69(3):419-24.
12. Schoolcraft W, Schlenker T, Gee M, Stevens J, Wagley L. Improved controlled ovarian hyperstimulation in poor responder in vitro fertilization patients with a microdose follicle-stimulating hormone flare, growth hormone protocol. *Fertil Steril.* 1997;67(1):93-7.
13. Shaker AG, Fleming R, Jamieson ME, Yates RW, Coutts JR. Absence of effect of adjuvant growth hormone therapy on follicular responses to exogenous gonadotropins in women: normal and poor responders. *Fertil Steril.* 1992;58(5):919-23.
14. Toth TL, Awwad JT, Veeck LL, Jones HW Jr, Muasher SJ. Suppression and flare regimens of gonadotropin-releasing hormone agonist. Use in women with different basal gonadotropin values in an in vitro fertilization program. *J Reprod Med.* 1996;41(5):321-6.
15. Droesch K, Muasher SJ, Brzyski RG, Jones GS, Simonetti S, Liu HC, et al. Value of suppression with a gonadotropin-releasing hormone agonist prior to gonadotropin stimulation for in vitro fertilization. *Fertil Steril.* 1989;51(2):292-7.
16. Feldberg D, Farhi J, Ashkenazi J, Dicker D, Shalev J, Ben-Rafael Z. Minidose gonadotropin-releasing hormone agonist is the treatment of choice in poor responders with high follicle-stimulating hormone levels. *Fertil Steril.* 1994;62(2):343-6.
17. Olivennes F, Righini C, Fanchin R, Torrisi C, Hazout A, Glissant M, et al. A protocol using a low dose of gonadotrophin-releasing hormone agonist might be the best protocol for patients with high follicle-stimulating hormone concentrations on day 3. *Hum Reprod.* 1996;11(6):1169-72.
18. Karande V, Morris R, Rinehart J, Miller C, Rao R, Gleicher N. Limited success using the "flare" protocol in poor responders in cycles with low basal follicle-stimulating hormone levels during in vitro fertilization. *Fertil Steril.* 1997;67(5):900-3.
19. Yang JH, Wu MY, Chao KH, Chen SU, Ho HN, Yang YS. Long GnRH-agonist protocol in an IVF program. Is it appropriate for women with normal FSH levels and high FSH/LH ratios? *J Reprod Med.* 1997;42(10):663-8.
20. Manzi DL, Thornton KL, Scott LB, Nulsen JC. The value of increasing the dose of human menopausal gonadotropins in women who initially demonstrate a poor response. *Fertil Steril.* 1994;62(2):251-6.
21. Ibrahim ZH, Matson PL, Buck P, Lieberman BA. The use of biosynthetic human growth hormone to augment ovulation induction with buserelin acetate/human menopausal gonadotropin in women with a poor ovarian response. *Fertil Steril.* 1991;55(1):202-4.
22. van Rooij IA, Bancsi LF, Broekmans FJ, Looman CW, Habbema JD, te Velde ER. Women older than 40 years of age and those with elevated follicle-stimulating hormone levels differ in poor response rate and embryo quality in in vitro fertilization. *Fertil Steril.* 2003;79(3):482-8.
23. Schachter M, Friedler S, Raziel A, Strassburger D, Bern O, Ron-el R. Improvement of IVF outcome in poor responders by discontinuation of GnRH analogue during the gonadotropin stimulation phase--a function of improved embryo quality. *J Assist Reprod Genet.* 2001;18(4):197-204.
24. Sallam HN, Ezzeldin F, Agameya AF, Rahman AF, El-Garem Y. Defining poor responders in assisted reproduction. *Int J Fertil Womens Med.* 2005;50(3):115-20.

25. Kailasam C, Keay SD, Wilson P, Ford WC, Jenkins JM. Defining poor ovarian response during IVF cycles, in women aged <40 years, and its relationship with treatment outcome. *Hum Reprod.* 2004;19(7):1544-7.
26. Yarali H, Esinler I, Polat M, Bozdogan G, Tiras B. Antagonist/letrozole protocol in poor ovarian responders for intracytoplasmic sperm injection: a comparative study with the microdose flare-up protocol. *Fertil Steril.* 2009;92(1):231-5.
27. Gorgy A, Taranissi M. Defining and predicting the poor responder. *Fertil Steril.* 2001;75(1):226-7.
28. Wang PT, Lee RK, Su JT, Hou JW, Lin MH, Hu YM. Cessation of low-dose gonadotropin releasing hormone agonist therapy followed by high-dose gonadotropin stimulation yields a favorable ovarian response in poor responders. *J Assist Reprod Genet.* 2002;19(1):1-6.
29. Mahutte NG, Arici A. Poor responders: does the protocol make a difference? *Curr Opin Obstet Gynecol.* 2002;14(3):275-81.
30. Ubaldi FM, Rienzi L, Ferrero S, Baroni E, Sapienza F, Cobellis L, et al. Management of poor responders in IVF. *Reprod Biomed Online.* 2005;10(2):235-46.
31. Pellicer A, Ardiles G, Neuspiller F, Remohí J, Simón C, Bonilla-Musoles F. Evaluation of the ovarian reserve in young low responders with normal basal levels of follicle-stimulating hormone using three-dimensional ultrasonography. *Fertil Steril.* 1998;70(4):671-5.
32. Nargund G, Bromhan D. Comparison of endocrinological and clinical profiles and outcome of IVF cycles in patients with one ovary and two ovaries. *J Assist Reprod Genet.* 1995;12(7):458-60.
33. Keay SD, Liversedge NH, Jenkins JM. Could ovarian infection impair ovarian response to gonadotrophin stimulation? *Br J Obstet Gynaecol.* 1998;105(3):252-3.
34. Sharara FI, Beatse SN, Leonardi MR, Navot D, Scott RT Jr. Cigarette smoking accelerates the development of diminished ovarian reserve as evidenced by the clomiphene citrate challenge test. *Fertil Steril.* 1994;62(2):257-62.
35. Ragni G, De Lauretis Yankowski L, Piloni S, Vegetti W, Guermandi E, Colombo M, et al. In vitro fertilization for patients with poor response and occult ovarian failure: a randomized trial. *Reprod Technol.* 2000;10:98-102.
36. Loh S, Wang JX, Matthews CD. The influence of body mass index, basal FSH and age on the response to gonadotrophin stimulation in non-polycystic ovarian syndrome patients. *Hum Reprod.* 2002;17(5):1207-11.
37. Stillman RJ, Rosenberg MJ, Sachs BP. Smoking and reproduction. *Fertil Steril.* 1986;46(4):545-66.
38. Nikolaou D, Templeton A. Early ovarian ageing: a hypothesis. Detection and clinical relevance. *Hum Reprod.* 2003;18(6):1137-9.
39. Beckers NG, Macklon NS, Eijkemans MJ, Fauser BC. Women with regular menstrual cycles and a poor response to ovarian hyperstimulation for in vitro fertilization exhibit follicular phase characteristics suggestive of ovarian aging. *Fertil Steril.* 2002;78(2):291-7.
40. de Boer EJ, den Tonkelaar I, te Velde ER, Burger CW, Klip H, van Leeuwen FE, et al. A low number of retrieved oocytes at in vitro fertilization treatment is predictive of early menopause. *Fertil Steril.* 2002;77(5):978-85.
41. Martinez F, Barri PN, Coroleu B, Tur R, Sorsaleslie T, Harris WJ, et al. Women with poor response to IVF have lowered circulating gonadotrophin surge-attenuating factor (GnSAF) bioactivity during spontaneous and stimulated cycles. *Hum Reprod.* 2002;17(3):634-40.
42. Ulug U, Turan E, Tosun SB, Erden HF, Bahceci M. Comparison of preovulatory follicular concentrations of epidermal growth factor, insulin-like growth factor-I, and inhibins A and B in women undergoing assisted conception treatment with gonadotropin-releasing hormone (GnRH) agonists and GnRH antagonists. *Fertil Steril.* 2007;87(4):995-8.
43. Neulen J, Wenzel D, Hornig C, Wunsch E, Weisenborn U, Grunwald K, et al. Poor responder-high responder: the importance of soluble vascular endothelial growth factor receptor 1 in ovarian stimulation protocols. *Hum Reprod.* 2001;16(4):621-6.
44. Pellicer A, Ballester MJ, Serrano MD, Mir A, Serra-Serra V, Remohi J, et al. Aetiological factors involved in the low response to gonadotrophins in infertile women with normal basal serum follicle stimulating hormone levels. *Hum Reprod.* 1994;9(5):806-11.
45. Hernandez ER. Embryo implantation and GnRH antagonists: embryo implantation: the Rubicon for GnRH antagonists. *Hum Reprod.* 2000;15(6):1211-6.
46. Lee DW, Grasso P, Dattatreyaumurthy B, Deziel MR, Reichert LE Jr. Purification of a high molecular weight follicle-stimulating hormone receptor-binding inhibitor from human follicular fluid. *J Clin Endocrinol Metab.* 1993;77(1):163-8.
47. Zeleznik AJ, Schuler HM, Reichert LE Jr. Gonadotropin-binding sites in the rhesus monkey ovary: role of the vasculature in the selective distribution

- of human chorionic gonadotropin to the pre-ovulatory follicle. *Endocrinology*. 1981;109(2):356-62.
48. Loutradis D, Drakakis P, Vomvolaki E, Antsaklis A. Different ovarian stimulation protocols for women with diminished ovarian reserve. *J Assist Reprod Genet*. 2007;24(12):597-611.
 49. Cameron IT, O'Shea FC, Rolland JM, Hughes EG, de Kretser DM, Healy DL. Occult ovarian failure: a syndrome of infertility, regular menses, and elevated follicle-stimulating hormone concentrations. *J Clin Endocrinol Metab*. 1988;67(6):1190-4.
 50. Scott RT, Toner JP, Muasher SJ, Oehninger S, Robinson S, Rosenwaks Z. Follicle-stimulating hormone levels on cycle day 3 are predictive of in vitro fertilization outcome. *Fertil Steril*. 1989;51(4):651-4.
 51. Toner JP, Philput CB, Jones GS, Muasher SJ. Basal follicle-stimulating hormone level is a better predictor of in vitro fertilization performance than age. *Fertil Steril*. 1991;55(4):784-91.
 52. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. *Hum Reprod Update*. 2006;12(6):685-718.
 53. Mukherjee T, Copperman AB, Lapinski R, Sandler B, Bustillo M, Grunfeld L. An elevated day three follicle-stimulating hormone:luteinizing hormone ratio (FSH:LH) in the presence of a normal day 3 FSH predicts a poor response to controlled ovarian hyperstimulation. *Fertil Steril*. 1996;65(3):588-93.
 54. Licciardi FL, Liu HC, Rosenwaks Z. Day 3 estradiol serum concentrations as prognosticators of ovarian stimulation response and pregnancy outcome in patients undergoing in vitro fertilization. *Fertil Steril*. 1995;64(5):991-4.
 55. Seifer DB, MacLaughlin DT. Mullerian Inhibiting Substance is an ovarian growth factor of emerging clinical significance. *Fertil Steril*. 2007;88(3):539-46.
 56. Oosterhuis GJ, Vermes I, Lambalk CB, Michgelsen HW, Schoemaker J. Insulin-like growth factor (IGF)-I and IGF binding protein-3 concentrations in fluid from human stimulated follicles. *Hum Reprod*. 1998;13(2):285-9.
 57. Scott RT Jr, Hofmann GE, Oehninger S, Muasher SJ. Intercycle variability of day 3 follicle-stimulating hormone levels and its effect on stimulation quality in in vitro fertilization. *Fertil Steril*. 1990;54(2):297-302.
 58. Scott RT Jr, Hofmann GE. Prognostic assessment of ovarian reserve. *Fertil Steril*. 1995;63(1):1-11.
 59. Seifer DB, Lambert-Messerlian G, Hogan JW, Gardiner AC, Blazar AS, Berk CA. Day 3 serum inhibin-B is predictive of assisted reproductive technologies outcome. *Fertil Steril*. 1997;67(1):110-4.
 60. Van Rooij IA, Broekmans FJ, te Velde ER, Fauser BC, Bancsi LF, de Jong FH, et al. Serum anti-Müllerian hormone levels: a novel measure of ovarian reserve. *Hum Reprod*. 2002;17(12):3065-71.
 61. Seifer DB, MacLaughlin DT, Christian BP, Feng B, Shelden RM. Early follicular serum müllerian-inhibiting substance levels are associated with ovarian response during assisted reproductive technology cycles. *Fertil Steril*. 2002;77(3):468-71.
 62. Hazout A, Bouchard P, Seifer DB, Aussage P, Juncà AM, Cohen-Bacrie P. Serum antimüllerian hormone/müllerian-inhibiting substance appears to be a more discriminatory marker of assisted reproductive technology outcome than follicle-stimulating hormone, inhibin B, or estradiol. *Fertil Steril*. 2004;82(5):1323-9.
 63. Muttukrishna S, Suharjono H, McGarrigle H, Sathanandan M. Inhibin B and anti-Müllerian hormone: markers of ovarian response in IVF/ICSI patients? *BJOG*. 2004;111(11):1248-53.
 64. Eldar-Geva T, Ben-Chetrit A, Spitz IM, Rabino-witz R, Markowitz E, Mimoni T, et al. Dynamic assays of inhibin B, anti-Müllerian hormone and estradiol following FSH stimulation and ovarian ultrasonography as predictors of IVF outcome. *Hum Reprod*. 2005;20(11):3178-83.
 65. Tremellen KP, Kolo M, Gilmore A, Lekamge DN. Anti-müllerian hormone as a marker of ovarian reserve. *Aust N Z J Obstet Gynaecol*. 2005;45(1):20-4.
 66. Peñarrubia J, Fábregues F, Manau D, Creus M, Carmona F, Casamitjana R, et al. Previous cycle cancellation due to poor follicular development as a predictor of ovarian response in cycles stimulated with gonadotrophin-releasing hormone agonist-gonadotrophin treatment. *Hum Reprod*. 2005;20(3):622-8.
 67. Nelson SM, Yates RW, Fleming R. Serum anti-Müllerian hormone and FSH: prediction of live birth and extremes of response in stimulated cycles--implications for individualization of therapy. *Hum Reprod*. 2007;22(9):2414-21.
 68. Lekamge DN, Barry M, Kolo M, Lane M, Gilchrist RB, Tremellen KP. Anti-Müllerian hormone as a predictor of IVF outcome. *Reprod Biomed Online*. 2007;14(5):602-10.
 69. La Marca A, Giulini S, Tirelli A, Bertucci E, Marsella T, Xella S, et al. Anti-Müllerian hormone measurement on any day of the menstrual cycle strongly predicts ovarian response in assisted re-

- productive technology. *Hum Reprod.* 2007;22(3):766-71.
70. Smeenk JM, Sweep FC, Zielhuis GA, Kremer JA, Thomas CM, Braat DD. Antimüllerian hormone predicts ovarian responsiveness, but not embryo quality or pregnancy, after in vitro fertilization or intracytoplasmic sperm injection. *Fertil Steril.* 2007;87(1):223-6.
 71. Lass A, Skull J, McVeigh E, Margara R, Winston RM. Measurement of ovarian volume by transvaginal sonography before ovulation induction with human menopausal gonadotrophin for in-vitro fertilization can predict poor response. *Hum Reprod.* 1997;12(2):294-7.
 72. Gibreel A, Maheshwari A, Bhattacharya S, Johnson NP. Ultrasound tests of ovarian reserve; a systematic review of accuracy in predicting fertility outcomes. *Hum Fertil (Camb).* 2009;12(2):95-106.
 73. Chang MY, Chiang CH, Hsieh TT, Soong YK, Hsu KH. Use of the antral follicle count to predict the outcome of assisted reproductive technologies. *Fertil Steril.* 1998;69(3):505-10.
 74. Bancsi LF, Broekmans FJ, Eijkemans MJ, de Jong FH, Habbema JD, te Velde ER. Predictors of poor ovarian response in in vitro fertilization: a prospective study comparing basal markers of ovarian reserve. *Fertil Steril.* 2002;77(2):328-36.
 75. Hendriks DJ, Broekmans FJ, Bancsi LF, de Jong FH, Looman CW, Te Velde ER. Repeated clomiphene citrate challenge testing in the prediction of outcome in IVF: a comparison with basal markers for ovarian reserve. *Hum Reprod.* 2005;20(1):163-9.
 76. Engmann L, Sladkevicius P, Agrawal R, Bekir JS, Campbell S, Tan SL. Value of ovarian stromal blood flow velocity measurement after pituitary suppression in the prediction of ovarian responsiveness and outcome of in vitro fertilization treatment. *Fertil Steril.* 1999;71(1):22-9.
 77. Navot D, Rosenwaks Z, Margalioth EJ. Prognostic assessment of female fecundity. *Lancet.* 1987;2(8560):645-7.
 78. Fanchin R, de Ziegler D, Olivennes F, Taieb J, Dzik A, Frydman R. Exogenous follicle stimulating hormone ovarian reserve test (EFORT): a simple and reliable screening test for detecting 'poor responders' in in-vitro fertilization. *Hum Reprod.* 1994;9(9):1607-11.
 79. Karande V, Gleicher N. A rational approach to the management of low responders in in-vitro fertilization. *Hum Reprod.* 1999;14(7):1744-8.
 80. Maheshwari A, Gibreel A, Bhattacharya S, Johnson NP. Dynamic tests of ovarian reserve: a systematic review of diagnostic accuracy. *Reprod Biomed Online.* 2009;18(5):717-34.