Is there an ideal stimulation regimen for IVF for poor responders and does it change with age?

Beverley Vollenhoven · Tiki Osianlis · James Catt

Received: 17 June 2008 / Accepted: 17 October 2008 / Published online: 4 November 2008
© Springer Science + Business Media, LLC 2008

Abstract

Purpose To determine whether there is a superior treatment modality for ‘poor’ responders.

Method Retrospective analysis of three stimulation regimens, with patients stratified based on age, stimulation regime and response in previous cycles (‘poor’ responder or ‘non poor’ responder). Fertilisation, embryo utilisation and clinical pregnancy rates were assessed. There were a total of 1,608 cycles in the ‘poor’ responder and 8,489 cycles in the ‘non poor’ responder groups.

Results In ‘poor’ responders there was no significant difference in fertilisation rate, nor utilisation rate between the three stimulation regimes and no differences in the pregnancy rate/initiated cycle irrespective of age and stimulation regimen in any of the groups. ‘Non poor’ responders had a significantly greater pregnancy rate/initiated cycle for all stimulation regimens in both age groups compared with ‘poor’ responders.

Capsule The type of stimulation regime, be it down regulation, boost or GnRH-antagonist does not improve IVF success for patients classified as poor responders.

B. Vollenhoven
Department of Obstetrics and Gynaecology, Monash University,
Level 5, Monash Medical Centre, 246 Clayton Rd,
Clayton, Victoria 3168, Australia

B. Vollenhoven
Department of Gynaecology, Southern Health,
246 Clayton Rd,
Clayton, Victoria 3168, Australia

B. Vollenhoven (✉) · T. Osianlis · J. Catt
Monash IVF, Suite 1,
252 Clayton Rd,
Clayton, Victoria 3168, Australia
e-mail: beverley.vollenhoven@med.monash.edu.au

Conclusion This large retrospective study of ‘poor’ responders has not shown a difference in pregnancy rates/initiated cycle between stimulation regimens.

Keywords IVF success · Poor responder · Stimulation regimen

Introduction

Treatment outcomes for IVF are the best they have ever been. Generally, for IVF to be successful, adequate follicular recruitment and maturation is essential. Stimulating follicle production in poor responder patients can be a challenge. A poor responder was first described in 1983 as one who on a standard stimulation regimen (150 IU human menopausal gonadotrophin), had a peak oestradiol (E₂) concentration <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. There was also a lower ongoing pregnancy rate in this group [1]. It is estimated that the incidence of poor response varies from 9–26%. This incidence is wide as the basis for the incidence varies in the definition of poor response between studies [2]. For some women a poor response is not unexpected, for example the woman in her forties or one who has low ovarian reserve on biochemical testing or the woman who smokes [3, 4]. However it is the young woman who is a non smoker and who has apparent normal ovarian reserve but who unexpectedly responds poorly and who keeps responding poorly despite increases in the dose of her stimulation regimen who remains a particular challenge. Why these women have a poor response is unknown but they obviously have a discrepancy between their chronological age and the biological age of the ovary

[2] and display early ovarian ageing [5] which may be clinically displayed by a shortened follicular phase which limits the time available to recruit an adequate number of follicles [6]. There may also be changes within the ovary at a FSH receptor level [7, 8] or at a molecular level with abnormal signal transduction [9].

There are also problems with biochemical testing of ovarian reserve based on a single measurement of early follicular phase (cycle days 2–4) FSH, LH and E₂. There is an intercycle variability that is well known [10–12] and 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. With the introduction and more widespread use of anti-müllerian hormone (AMH), which does not display this intercycle variability and can be measured at any time of the menstrual cycle, this problem will potentially be solved [13, 14]. At present, in Australia, at least, AMH is still not in widespread use due to the cost of testing. It is hoped that this will change for the future as AMH promises to be a better prognostic indicator of ovarian reserve.

At present the ideal stimulation regimen for poor responders is not known. There have been a number of randomised controlled trials that have examined this and no particular stimulation protocol has been found to be superior. The stimulation regimens that have been investigated have been comparisons between Boost or Flare protocols with down regulation (DR) protocols and antagonist (Ant) protocols with boost and DR protocols [summarized in 15–18]. Most studies have defined poor responders in different ways making it difficult to compare trials and there have been inadequate numbers in the trials with therefore a lack of power to show a positive treatment response [19]. There has not been a comparison in the one study between the three different protocols, namely Boost versus DR versus Ant protocols.

Our aim was to investigate three different stimulation regimens to determine whether there is a suitable treatment modality for poor responders with respect to clinical pregnancy rate and to determine if age is a factor in determining this regimen. The stimulation protocols were chosen for the patient based on individual clinician's choice.

Materials and methods

This was a retrospective study examining cycle outcome within responder groups to three stimulation regimens with or without the oral contraceptive pill (OCP; Microgynon or Levlen Schering Australia). The regimens were Boost/FSH (Boost), Down Regulation (DR)/FSH (DR/FSH) and FSH/GnRH antagonist (Ant/FSH). A 'poor' responder was defined as a woman who had at least two unsuccessful

commenced stimulation cycles with a total of <4 mature eggs collected with a dose of ≥ 450 IU recombinant FSH (rFSH). Previous cycles may have used either an agonist or an antagonist. A 'non poor' responder was a woman outside of these parameters.

In Boost cycles the patient started the GnRHa on days 1 or 2 after a spontaneous or OCP induced bleed. The FSH stimulation was begun the following day. In DR/FSH cycles the GnRHa was begun in the mid luteal phase of a spontaneous cycle or on day 17 of active OCP and the FSH stimulation begun once down regulation was confirmed biochemically with an estradiol (E₂) concentration of ≤ 200 pmol/L. In Ant /FSH cycles the FSH stimulation was begun on days 1–3 of a spontaneous or OCP induced bleed with the GnRH antagonist starting once the leading follicle was found to be 14 mm on ultrasound (usually day 6). The GnRHa was Synarel (Pharmacia Australia) in all cycles with the dose being 0.4 mg/ day. The stimulation was 450 or 600IU rFSH (Gonal F:Merck Serono Australia; Puregon: Organon Australia) in the "poor responder" group and less than 450 in the "non-poor responder" group and the antagonist was Cetrorelix (Cetrotide: Merck Serono Australia) with a daily dose of 250 μ g. The OCP was a standard 30 μ g ethinyl oestradiol and 150 μ g laevonorgestrel containing preparation.

Standard cancellation criteria included patients having less than three follicles greater than 16 mm at the time of stimulation. A patient classified as a poor responder may have chosen to have oocyte retrieval even with one follicle on ultrasound. Cancellation with follicle numbers under three is at the discretion of the patient and clinician after discussion of previous cycles.

Oocyte retrievals were performed 38 h post human chorionic gonadotrophin (hCG) administration (either recombinant [rhCG] Ovidrel (Merck Serono Australia) at 250 μ g or urinary [uhCG] Pregnyl (Organon Australia) at 10,000 IU). Oocytes were fertilised using either standard insemination or ICSI and fertilisation results assessed between 16–20 h post sperm insemination. Embryos were transferred (ET) between day 2 to 5 with no more than two embryos being transferred at any one time. Patients may elect to have one or two embryos transferred or alternatively patients may only have one or two embryos available for transfer with no other embryos available. Luteal support consisted of either Crinone (Merck Serono Australia) or Progesterone Pessaries (Orion Australia).

Patients were stratified for age as being <40 years or ≥ 40 years at time of cycle initiation. Fertilisation, embryo utilisation and clinical pregnancy rates were investigated between the various stimulation regimens and responder groups. Pregnancy outcomes in relation to number of embryos transferred and age of embryos at transfer (day of transfer) were also investigated. Embryo utilisation rate

was defined as the number of embryos transferred and frozen divided by the number of eggs fertilised. Clinical pregnancy rate was defined as an intrauterine gestational sac with an embryo and foetal heart motion being present on ultrasound examination.

Statistical analysis was undertaken using paired χ^2 analyses (Minitab® Version 7.0) with significance considered at a P value of 0.05.

The study was approved by the Ethics Committee of the Monash Surgical Private Hospital.

Cycles between January 2004– July 2007 were examined.

Results

There were a total of 1,608 cycles in the ‘poor’ responder group with 720 patients, 46.2% under 40 years, and, 8,489 cycles with 5,127 patients in the ‘non poor’ responder group, of which, as expected, 92% were under 40 years.

In the ‘poor’ responder group, patient outcomes were examined with and without the OCP as part of the stimulation regimen. In the <40 year olds, in the Boost group 28 had the OCP, in the DR/FSH group 280 had the OCP and in the Ant/FSH group 44 had the OCP. In the ≥ 40 years olds, in the Boost group 52 had the OCP, in the DR/FSH group 261 had the OCP and in the Ant/FSH group 36 had the OCP. There were no statistically significant differences between patients within the respective groups with or without the OCP, therefore groups were examined as a cumulative of the stimulation regimens with and without the OCP. This was also the case in the ‘non poor’ responder group.

The average age in the overall ‘poor’ responder group was 36.6 years in the <40 year group and the average number of oocyte retrievals was 2.5. In the ≥ 40 year group, the average age was 41.9 years and the average number of

oocyte retrievals was 2.3. Overall, in the ‘non poor’ responder group the average ages were 33.4 years and 41.2 years respectively with average oocyte retrievals of 2.0 and 2.9 respectively.

In ‘poor’ responders there was no significant difference in fertilisation rate, nor utilisation rate between the three stimulation regimes. There were no differences in the pregnancy rate/initiated cycle irrespective of age and stimulation regimen in any of the groups. Under the age of 40 years in the Boost group, the pregnancy rate/initiated cycle was 6.5%, DR/FSH was 6.6% and Ant/FSH was 8.0%. In the patients ≥ 40 years, the pregnancy rate was 4.1%, 5.0% and 3.2% respectively (Table 1).

In the ‘non poor’ responders (<40 years) there was a significantly lower pregnancy rate/initiated cycle in Boost compared with DR/FSH ($p = 0.000$) and Ant/FSH ($p = 0.029$). Patients <40 years exposed to a Boost regimen had a 20% pregnancy rate/initiated cycle compared to 32% and 30% for DR/FSH and Ant/FSH respectively. Patients ≥ 40 years had a pregnancy rate/initiated cycle of 10%, 19% and 11% for Boost, DR/FSH and Ant/FSH cycles respectively with no significant difference between groups. Overall, ‘non poor’ responders had a significantly greater pregnancy rate/initiated cycle for all stimulation regimens in both age groups compared with ‘poor’ responders ($P = 0.001$).

Overall, there was a high cancellation rate in the ‘poor’ responder group compared with the ‘non poor’ responder group for all stimulation regimens in both age groups ($p = <0.001$). There was however a significantly lower cancellation rate defined as discharges per initiated cycles, in the DR/FSH group, with 28.1% of patients initiating a cycle not having an oocyte retrieval compared to 41.9% of Boost patients and 43.9% of Ant/FSH patients in the <40 year age group. In the age group ≥ 40 years the cancellation rate was 35.6%, 32.2% and 36.9% in the Boost, DR/FSH and Ant/FSH groups respectively with no significant difference

Table 1 Poor responders

	Boost		DR/FSH		Ant/FSH	
	<40	≥ 40	<40	≥ 40	<40	≥ 40
N (number of initiated cycles)	246	365	310	283	187	217
Average Age $\pm$ SD (years)	36.5 $\pm$ 2.5	42.0 $\pm$ 1.5	36.5 $\pm$ 2.4	41.9 $\pm$ 1.4	36.9 $\pm$ 2.3	41.8 $\pm$ 1.4
Average number of initiated cycles $\pm$ SD	2.2 $\pm$ 1.8	2.5 $\pm$ 2.0	2.6 $\pm$ 2.1	2.4 $\pm$ 2.3	2.4 $\pm$ 2.3	2.8 $\pm$ 2.4
Average number of oocyte retrieved $\pm$ SD	2.0 $\pm$ 2.4	2.2 $\pm$ 2.5	3.0 $\pm$ 3.1	2.5 $\pm$ 2.7	2.4 $\pm$ 3.1	2.0 $\pm$ 2.6
Fertilisation rate (%)	67.0	64.2	63.6	64.0	66.9	68.6
Utilisation rate (%)	77.6	78.6	73.6	74.6	75.9	80.2
Pregnancies/initiated cycles (%)	6.5	4.1	6.6	5.0	8.0	3.2
Pregnancies/oocyte retrieval (%)	11.2	6.4	9.0	7.3	14.3	5.1
Cancelled cycles (%)	41.9*	35.6	28.1*	32.2	43.9*	36.9
Pregnancies/transfer (%)	14.5	8.7	10.9	9.5	18.1	6.8

* $p=0.001$ DR/FSH vs Boost and Ant/FSH

amongst the groups (Table 1). In the ‘non poor’ responders under the age of 40 years the cancellation rate was 8%, 6% and 4% in the Boost, DR/FSH and Ant/FSH groups respectively. At the age of ≥ 40 years the cancellation rates were 6%, 7% and 8% in the three groups respectively.

The pregnancy outcome for the ‘poor’ responders was significantly lower than the ‘non poor’ responders. When the number of embryos transferred within the two groups was examined (Table 2), there were a higher number of double embryo transfers in the ‘non poor’ responder group. The average number of oocytes retrieved in the ‘poor’ responder group ranged between 2 and 3 (Table 1) whereas in the ‘non poor’ responders the average number of oocytes collected was approximately 10. The fewer embryos generated in the ‘poor’ responder group meant that there were no selection criteria for transfer in this group, embryos that fertilised and cleaved were transferred. In the ‘poor’ responder group <40 years there was a significant difference in pregnancy rate when one embryo was transferred in the FSH/Ant group as opposed to the DR/FSH group. In the ‘non poor’ responders there was no difference in the pregnancy rate/transfer between single versus a double embryo transfer although the numbers in some groups were too small to yield accurate statistics.

Discussion

We have shown no difference in the pregnancy rate/initiated cycle irrespective of age and the stimulation regimen used in ‘poor’ responders. In both age groups and all three stimulation regimens the success rate was lower and the cancellation rate higher when compared to ‘non poor’ responders. In the ‘poor responder’ DR/FSH group the cancellation rate was lower than with the other 2 stimula-

tion regimens but this did not translate to a better success even using embryo transfer as the denominator probably as a result of overall poor embryo quality in these patients. This was demonstrated by the majority of patients having a day 3 embryo transfer rather than a day 5 transfer.

In ‘non poor’ responders under the age of 40 years there was a significantly lower pregnancy rate/initiated cycle in Boost compared with DR/FSH and Ant/FSH regimens. This was also shown in a Cochrane review [20] of 26 randomised trials comparing the long protocol (DR/FSH) with the short (Boost/FSH) or ultrashort protocols. These data suggest that there is no place for the use of Boost/FSH cycles in IVF irrespective of age.

The ‘poor’ responder group had fewer embryos produced, therefore fewer of them had a double embryo transfer compared to the ‘non-poor’ responder group. If a single embryo was transferred in a woman less than 40 years in the FSH/Ant group, statistically, pregnancy was more likely to occur than in the same situation in the DR/FSH group.

The rationale for the use of a Boost regimen in poor responders is the theoretical promotion of follicular growth which may occur with the boost or flare effect that occurs on initiation of the GnRHa. The disadvantage is that there can be a premature LH surge that causes cycle cancellation [21]. The use of an Antagonist in these patients will prevent the LH surge and not cause suppression in the early follicular phase which is a crucial time for follicular recruitment and which occurs with the DR protocol [22]. However as has been shown by us in this study and by others (as discussed below) the relative advantage of one protocol against another does not translate to better success in this patient group.

In the literature there is no consistent definition of a ‘poor’ responder therefore making comparison between studies difficult. ‘Poor’ responders have variously been

Table 2 Single vs double embryo transfers

Poor responders	Boost		DR/FSH		Ant/FSH	
	<40	≥ 40	<40	≥ 40	<40	≥ 40
Number of single ET	58	68	78	66	27	43
Pregnancy/transfer (%)	8.6	2.9	7.7*	3.0	22.2**	4.7
Number of double ET	52	104	105	82	56	60
Pregnancy/transfer (%)	21.2	12.5	13.3	14.6	16.1	8.3
% of Single/Double ET	52.7	39.5	42.6	44.6	32.5	41.8
Non-poor responders						
Number of single ET	19	8	1209	45	38	9
Pregnancy/transfer (%)	26.3%	0	31.8%	22.2%	18.4%	0
Number of double ET	75	26	2045	209	175	41
Pregnancy/transfer (%)	29.3%	15.4%	39.7%	24.4%	39.35%	17.1%
% Single/Double ET	20.2	24%	37%	18%	18%	18%

* $p=0.04$ Ant/FSH vs DR/FSH

defined based on age, the number of mature follicles, the number of eggs retrieved, maximal E_2 concentrations, daily dose of FSH, number of days of stimulation, the number of embryos available for transfer and the pregnancy rate [23]. In addition ‘poor response’ and ‘poor responder’ have been used interchangeably, which further makes comparison difficult. A patient may have a poor response in a single cycle but may not in a subsequent cycle: therefore she is not a ‘poor’ responder. Definition of a ‘poor’ responder based on 1 previous event does not take into account the cycle to cycle variability that occurs in patients undertaking IVF. Klinkert et al [24] demonstrated this in a retrospective analysis of 225 patients who had had a poor response in their first cycle. They reported that 64% who had had an unexpected poor response in their first cycle had a normal response in their second. In contrast in our current retrospective study we used stricter criteria for ‘poor responder’ and provide data on a large number of patients in each of the treatment groups.

Previous randomised trials have examined different regimens of treatment in ‘poor’ responders based on the timing of administration of the GnRHa (Boost/FSH or DR/FSH) or use of a GnRH antagonist. Weissman et al [25] examined the use of a Boost/FSH (initial higher dose of GnRHa for 4 days then standard dose) versus a DR/FSH (standard dose of GnRHa until down regulation then a half of the dose) protocol in a randomised trial of 60 women. They defined poor response based on the number of eggs retrieved (≤ 5), or ≤ 3 mature follicles on the day of cancellation, or $E_2 < 500$ pg/mL on the day of hCG administration, but identified their subjects based on a single prior poor response. There was a trend for a better outcome in the DR/FSH group but there was no statistically significant difference between protocols. Dimfield et al [26] examined the same protocols in a randomised trial in 54 women. They defined poor response based on only one previous cancelled cycle due to a low E_2 concentration or a premature LH surge. They also reported no change in pregnancy rate between protocols.

Ant/FSH has been compared to DR/FSH and Boost/FSH protocols in poor responders. The first published randomised trial comparing a fixed dose Ant/FSH regimen to DR/FSH in ‘poor’ responders was performed by Cheung et al [22]. They randomized 66 women to the 2 groups. They showed no difference in ovarian response between the groups. A ‘poor’ responder was defined as a woman who had had < 3 mature follicles using a DR/FSH regimen in the past but did not state how many previous cycles had been undertaken. Two separate meta analyses and a summary of previous trials have been reported by Griesinger et al [16], Franco et al [15] and Mahutte & Arici [17] respectively. In the first, Griesinger et al [16] investigated 8 Ant/FSH trials [6 studies were Ant/FSH versus Boost/FSH and 2 were

Ant/FSH versus DR/FSH) involving 575 poor responders. There was no difference in the clinical pregnancy rate between groups. In the second meta analysis, Franco et al [15] investigated 6 trials (4 were Ant/FSH versus Boost/FSH and 2 were Ant/FSH versus DR/FSH.) and similar results were obtained. The trials used different criteria for defining ‘poor’ responders with the majority in fact being based on a single previous poor response making comparison between trials difficult. Mohamed et al [27] retrospectively examined Boost versus Antagonist regimens in 134 women who had previously had a cancelled cycle due to poor response using a DR regimen. While no cycles were cancelled in the group of women treated with the Boost protocol there was no difference in pregnancy rate between the 2 groups.

Shanbhag et al [18] examined, as part of a Cochrane review, a number of different interventions for ‘poor’ responders. They examined nine randomised trials. The type of protocol (Boost or DR or Ant) ultimately made no difference to the pregnancy rate.

Other variations to the stimulation regimen that have been examined, in randomised trials, include DR/FSH versus stop agonist long protocol once DR has been achieved [28, 29], Ant/FSH versus no down regulation [30] and, Boost versus natural cycle IVF [31]. As with the other studies described there was no significant difference in pregnancy rates between groups and no consistent definition of a ‘poor’ responder.

The addition of the OCP does not affect cycle outcome in ‘poor’ responder patients as seen in our own population of patients. This was also shown in a retrospective study of 194 cycles in women with low ovarian reserve some of whom ($n=146$) were pre treated with the OCP prior to an Ant/FSH cycle [32].

Conclusion

In our large retrospective study of ‘poor’ responders we have not shown a difference in pregnancy rates/initiated cycle between stimulation regimens. Randomised studies with smaller patient numbers have yielded similar results. Our study has shown that there is no ideal stimulation for ‘poor’ responders and that age is not a factor. This question will only be answered by a large randomised trial. Based on our data, if two stimulation regimens such as DR/FSH and Ant/FSH are to be compared in this manner with pregnancy rate/initiated cycle as the outcome and sufficient power to detect a 3% difference in pregnancy rates between groups, approximately 2,000 patients will be required in each arm (personal communication, Claire Methven, Merck Serono Australia). If such a trial is ever to be carried out a strict definition of a ‘poor’ responder needs to be adopted. In

addition, if smaller trials of ‘poor’ responders are performed in the future a strict defining of a ‘poor’ responder needs to be undertaken in order to be able to confidently compare studies and to perform meaningful meta analyses. This is also a desire of other authors in this area of research [15]. While we do not want to appear presumptuous, based on this study and in the absence of other definitions we propose that our definition of a ‘poor’ responder is ideal as it does not depend on performance in just a single previous stimulated cycle.

References

- Garcia JE, Jones GS, Acosta AA, Wright G. HMG/HCG follicular maturation for oocytes aspiration: phase II, 1981. *Fertil Steril*. 1983;39:174–179.
- Keay SD, Liversedge NH, Mathur RS, Jemkins JM. Assisted conception following poor ovarian response to gonadotrophin stimulation. *Br J Obstet Gynaecol*. 1997;104:521–7.
- Sharara FI, Beatse SN, Leonard MR, Navot D, Scott RT. Cigarette smoking accelerates the development of diminished ovarian reserve as evidenced by clomiphene citrate challenge test. *Fertil Steril*. 1994;62:257–62.
- Stillman RJ, Rosenberg MJ, Sachs BP. Smoking and reproduction. *Fertil Steril*. 1986;46:545–66.
- Nikolaou D, Templeton A. Early ovarian ageing: A hypothesis. Detection and clinical relevance. *Hum Reprod*. 2003;18:1137–9. doi:10.1093/humrep/deg245.
- Speroff L, Glass RL, Kase NG. Clinical Gynaecologic Endocrinology and Infertility. 6th Edition. Baltimore, MD: Lippincott Williams and Wilkins, 1999. Nikolaou D, Templeton A: Early ovarian ageing: A hypothesis. Detection and clinical relevance. *Hum Reprod* 2003;18:1137–9. doi:10.1093/humrep/deg245.
- Lee DW, Grasso P, Dattatreya Murthy B, Deziel MR, Reichert LE Jr. Purification of a high molecular weight FSH-receptor binding inhibitor, from human follicular fluid. *J Clin Endocrinol Metab* 1993;77:160–8. doi:10.1210/jc.77.1.163.
- Zelevnik AJ, Schuler HM, Reichert LE. Gonadotrophin binding sites in the rhesus monkey ovary; role of the vasculature in the selective distribution of HCG to the preovulatory follicle. *Endocrinology*. 1981;109:356–62.
- Hernandez ER, Hurwitz A, Vera A, Pellicer A, Adashi EY, LeRoith D, et al. Expression of the genes encoding the IGFs and their receptors in the human ovary. *J Clin Endocrinol Metab* 1992;74:419–25. doi:10.1210/jc.74.2.419.
- Scott RT, Hofmann GE, Oehninger S, Muasher SJ. Intercycle variability of day 3 follicle-stimulating hormone concentrations and its effect on stimulation quality in in-vitro fertilization. *Fertility & Sterility* 1990;54:297–302.
- Scott RT, Hofmann GE. Prognostic assessment of ovarian reserve. *Fertil Steril*. 1995;63:1–11.
- Seifer DB, Lambert-Mersserlian G, Hogan J, Gardiner AC, Blazar AS. Day 3 serum inhibin-B is predictive of assisted reproductive technologies outcome. *Fertil Steril*. 1997;67:110–4. doi:10.1016/S0015-0282(97)81865-1.
- Seifer DB, MacLaughlin DT. Mullerian inhibiting substance is an ovarian growth factor of emerging clinical significance. *Fertil Steril*. 2007;88:539–46. doi:10.1016/j.fertnstert.2007.02.014.
- Van Rooij IAJ, Broekmans FJM, te Velde ER, Fauser BCJM, Bancsi LFJMM, de Jong FH. Serum antimullerian hormone levels: a novel measure of ovarian reserve. *Hum Reprod*. 2002;17:3065–71. doi:10.1093/humrep/17.12.3065.
- Franco JG Jr, Baruffi RL, Mauri AL, et al. GnRH agonist versus GnRH antagonist in poor responders: a meta analysis. *Reprod Biomed Online*. 2006;13:618–27.
- Griesinger G, Diedrich K, Tarlatzis BC, Kolibianakis EM. GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: A meta analysis. *Reprod Biomed Online*. 2006;13:628–38.
- Mahutte NG, Arici A. Role of gonadotropin-releasing hormone antagonists in poor responders. *Fertil Steril*. 2007;87:241–9. doi:10.1016/j.fertnstert.2006.07.1457.
- Shanbhag S, Aucott L, Bhattacharya S, Hamilton MA, McTavish AR. Interventions for ‘poor responders’ to controlled ovarian hyperstimulation (COH) in in-vitro fertilisation (IVF). *Cochrane Database Syst Rev Issue* 2007;1:CD004379. doi:10.1002/14651858.CD004379.pub2.
- Tarlatzis BC, Kirou D, Venetis CA. Management of poor response: Facts or myths In *Advances in Fertility Studies and Reproductive Medicine*, IFFS 2007 In: Kruger TF, Van Der Spuy Z, Kempers RD editors. Juta & Co Ltd; 2007. p. 311–318.
- Daya S. Gonadotropin releasing hormone agonist protocols for pituitary desensitization in an in vitro fertilization and gamete intrafallopian transfer cycles (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2000. Oxford: Update Software.
- Akman MA, Erden HF, Tosun SB, Bayazit N, Aksoy E, Bahceci M. Comparison of agonistic flare-up protocol and antagonistic multiple dose protocol in ovarian stimulation of poor responders: results of a prospective randomized trial. *Hum Reprod*. 2001;16:868–70. doi:10.1093/humrep/16.5.868.
- Cheung LP, Lam PM, Lok IH, et al. GnRH antagonist versus long GnRH agonist protocols in poor responders undergoing IVF: a randomized controlled trial. *Hum Reprod*. 2005;20:616–21. doi:10.1093/humrep/deh668.
- Surrey ES, Schoolcraft WB. Evaluating strategies for improving ovarian response of the poor responder undergoing assisted reproductive techniques. *Fertil Steril*. 2000;73:667–76. doi:10.1016/S0015-0282(99)00630-5.
- Klinkert ER, Broekmans FJ, Billman CW, Te Velde ER. A poor response in the first in vitro fertilization cycle is not necessarily related to a poor prognosis in subsequent cycles. *Fertil Steril* 2004;81:1247–53. doi:10.1016/j.fertnstert.2003.10.030.
- Weissman A, Farhi J, Royburt M, et al. Prospective evaluation of 2 stimulation protocols for low responders who were undergoing in-vitro fertilization-embryo transfer. *Fertil Steril*. 2003;79:886–92. doi:10.1016/S0015-0282(02)04928-2.
- Dirnfield M, Gonen Y, Lissak A, Goldman S, Koifman M, Sorokin Y. A randomized prospective study on the effect of short and long buserelin treatment in women with repeated unsuccessful in-vitro fertilization (IVF) cycles due to inadequate ovarian response. *J In Vitro Fert Embryo Transf*. 1991;8:339–43. doi:10.1007/BF01133025.
- Mohamed KA, Davies WA, Allsopp J, Lashen H. Agonist “flare-up” versus antagonist in the management of poor responders undergoing in vitro fertilization treatment. *Fertil Steril*. 2005; 84:331–5. doi:10.1016/j.fertnstert.2004.07.963.
- Dirnfield M, Fruchter O, Yshai D, et al. Cessation of gonadotrophin-releasing hormone analogue (GnRH-a) upon down-regulation versus conventional long GnRH: A protocol in poor responders undergoing in vitro-fertilization. *Fertil Steril*. 1999;72:406–11. doi:10.1016/S0015-0282(99)00289-7.
- Garcia-Velasco JA, Isaza V, Requena A, et al. High doses of gonadotrophins combined with stop versus non-stop protocol of GnRH analogue administration in low responder IVF patients; a

- prospective, randomized, controlled trial. *Hum Reprod.* 2000;15:2292–6. doi:[10.1093/humrep/15.11.2292](https://doi.org/10.1093/humrep/15.11.2292).
30. Akman MA, Erden HF, Tosun SB, Bayazit N, Aksoy E, Bahceci M. Addition of GnRH antagonist in cycles of poor responders undergoing IVF. *Hum Reprod.* 2000;15:2145–7. doi:[10.1093/humrep/15.10.2145](https://doi.org/10.1093/humrep/15.10.2145).
31. Morgia F, Sbracia M, Schimberni M. A controlled trial of natural cycle versus microdose gonadotrophin-releasing hormone analog flare cycles in poor responders undergoing in-vitro fertilization. *Fertil Steril.* 2004;81:1542–7. doi:[10.1016/j.fertnstert.2003.11.031](https://doi.org/10.1016/j.fertnstert.2003.11.031).
32. Bendikson K, Milki AA, Speck-Zulak A, Westphal LM. Comparison of GnRH antagonist cycles with or without oral contraceptive pre-treatment in potential poor prognosis patients. *Clin Exp Obstet Gynecol.* 2006;33:145–7. doi:[10.1016/j.ogc.2005.12.008](https://doi.org/10.1016/j.ogc.2005.12.008).