How to define, diagnose and treat poor responders? Responses from a worldwide survey of IVF clinics

Pasquale Patrizio, Alberto Vaiarelli, Paolo E Levi Setti, Kyle J Tobler, Gon Shoham, Milton Leong, Zeev Shoham

Yale University Fertility Center, New Haven, Connecticut, USA; Centre for Reproductive Medicine, Vrije University Brussels, Belgium; Department of Gynecology, Division of Gynecology and Reproductive Medicine, Humanitas Research Hospital Fertility Center, Rozzano, Milan 20084, Italy; Department of Gynecology and Obstetrics, Division of Reproductive Endocrinology and Infertility, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel; The Women’s Clinic, Hong Kong; Department of Obstetrics and Gynaecology, Kaplan Medical Center, Rehovot, Israel; Hadassah Medical School, Jerusalem, Israel

Dr Pasquale Patrizio is a board certified specialist in Obstetrics and Gynecology and Reproductive Endocrinology and Infertility. He is Professor of Obstetrics and Gynecology, and Director of the Yale Fertility and Preservation program. He received his MD from the University of Napoli, Italy, and completed residencies in Obstetrics and Gynaecology and Andrology in Italy and the USA. In 2003, he became a certified High Complexity Laboratory Director and completed a Master of Bioethics at the University of Pennsylvania. Dr Patrizio has published extensively in IVF, male infertility and ICSI. Research includes cumulus cells gene expression and oocyte aging and embryo competence.

Abstract
Poor responders represent a significant percentage of couples treated in IVF units (10–24%), but the standard definition of poor responders remains uncertain and consequently optimal treatment options remain subjective and not evidence-based. In an attempt to provide uniformity on the definition, diagnosis and treatment of poor responders, a worldwide survey was conducted asking IVF professionals a set of questions on this complex topic. The survey was posted on www.IVF-worldwide.com, the largest and most comprehensive IVF-focused website for physicians and embryologists. A total of 196 centres replied, forming a panel of IVF units with a median of 400 cycles per year. The present study shows that the definition of poor responders is still subjective, and many practices do not use evidence-based treatment for this category of patients. Our hope is that by leveraging the great potential of the internet, future studies may provide immediate large-scale sampling to standardize both poor responder definition and treatment options.

© 2015 Reproductive Healthcare Ltd. Published by Elsevier Ltd. All rights reserved.

KEYWORDS: decreased ovarian function, IVF, management, ovarian stimulation, poor responder, survey
Introduction

Physiologically, after the period of optimal fertility (at age 18-31 years), oocyte quality decreases in parallel with the progressive reduction in number of follicles, and this deterioration accelerates after 37-38 years of age (Faddy, 2000; Faddy et al., 1992; Gougeon, 1996). It has been estimated that, in the general population, about 10% of women younger than 40 years have a premature reduction in the number of ovarian follicles (Nikolaou and Templeton, 2003; van Noord et al., 1997).

Several possible causes for diminished ovarian reserve have been identified, and include inherited chromosomal (De Vos et al., 2010; Gleicher et al., 2009) and genetic disorders (e.g. Fragile-X and galactosaemia) (te Velde and Pearson, 2002) and iatrogenic causes (Treloar, 1981; Ferraretti et al., 2011); however, most cases of premature ovarian insufficiency are still unexplained (Nikolaou and Templeton, 2003).

Additionally, in recent years, there has been an increased tendency to delay pregnancy, for social, economic reasons, or both, resulting in an increasing number of women seeking infertility treatment at an advanced age, when their chances of optimal ovarian response and live birth are severely compromised (Wyndham et al., 2012). Assisted reproduction technology data available through the Society for Assisted Reproductive Technologies show that, between 1999 and 2008, the number of women aged 40 years or older seeking fertility treatment increased by more than 80%, whereas, for women younger than 35 years, the increase was about 45%.

As a consequence, fertility clinics worldwide need to address the reproductive desires of women who are labelled as poor responders. Various methods have been proposed to assess ovarian reserve before starting a cycle of ovarian stimulation, such as basal hormone assessment (cycle day 3 FSH and oestradiol), anti-Müllerian hormone (AMH) and antral follicle count (AFC) (Penzias, 2004). Age, however, remains the single most important factor in predicting ovarian reserve.

At present, it is increasingly difficult to compare treatment protocols owing to the absence of a uniform method for defining poor responders; a disparity that in turn leads to a lack of standardization in treatment modes. In previous studies, the definition of a poor responder has represented a broad range of metrics and categories from the number of follicles produced, number of oocytes retrieved, use of a variety of laboratory values and ultrasound findings as well as gonadotrophin doses. Some define poor responders as patients who produce no more than five follicles after ovarian stimulation; others, no more than three or four. Some define poor responders as patients having at least two of the following criteria: a previous episode of poor ovarian response (three oocytes or less) with standard dosing of medications; an abnormal ovarian reserve with AFC less than five to seven follicles or AMH less than 0.5-1.1 ng/ml; or women above 40 years of age or presenting other risk factors for poor response (Ferraretti et al., 2011).

It is sufficient, however, to categorize women above the age of 40 years as poor responders or reduced ovarian reserve based on their age alone in the absence of ovarian stimulation or other defining metrics.

Despite attempts to more uniformly classify patients with poor ovarian response (POR), these definitions have not yet proved helpful in identifying optimal treatment protocols for assisted reproduction (Oudendijk et al., 2012). Various strategies have been proposed to improve outcomes in patients with low ovarian reserve. No overarching agreement has been reached, however, on the most optimal management strategy for patients with POR caused by the heterogeneous and varying parameters used to define POR. In both prospective (van Hooff et al., 1993) and retrospective studies (Karande and Gleicher, 1999; Land et al., 1996), increasing the daily dose of gonadotrophins to 450 IU proved ineffective in enhancing ovarian response, increasing pregnancy rates, or both.

With the aim of providing greater clarity on the definition, diagnosis and treatment of patients with reduced ovarian reserve, an online worldwide survey of IVF practices was conducted, taking advantage of new and innovative web-based technologies. In particular, our survey leveraged the IVF-Worldwide network (www.IVF-Worldwide.com), a comprehensive IVF-focused website for doctors, embryologists, nurses and social workers, providing its members with the ability to locate IVF units anywhere in the world and communicate directly with them.

Materials and methods

A web-based questionnaire entitled ‘Poor responders: how to define, diagnose and treat?’ was posted on the IVF-Worldwide website on 25 June 25, 2010, and was open for data entry until 25 July, 2010. The survey collected the following demographic information: the name of the IVF clinic and medical director, email address, country and number of IVF cycles completed by the unit in the most recent year. The survey was divided into three parts: the first focused on the various modes of defining poor responders, the second on screening methods to facilitate the diagnosis and the third on treatment strategies. The respondent’s practice patterns and opinions were evaluated through ‘Yes’, ‘No’, and multiple choice questions. The survey question stems are listed in Appendix I.

Quality-assurance methods

To minimize duplicates and inaccurate reports from responding units, computerized software compared four demographic
parameters in the self-reported data obtained in the survey with the IVF units previously registered data within the IVF-Worldwide website. These parameters included the name of the unit, the name of its director, country and email address. If at least three of these parameters from the survey matched the website’s archive data, the survey responses were included in the statistical analyses. Additionally, duplicate responses were also screened and removed before data analysis.

Statistical analysis

The analysis was based on the number of IVF cycles reported by the unit and not on the number of units in the study. Therefore, the relative proportion of answers reflects the total proportion of IVF cycles represented rather than the proportion of individual respondents to the survey questions. The survey was structured as a sequence of multiple choice questions, in which respondents could select a single answer. For example, for a question with four possible answers (a, b, c, d), results were calculated by using the following formulas as described in previously reported research from the IVF-Worldwide network (Vaisbuch et al., 2012):

\[
\%a' = \frac{\sum \text{Number of cycles of units who answered 'a'}}{\sum \text{Number of cycles of all the units}} \times 100
\]

\[
\%b' = \frac{\sum \text{Number of cycles of units who answered 'b'}}{\sum \text{Number of cycles of all the units}} \times 100
\]

\[
\%c' = \frac{\sum \text{Number of cycles of units who answered 'c'}}{\sum \text{Number of cycles of all the units}} \times 100
\]

\[
\%d' = \frac{\sum \text{Number of cycles of units who answered 'd'}}{\sum \text{Number of cycles of all the units}} \times 100
\]

Results

A total of 272 IVF units from 45 countries responded to the survey. Of those, responses from 196 units met the quality-assurance parameters representing a total of 124,700 IVF cycles.

The geographical regions of the 196 participating units and the total number of cycles per geographical unit carried out in a year are presented in Table 1. Most reporting IVF centres carried out up to 400 cycles per year. Seventeen centres reported between 1000 and 2000 cycles, four centres between 2001 and 3000 cycles, three centres carried out over 3000 cycles in a year, and two centres carried out more than 4000 in a year.

Section one: how to define poor responders

For convenience, we have combined a few questions and present the results within the discussion portion of the paper.

<table>
<thead>
<tr>
<th>Continent</th>
<th>Number of centres</th>
<th>Number of respondent-cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>72</td>
<td>41,400 (33)</td>
</tr>
<tr>
<td>Asia</td>
<td>34</td>
<td>24,300 (19)</td>
</tr>
<tr>
<td>USA and Canada</td>
<td>40</td>
<td>22,700 (18)</td>
</tr>
<tr>
<td>South America</td>
<td>30</td>
<td>13,200 (11)</td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>9</td>
<td>13,800 (11)</td>
</tr>
<tr>
<td>Africa</td>
<td>11</td>
<td>9300 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>196</td>
<td>124,700 (100)</td>
</tr>
</tbody>
</table>

The responses on ‘the definition of poor responders’ varied widely.

Number of follicles

Interestingly, in 97,988 (79%) respondent-cycles, patients were defined as ‘poor responders’ by only the number of follicles produced whereas, in the remaining 26,712 cycles (21%), additional factors were considered; in most cycles using follicle number (70,648 cycles [72%]) patients with fewer than four follicles at the time of oocyte retrieval were defined as ‘poor responders’ (Table 2).

In published research, the number of follicles recruited, the number of oocytes retrieved, or both, are the most frequently used criteria to define poor responders. A high level of variation exists among investigators in the number of follicles or oocytes retrieved, proposed as the basis for the definition, ranging from fewer than three to fewer than six follicles on the day of human chorionic gonadotrophin (HCG) administration (Fridström et al., 1997; Raga et al., 1999) to fewer than three to five oocytes harvested (Chong et al., 1986; Rombauts et al., 1998; Surrey et al., 1998). In addition to including the number of follicles observed, the number of oocytes retrieved is also clearly correlated to ovarian response. Sallam et al. (2005, 2012) used receiver operator characteristic curves to show that a poor ovarian response with five (ICSI) and six (IVF) or fewer oocytes retrieved was correlated with lower pregnancy rates.

Levels of oestradiol

To corroborate the diagnosis of poor responders, the peak ‘level of oestradiol’ was chosen by 68% of respondent-cycles. Although no clear cut-off exists for serum concentrations, a value below 2500 pmol/l (or 650 pg/ml) was reported by 60% of cycles as indicative of POR (Table 3). In agreement with

<table>
<thead>
<tr>
<th>Number of follicles alone or combined with other factors to determine poor ovarian response</th>
<th>Number of respondent-cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use other factors</td>
<td>26,712 (21)</td>
</tr>
<tr>
<td>Less than two follicles</td>
<td>4170 (4)</td>
</tr>
<tr>
<td>Less than three follicles</td>
<td>30,793 (31)</td>
</tr>
<tr>
<td>Less than four follicles</td>
<td>35,685 (36)</td>
</tr>
<tr>
<td>Less than five follicles</td>
<td>27,340 (28)</td>
</tr>
</tbody>
</table>
the findings of our survey, a review of the literature showed that different investigators have considered various cut-offs in peak oestradiol levels with no clear consensus of what level conclusively defines a poor responder. Further, reported oestradiol levels have been measured as peak values during ovarian stimulation or measured on the day of HCG administration and represent a broad range (<300 pg/ml to <500 pg/ml to <1000 pg/ml) to define a poor responder (Garcia et al., 1983; Brzyski et al., 1988; Hanoch et al., 1998; Raga et al., 1997; Ferraretti et al., 2011). Another report considered a level of less than 100 pg/ml on day 5 of stimulation as early proof of a poor ovarian response (Schoolcraft et al., 1997). In contrast to a low peak oestradiol during ovarian stimulation, elevated oestradiol levels at baseline (menstrual cycle day 2 or 3), in the presence of a normal FSH concentration, is considered evidence of early follicular recruitment and a marker of reduced ovarian reserve in most studies measuring oestradiol. Basal oestradiol concentrations >30, >45 or >70 pg/mg have all been associated with poor IVF outcomes (Licciardi et al., 1995; Smotrich et al., 1995; Ubaldi et al., 2005).

Endometrial response

The endometrial response was included in the criteria to define poor responders by only 14% of respondents (16,900 cycles). At this time, no compelling evidence has been published to support the use of endometrial response to ovarian stimulation as part the definition for POR. Although 14% of respondents reported including endometrial response in the definition, this survey did not include follow-up questions to further assess what metrics were used to assess the endometrial response.

Patient history of prior ovarian response

A patient’s medical history of poor response to a prior cycle of ovarian stimulation was an important predictive criterion for 119,712 (96%) of respondent-cycles. Concerning medical history, POR can be anticipated in women with genetic or chromosomal disorders, or women with a history of pelvic infection, before ablative ovarian surgery for endometriomas or ovarian cysts (Nargund et al., 1996; Garcia-Velasco and Somigliana, 2009; Ferraretti et al., 2011) or severe endometriosis (Barnhart et al., 2002). Additionally, the exposure to chemotherapy, radiotherapy, or both, reduces the pool of resting follicles and is associated with premature ovarian insufficiency (De Vos et al., 2010; Oktem and Oktay, 2007). Other acquired conditions associated with POR are obesity with body mass index greater than 30 kg/m² (Déchaud et al., 1998; Orvieto et al., 2009) and heavy smoking (El-Nemr et al., 1998). In addition to the above listed exposures, a history of POR in a previous IVF cycle is strongly indicative of a subsequent poor response, with pregnancy rates reported between 7% and 9% in a second cycle and 0% in a third subsequent cycle (Hendriks et al., 2008; Klinkert et al., 2004).

Section two: how to screen for poor responders

The purpose of the second section of the survey was to query respondents about their screening methods used to identify poor responders. The first question sought to identify what proportion of respondents used a combination of serum markers, an AFC, or both (Table 4). One hundred per cent of respondent-cycles reported using FSH, alone (4%) or in combination (96%) with other measures. The second most commonly used measure was the AFC (79%), but always assessed in combination with another variable. The most common combination of measures included FSH, oestradiol, AFC and AMH (45%) followed by FSH, oestradiol and AFC (24%). Compelling evidence supports screening for POR by assessing basal FSH and oestradiol, AFC, ovarian volume and most recently AMH (Navot et al., 1987; Fanchin et al., 1994; Lass et al., 1997; Tomas et al., 1997; Muasher et al., 1988; Hall et al., 1999; Bancsi et al., 2004; Broekmans et al., 2006; La Marca et al., 2010; La Marca et al., 2011; Ferraretti et al., 2011). Among these tests, AFC has been reported to have a high correlation to the ovarian response to ovarian stimulation (Ferraretti et al., 2011). Age-adjusted AMH seems to have also good sensitivity and specificity for predicting ovarian response, with a false positive rate of 10–20% (Broekmans et al., 2006; La Marca et al., 2010; Broer et al., 2013). A meta-analysis of cohort studies showed that the use of combined tests to improve overall predictive accuracy does not offer an improvement over single tests in predicting a poor responder (Verhagen et al., 2008).

Table 3 Use of oestradiol levels as indicative of poor ovarian response.

<table>
<thead>
<tr>
<th>Level of oestradiol indicative of a poor ovarian response</th>
<th>Number of respondent-cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not use oestradiol for screening</td>
<td>39,500 (32)</td>
</tr>
<tr>
<td>Less than 3500 pmol/l (910 pg/ml)</td>
<td>3100 (2)</td>
</tr>
<tr>
<td>Less than 3000 pmol/l (780 pg/ml)</td>
<td>6200 (5)</td>
</tr>
<tr>
<td>Less than 2500 pmol/l (650 pg/ml)</td>
<td>7900 (6)</td>
</tr>
<tr>
<td>Less than 2000 pmol/l (520 pg/ml)</td>
<td>28,200 (23)</td>
</tr>
<tr>
<td>Less than 1500 pmol/l (390 pg/ml)</td>
<td>6500 (5)</td>
</tr>
<tr>
<td>Less than 1000 pmol/l (260 pg/ml)</td>
<td>16,500 (13)</td>
</tr>
<tr>
<td>Less than 500 pmol/l (130 pg/ml)</td>
<td>16,800 (13)</td>
</tr>
</tbody>
</table>

Table 4 Use of a combination of FSH, oestradiol, antral follicle count, anti-Müllerian hormone as indicative of poor ovarian response.

<table>
<thead>
<tr>
<th>Measures used to screen for poor ovarian response</th>
<th>Number of respondent-cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH alone</td>
<td>5100 (4)</td>
</tr>
<tr>
<td>FSH and oestradiol</td>
<td>10,300 (8)</td>
</tr>
<tr>
<td>FSH and AFC</td>
<td>11,700 (9)</td>
</tr>
<tr>
<td>FSH, oestradiol, AFC</td>
<td>30,200 (24)</td>
</tr>
<tr>
<td>FSH, AMH</td>
<td>11,000 (9)</td>
</tr>
<tr>
<td>FSH, oestradiol, AFC, AMH</td>
<td>56,400 (46)</td>
</tr>
</tbody>
</table>

AFC = antral follicle count; AMH = anti-Müllerian hormone.
Additional screening methods used to diagnose poor ovarian response

Although the clomiphene citrate challenge test (CCCT) was frequently used in the past to identify POR, this survey identified only 14,964 (12%) of the total respondent-cycles as users of dynamic testing to identify poor responders. Among the users of dynamic testing, most (12,470) used CCCT and very few (2494) used the gonadotrophin-releasing hormone agonist combined with the CCCT.

FSH and LH ratio and day 2–3 FSH levels

In 78,561 (63%) of total respondents-cycles the FSH–LH ratio was not considered important. A total of 66% of respondents reported that a day 2 or 3 FSH level of 12 IU/ml or greater was considered indicative of POR, whereas, in 27%, the FSH level indicative of POR was set at 10–12 IU/ml (Table 5). The survey also asked whether, in normally cycling patients, IVF treatments would be cancelled based on cycle day 2–3 FSH values. In over one-half the respondent-cycles (54%), if the patient is still cycling, the FSH serum concentrations are not used to determine if an IVF cycle should be continued. If FSH values at baseline are above 18 IU/ml, however, 22% of respondents-cycles would cancel the ovarian stimulation (Table 6).

Many definitions exist for 'high' FSH values: basal levels of FSH greater than 10, 12 or 15 IU/ml have all been reported as predictive of a POR and poor clinical outcome (Cameron et al., 1988; Faber et al., 1998; Toner et al., 1991). It is, however, necessary to take into account possible intercycle variability of day 3 FSH (Brown et al., 1995). In the analysis of 163 poor responders with either normal or elevated basal FSH levels (cut-off 12 IU/ml), a significant decrease in pregnancy rates were reported for women with an elevated basal FSH compared with those with normal FSH (4.0% versus 14.8%, respectively) (Galey-Fontaine et al., 2005).

Use of ultrasound and genetic tests for diagnosis

Assessment of AFC and ovarian volume by ultrasound have been proposed as predictive of ovarian response (Ubaldi et al., 2005). In our survey, a total of 109,736 of respondents-cycles (88%) relied on standard ultrasound to evaluate AFC, 6235 (0.5%) using three-dimensional and Doppler imaging, 7233 (5.8%) using both AFC and Doppler and 7108 (5.7%) not using ultrasound. Concerning the use of genetic testing for the diagnosis of poor responders, 72,326 (58%) stated that they did not use it whereas 52,374 (42%) perform karyotype, Fragile X, testing, or both.

Clinical trends in poor ovarian response (percentage of POR per clinic and incidence rates)

When asked to estimate the proportion of poor responders in their clinic, 41% of respondents-cycles reported that POR represented about 6–10% of their overall cycles of treatment. A total of 56% of respondents, however, indicated that POR represented more than 10% of their cycles and, of these, 15% indicated POR as being more than 20% (Table 7). In response to the question of whether the incidence of patients with POR has increased during the past 10 years, 131 (67%) of clinics reported an increase whereas 61 (31%) noted no changes; interestingly, four (2%) noted a decrease. Overall, these findings reflect the Society for Assisted Reproductive Technologies data available to the public, which show a 70% increase in the proportion IVF cycles completed for patients with POR treated in the USA in 2003 (10%) compared with 2012 (17%) (www.sart.org; accessed 18 August 2014).

Section three: treatment protocols for poor responders

The third section of the survey addressed the choice of treatment protocols for patients with POR. This is a major challenge for IVF centres worldwide given the lack of definitive evidence for the many and highly varying protocols combined with the challenge of applying the findings obtained from an often heterogeneous diagnosed patient population.

The survey asked questions pertaining to the following: gonadotrophin-releasing hormone (GnRH) analogue protocols; combination of gonadotrophins; starting and maximum dose of gonadotrophins, recombinant FSH (rFSH) and human menopausal gonadotropins (HMG); providing LH by HMG or recombinant LH (rLH); administering gonadotrophins with single or multiple daily injections; use of clomiphene citrate in combination with gonadotrophins; the adjuvant use of HCG, baby

<table>
<thead>
<tr>
<th>FSH level</th>
<th>Number of respondent-cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None of the above listed FSH values</td>
<td>8900 (7)</td>
</tr>
<tr>
<td>10–12 IU/ml</td>
<td>34,200 (27)</td>
</tr>
<tr>
<td>&gt;12–15 IU/ml</td>
<td>56,900 (46)</td>
</tr>
<tr>
<td>&gt;15–19 IU/ml</td>
<td>20,100 (16)</td>
</tr>
<tr>
<td>&gt;19 IU/ml</td>
<td>4600 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FSH level greater than</th>
<th>Number of respondent-cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 IU/ml</td>
<td>1000 (1)</td>
</tr>
<tr>
<td>13 IU/ml</td>
<td>15,300 (12)</td>
</tr>
<tr>
<td>18 IU/ml</td>
<td>27,900 (22)</td>
</tr>
<tr>
<td>20 IU/ml</td>
<td>12,900 (10)</td>
</tr>
<tr>
<td>Will not cancel if patient is cycling</td>
<td>67,600 (54)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated proportion of poor ovarian response patients treated at the IVF clinic (%)</th>
<th>Number of respondent-cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>3000 (2)</td>
</tr>
<tr>
<td>6–10</td>
<td>51,700 (41)</td>
</tr>
<tr>
<td>11–15</td>
<td>28,000 (22)</td>
</tr>
<tr>
<td>16–20</td>
<td>23,900 (19)</td>
</tr>
<tr>
<td>21–25</td>
<td>7500 (6)</td>
</tr>
<tr>
<td>26–30%</td>
<td>10,100 (8)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>500 (0)</td>
</tr>
</tbody>
</table>
aspirin, low molecular weight heparin (LMWH), dehydroepiandrosterone (DHEA); use of natural cycle IVF or in-vitro maturation (IVM) of immature oocytes; luteal phase support with progesterone only or with the addition of oestradiol; when to stop treatment.

**GnRH analogue protocols**

Overall, the preferred protocol for POR was the GnRH antagonist protocol (52% of the respondent-cycles) followed by the short GnRH agonist flare-up (20%) and the micro-dose (15%) protocols, respectively (Table 8).

In a review of the many trials comparing the differing protocols to treat POR, a Cochrane Review reported that the GnRH antagonist protocol produced higher number of oocytes and used a lower dose of gonadotrophins compared with the GnRH agonist long protocol. The GnRH agonist flare-up protocol had an increased frequency of IVF cancellation compared with the GnRH agonist long protocol. No study reported on spontaneous abortion rates. Only one study included live birth rates. Overall the Cochrane review concluded that, at this time (2010), insufficient evidence was available to support the routine use of any IVF protocol over another (Pandian et al., 2011). In a more recent review and meta-analysis of the literature, it seems that the GnRH antagonist protocol may be more beneficial to patients with POR (Pu et al., 2011); however, more robust clinical trials are still required.

**Combination of gonadotrophins**

To the question, ‘what combination of gonadotrophins do you use?’; 43% of respondent-cycles chose HMG with rFSH, 20% used rFSH alone, 20% HMG alone, 9% rFSH with rLH and 6% rFSH with low-dose hCG (Table 9).

<table>
<thead>
<tr>
<th>Protocol used</th>
<th>Number of respondent-cycles (%)</th>
<th>Protocol used</th>
<th>Number of respondent-cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No GnRH analogues</td>
<td>1200 (1)</td>
<td>rFSH and hMG</td>
<td>53,100 (43)</td>
</tr>
<tr>
<td>GnRH agonist using a flexible regimen</td>
<td>2500 (2)</td>
<td>HMG alone</td>
<td>25,500 (20)</td>
</tr>
<tr>
<td>GnRH agonist, long protocol</td>
<td>11,800 (9)</td>
<td>rFSH alone</td>
<td>25,100 (20)</td>
</tr>
<tr>
<td>GnRH agonist microdose, short protocol</td>
<td>18,900 (15)</td>
<td>rFSH and rLH</td>
<td>11,700 (9)</td>
</tr>
<tr>
<td>GnRH agonist, short protocol</td>
<td>25,400 (20)</td>
<td>rFSH and low dose hCG</td>
<td>7200 (6)</td>
</tr>
<tr>
<td>GnRH antagonist protocol</td>
<td>64,900 (52)</td>
<td>None of the above</td>
<td>2100 (2)</td>
</tr>
</tbody>
</table>
|                            |                                 | HCG = human chorionic gonadotrophin; HMG = human menopausal gonadotropin; rFSh = recombinant follicle stimulating hormone; rLH = recombinant luteinizing hormone.

(UBaldi et al., 2005). For van Hooff et al., 1993 (prospective study) and for Land et al., 1996 (retrospective study), an increase of the starting dose up to 450 IU was ineffective in improving ovarian response, increasing pregnancy rates, or both.

**Providing LH by using HMG or recombinent LH**

To the question of whether HMG is added to the protocol and, if yes, when and how many daily units, 78,561 (63%) respondent-cycles replied that they use HMG, whereas 46,139 (37%) do not. Among the users, 33,047 (26.5%) use a dose between 75 and 150 IU from the onset of stimulation; 14,340 (11.5%) uses 75–150 IU after the first 5–6 days of stimulation; 11,223 (9%) use a dose between 225 and 300 IU from the onset of ovarian stimulation; 13,093 (10.5%) use between 225 and 300 IU and 6,858 (5.5%) higher doses after the first 56 days of ovarian stimulation. Therefore, 34,291 (27%) of respondent-cycles add HMG after 5–6 days of stimulation, whereas 44,270 (36%) use HMG from the onset of ovarian stimulation.

Concerning the starting time and dose of rLH, the responses revealed that rLH is used by 11,223 (9%) of respondent-cycles; of these 5387 (48%) use a dose between 75 and 150 IU from the onset of ovarian stimulation; 4826 (43%) use a dose between 75 and 150 IU after the first 5–6 days; 337 (3%) use a dose between 225 and 300 IU from the onset of ovarian stimulation; 337 (3%) use a dose between 225 and 300 IU after 5–6 days of stimulation and 336 (3%) use a higher dose from the outset. In summary, most of the respondents used a dose of rLH (whether from the onset of stimulation or after 5–6 days) between 75 and 150 IU.

A recent meta-analysis (Bosdou et al., 2012) compared seven studies (630 patients in total), which investigated the addition of rLH during ovarian stimulation in patients with POR; no significant increase was found in the clinical pregnancy rate for patients receiving rLH compared with those who did not. The measure of live births, however, was only available in one of these seven studies, which demonstrated a significant increase in live births when poor responders received rLH (Ferraretti et al., 2004). No significant differences either in the total dose of rFSH required for ovarian stimulation, in the duration of stimulation, or in the number of oocytes retrieved between patients stimulated with rFSH and rLH compared with patients who were stimulated with rFSH alone.

A recent meta-analysis (Hill et al., 2012), however, showed higher implantation and clinical pregnancy rates in the...
recombinant LH-supplemented group compared with recombinant FSH alone.

**Administering gonadotrophins in single or multiple daily injections**

Regarding the mode of administration, the survey asked whether participants divide the daily dose into two administrations. A total of 91,031 (73%) respondents—cycles answered that they always use one administration; the remaining 33,669 (27%) are divided into three subcategories: 12,470 (10%) divide the daily dose if it is more than 225/day; 7482 (6%) if is more than 300/day, and 13,717 (11%) if it is equal to or more than 450 per day.

**Use of clomiphene citrate and gonadotrophins**

In response to the question on the use of clomiphene citrate and gonadotrophins, 78,561 (63%) of respondent-cycles said that they do not use clomiphene citrate, whereas 46,139 (37%) incorporated clomiphene citrate together with gonadotrophins in patients with POR. In a prospective randomized study, D’Amato et al. (2004) found a higher number of oocytes and a significantly lower cancellation rate by using GnRH antagonist in combination with clomiphene citrate and gonadotrophins. Unfortunately, we did not specifically ask for the use of clomiphene citrate alone or with low-dose gonadotrophins for mild stimulation protocols. It is likely that, in the future, mild stimulation protocols may have a more definitive role in poor responders.

**Use of HCG, baby aspirin, low molecular weight heparin and DHEA**

To strengthen the effect of exogenous gonadotrophins, alternative approaches have been proposed. To the question, ‘Will you add HCG to the treatment protocols?’ 51,376 (41.2%) of the respondent-cycles said yes, whereas 73,324 (58.8%) do not add HCG to treatment protocols in patients with POR. The literature reports that LH activity provided by HCG addition in the late stages of ovarian stimulation is able to promote and complete the growth of the large follicle (Filicori et al., 2002, 2005). But one study evaluated the addition of recombinant HCG and concluded that clinical pregnancy rate was not significantly different between patients who received recombinant HCG with FSH compared with those stimulated with FSH alone. The addition of HCG was associated with a decrease in the total dose of FSH required and the duration of stimulation (Berkkanoglu et al., 2007).

To the question, ‘do you add DHEA (75 mg daily) to the protocol?’ 92,527 (74.2%) of the respondent-cycles do not add DHEA to the protocol and 32,173 (25.8%) do. When DHEA is used, it is generally started around 3 months before IVF treatment. It has been suggested that the accumulation of androgens in the ovary plays a critical role in early follicular development and granulosa cell proliferation (Weil et al., 1999). This accumulation, however, has also been shown to stimulate early stages of follicular growth (Vendola et al., 1998; Weil et al., 1998, 1999), and to increase the number of preantral and antral follicles (Hillier et al., 1997; Weil et al., 1998, 1999). The increase of intraovarian concentration of androgens seems to augment the expression of FSH receptors in granulosa cells (Weil et al., 1998, 1999) and, thus, potentially lead to enhanced responsiveness of ovaries to FSH.

(Harlow et al., 1986; Hillier and De Zwart, 1981; Vendola et al., 1998; Weil et al., 1998). A recent meta-analysis (Bosdou et al., 2012), evaluated the role of androgens or androgen-modulating agents in poor responders undergoing IVF. This meta-analysis concluded, based on the limited available evidence, that transdermal testosterone pretreatment seems to increase clinical pregnancy and live birth rates in poor responders undergoing ovarian stimulation for IVF.

In summary however, insufficient data definitively support a beneficial role of clomiphene citrate, rLH, HCG, or DHEA administration for increasing pregnancy rates in poor responders.

Concerning the use of aspirin, 51,127 (41%) respondent-cycles stated that they used low-dose aspirin (81 mg), whereas 73,573 (59%) stated that they do not.

The evidence supporting the effect of low-dose aspirin in women undergoing IVF is poor and controversial (Nardo et al., 2009). Low-dose aspirin irreversibly inhibits the enzyme cyclooxygenase in platelets and, as a result, prevents the synthesis of the vasoconstrictive agent thromboxane and leads to vasodilation and increased peripheral blood perfusion (Patrono et al., 2005). Impaired uterine perfusion has been suggested as a possible cause of sub-fertility because of a negative effect on endometrial receptivity (Goswamy et al., 1988), which in turn may cause embryo implantation failure (Steer et al., 1992). Although some investigators have reported a beneficial effect of low-dose aspirin started from the day of embryo transfer (Rubinstein et al., 1999; Waldenström et al., 2004), others failed to confirm these findings in poor responders (Frattarelli et al., 2008; Hurst et al., 2005; Lok et al., 2004; Pålklät et al., 2005; Urman et al., 2005). The conclusion of the most recent meta-analysis (Gelbaya et al., 2007) was that the clinical pregnancy and spontaneous abortion rates were not significantly different between patients who received low-dose aspirin and those who received placebo or no treatment. Therefore, based on evidence from all the recent literature, low-dose aspirin has no substantial positive effect on likelihood of pregnancy and it should not be routinely recommended for patients with POR undergoing IVF.

To the question, ‘do you add low molecular LMWH at any time of stimulation or luteal phase?’ 107,491 (86.2%) respondents/cycles said they do not whereas 17,209 (13.8%) added LMWH either during the ovarian stimulation or during the luteal phase.

Treatment with LMWH (and low-dose aspirin) is considered by some investigators to be appropriate in women with anti-phospholipid syndrome (APS) and in those who have experienced recurrent pregnancy loss (Empson et al., 2005). No evidence supports the use of LMWH for improving IVF outcomes in patients with POR. Additionally, the American Society for Reproductive Medicine (ASRM) issued a practice committee statement concluding that the evidence does not support the evaluation for, and the treatment of, anti-phospholipid antibodies for couples undergoing IVF (Practice Committee of American Society for Reproductive Medicine, 2008).

**Use of natural cycle or IVM**

To the question, if IVM is used as an adjunct to natural cycle IVF, 114,350 (91.7%) of the respondents-cycles answered yes and 10,350 (8.3%) reported no. To the question, ‘would you prefer natural cycle in POR cases?’ 33,669 (27%) said yes and 91,031 (73%) said no. Morgia et al. (2004) reported that the
live birth rate was not significantly different between the low-dose GnRHα flare-up and spontaneous natural cycle IVF (Morgia et al., 2004; Schimberni et al., 2009). Natural IVF cycles with minimal stimulation can be considered as an easy and inexpensive approach in the management of poor responders. Large prospective randomized studies comparing natural IVF with or without IVM for poor responders are needed.

Support of luteal phase, progesterone only or with the addition of oestradiol

To the question, ‘in addition to progesterone, do you support the luteal phase with estrogen, aspirin, or steroids?’ 67,712 (54.3%) of respondent-cycles do not support the luteal phase only with progesterone. Of the remaining, 20,700 (16.6%) add oestradiol and baby aspirin to the progesterone; an additional 20,950 (16.8%) use oestradiol plus steroid plus baby aspirin; 14,216 (11.4%) add only oestradiol and 1122 (0.9%) add oestradiol and steroids.

When to stop treatment

To the question, ‘how long will you continue with the maximum dose before you will stop treatment (in other words when would the cycle be canceled)?’, 46% of respondent-cycles would stop treatment if there is no response after a minimum of 7–9 days, 31% after 4–6 days, and the remaining respondents would continue ovarian stimulation for up to 11 days before cycle cancellation (Table 10). No consensus has been reached on the minimum number of stimulation days a poorly responding patient should continue before cancelling an IVF cycle; the cut-off values used in determining cycle cancellation varies widely in previously published studies from less than three mature follicles (Biljan et al., 2000; Hendriks et al., 2008; Veleva et al., 2005) to no more than five follicles and an oestradiol level less than 1000 pg/ml (Yih et al., 2005).

To the question, ‘assuming no financial constraints, is there a maximum number of failed cycles after which you recommend stopping?’ 39% of the respondent-cycles reported that they would stop after two failed cycles; 34% after three failed cycles; 13% after four failed cycles; 7% after five failed cycles, and 7% had no limit on the number of failed cycles (Table 11). When asked whether the treatment would be continued if no oocytes were retrieved or no embryos developed during prior cycles, 75% responded that they will offer another cycle, whereas 25% would not offer additional cycles.

This extensive survey has given us the opportunity to conduct a review of the literature on the topic of poor responders, focusing on how the term is defined, and how poor responders are identified and treated.

<table>
<thead>
<tr>
<th>Number of days of stimulation before cancellation (days)</th>
<th>Number of respondent-cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–6</td>
<td>39,200 (31)</td>
</tr>
<tr>
<td>7–9</td>
<td>57,800 (46)</td>
</tr>
<tr>
<td>9–11</td>
<td>21,000 (17)</td>
</tr>
<tr>
<td>&gt;11</td>
<td>6700 (5)</td>
</tr>
</tbody>
</table>

Table 10 Distribution of responses concerning time to stop treatment.

Table 11 Assuming no financial constraints, the maximum number of failed cycles after which it would be recommended to cease IVF treatments (autologous oocyte).

<table>
<thead>
<tr>
<th>Number of failed IVF cycles</th>
<th>Number of respondent-cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two failed</td>
<td>48,200 (39)</td>
</tr>
<tr>
<td>Three failed</td>
<td>42,900 (34)</td>
</tr>
<tr>
<td>Four failed</td>
<td>15,600 (13)</td>
</tr>
<tr>
<td>Five failed</td>
<td>8700 (7)</td>
</tr>
<tr>
<td>No limit to</td>
<td>9300 (7)</td>
</tr>
</tbody>
</table>

In conclusion, insufficient evidence supports the use of any one particular intervention to improve treatment outcomes in poor responders undergoing IVF. It is a fact that poor responders have a diminished pregnancy rate compared with normal responders; however, it has also been demonstrated that several factors can modulate the prognosis in this patient group, with possible implications for clinical practice. Not all women who respond poorly to ovarian simulation have poor pregnancy rates. The problem that has emerged from two different recent reviews and from the responses obtained in this extensive survey is that poor responders are not a homogeneous group and the prognosis for these patients may vary greatly depending on patient characteristics, such as age or the actual number of oocytes obtained (Ferraretti et al., 2011; Oudendijk et al., 2012) and not on a particular ovarian stimulation protocol.

On the basis of this survey, we may state that there is still no international consensus for the definition of a poor responder and that the varying treatment strategies used are mostly not evidence based.

Appendix: Question stem and answers about how IVF clinics define and treat poor responders

Definition of ‘poor responder’ patients

Should it be based on ovarian response only? Should the definition include endometrial response? How do you define poor responders based on number of follicles? How do you define poor responders based on the level of estradiol? Is history important? Is previous performance before and during IVF important?

Screening methods for diagnosis

What screening methods to use to identify poor responders? Do you measure FSH/LH ratio? At what level of day two FSH would you identify a poor responder? In normally cycling patients, would you cancel IVF treatment if day 2 FSH is? Do you do any dynamic testing?
What, in your opinion and experience, is the most important predictor of the above?

Can you estimate the scale of poor responders in your clinic?

Have you seen any change in the incidence during the last 10 years?

**Treatment**

Would you continue treatment if no oocytes were retrieved in a prior cycle?

Would you continue treatment if oocytes were aspirated but no embryo developed?

Of the following GnRH analogue protocols, which one do you use more often for poor responders?

What combination of gonadotropins do you use?

What would be the starting dose of gonadotrophins (FSH alone or HMG) that you use?

What is the maximum daily dose of gonadotrophins (FSH alone or HMG) that you use?

If you add HMG, how many daily units and when do you start?

If you add recombinant LH how many daily units and when do you start?

Would you divide the daily dose into two administrations?

How long will you continue with the maximum dose, if there is no response, before you will stop treatment (cycle cancellation)?

Do you use clomiphene citrate in gonadotrophin cycles? Will you add human growth hormone (HGH) to the treatment protocols?

Do you use aspirin or do you add low molecular weight heparin at any time of the stimulation or Luteal phase?

Would you prefer natural cycle in these cases?

Would you recommend in-vitro maturation (IVM) in such cases?

Would you start gonadotrophins in the luteal phase before stimulation?

Do you increase the dose of exogenous luteal phase progesterone?

Will you add DHEA (dehydroepiandrosterone 75 mg daily) to the protocol?

In addition to progesterone, do you support the luteal phase with oestrogen, aspirin, or steroids?

Do you bank oocytes for poor responders?

Do you do embryo banking in this group of patients? (To accumulate embryos and then replace several embryos in one cycle)

Assuming no financial constraints, is there a maximum number of failed cycles after which you recommend to stop?

**References**


Declaration: The authors report no financial or commercial conflicts of interest.

Received 7 September 2014; refereed 26 February 2015; accepted 3 March 2015.