Dear Sir,

We read with interest the paper by Kailasam et al. (2004) on the definition of poor ovarian response in IVF. To enable a meaningful comparison of the many studies published on poor response, the development of a uniform definition is important, if feasible. The authors conclude that a degree of ovarian stimulation should be included in the definition of poor ovarian response. Although we do agree that only an insufficient ovarian reaction to a sufficient stimulation dose should be called a poor response, we are concerned about some methodological aspects of the study that led to this conclusion.

The authors suggest that the need for a total dose of $\geq 3000$ IU of FSH during stimulation objectively identifies a poor response in women aged $<40$ years. However, all patients aged $\geq 35$ years who were included in this study received a starting dose of $3001$ IU of FSH, whereas younger patients started their stimulation with $150$ IU per day. It is therefore not possible to determine whether the difference in poor response and pregnancy rate in the repeat cycle in patients stimulated with high doses compared with patients stimulated with lower doses is dose related or age related. We believe that the low implantation rates and pregnancy rates the authors observed in women who used $\geq 3000$ IU can be partly, if not fully, explained by the fact that most of these women will be $>35$ years of age. The age of a woman undergoing IVF treatment is known to be an important factor affecting the outcome of the treatment (Roseboom et al., 1995; Templeton et al., 1996). Also, the implantation rate shows a significant age-related decrease, with an acceleration of this decrease from $37$ years onwards (van Kooij et al., 1996). The authors did not compare the age of the patients treated with $<3000$ IU with that of the patients treated with $\geq 3000$ IU. It can, however, be assumed that there is a large and significant age difference, explaining the higher cancellation and lower pregnancy rates.

In our opinion, the definition of poor response suggested by the authors cannot be called objective, as they have wrongly assumed that patients older than $35$ years of age need a higher dose of gonadotrophins than younger patients. Most patients will respond maximally to $150$ IU of gonadotrophins. Young poor responders may respond better to higher FSH dosages (Out et al., 2000), but often do not need it because on the quality level they perform quite well. Older poor responders will usually not benefit from higher dosages as both cohort size and oocyte quality are diminished. As such, not the stimulation dose, but female age is the key factor. Although this study certainly is a valuable contribution to the discussion on the subject of poor response, we feel that our alternative interpretation is crucial to prevent the invalidate use of a high dosage of gonadotrophins in older poor responders.

References


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Reply to ‘Defining poor ovarian response during IVF cycles, in women aged $<40$ years, and its relationship with treatment outcome’

Sir,

We are very grateful to Klinkert et al. for drawing attention to the potential confounding effect of the different starting doses of FSH dependent on age. In our initial paper (Kailasam et al., 2004), we had chosen to present the statistics as simply as possible to illustrate our key message that in defining poor response one must consider both the response...
and the degree of stimulation. However, this letter provides
us with the opportunity to present further analyses illustrating
that this point remains true irrespective of age up to 40 years.

There is no doubt that ovarian responsiveness declines
with age. Our point is that if there is a satisfactory response
to the higher dose of gonadotrophin, couples retain a good
chance of success despite being aged up to 40 years, whereas
failure to respond to a high FSH dose is associated with a
poor outcome whatever the woman’s age.

Splitting the analysis of the effect of FSH dose and num-
ber of eggs recovered shown in Table III of our original
paper (Kailasam et al. 2004) into women <35 years versus
≥35 years yields Table I.

This illustrates that the association between the clinical
pregnancy rate and the number of eggs recovered related to
total FSH dose required is remarkably similar in women
above and below 35 years of age.

We used logistic regression to test further the effects of
age, total dose of FSH and the number of oocytes recovered.
The program (SPSS) was offered the following categorical
variables: age <35 years (reference) versus ≥35 years;
oocytes recovered >4 (reference) versus ≤4; FSH dose
≤3000IU (reference) versus >3000IU plus all possible
interaction terms. Models were derived by forward selection
using the likelihood ratio statistic based on maximum likeli-
hood estimates.

Forward selection derived a model where the only signifi-
cant predictors were the dose of FSH and the number of eggs
recovered (Table II).

Although it has been suggested that the maximum dose for
all patients should be 150IU, many may feel otherwise and
suggest benefit up to 300IU of FSH daily.

In our study, patients whose cycles were cancelled for
poor ovarian response on an initial gonadotrophin dose of
<300 IU had a clinical pregnancy rate of 22% during a sub-
sequent cycle when the dose of gonadotrophins was increased
to 300IU, thereby suggesting a beneficial effect.

Table I. Total FSH used
Woman’s age (years) No. of mature oocytes
<4 >4
≤35 ≤3000 24 (11.8–41.2) [37] 33 (28.3–37.5) [430]
>3000 5 (0.1–23.8) [21] 27 (19.8–35.2) [137]
≥35 ≤3000 40 (16.3–67.7) [15] 32 (24.4–41.1) [130]
>3000 7 (1.9–17.3) [56] 24 (18.6–30.7) [210]
The percentage of women in each group that achieved a clinical pregnancy
(95% confidence intervals) [n]

Table II. Significant predictors of clinical pregnancy identified by logistic
regression using forward selection

<table>
<thead>
<tr>
<th>Odds ratio (95% confidence limits)</th>
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<tbody>
<tr>
<td>&gt;3000 IU of FSH (reference ≤3000 IU)</td>
</tr>
<tr>
<td>≤4 eggs (reference &gt;4 eggs)</td>
</tr>
</tbody>
</table>

In conclusion, poor response to ovarian stimulation is
more common in women >35 years but is not confined to
them. At least up to 40 years of age, definition of the
response including the dose of gonadotrophin provides a
more accurate prognosis for pregnancy than age.

References

poor ovarian response during IVF cycles, in women aged <40 years, and
its relationship with treatment outcome. Hum Reprod 19,1544–1547.

C. Kailasam1, S.D. Keay, P. Wilson, W.C. Ford
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Coasting acts through downregulation of VEGF gene
expression and protein secretion

Sir,

We read with great interest the recent article of Garcia-
Velasco et al. (2004) which reported that coasting acts
through downregulation of vascular endothelial growth factor
(VEGF) gene expression and protein secretion. Although it is
of great clinical value to understand the mechanism(s)
involved in coasting and how it reduces the incidence of
ovarian hyperstimulation syndrome (OHSS), Ulug et al.
(2004) found no difference in terms of fertilization, implan-
tation and pregnancy rates, and incidence of severe OHSS
between coasted and non-coasted patients. However, there
are some points we would like to raise regarding the study of
Garcia-Velasco et al. (2004).

Garcia-Velasco and colleagues did not explain what P on
the y-axis of their Figure 1 graph represents. P was not
defined in the text and was not in the figure legend either.

It has been reported that estrogen (E2) upregulates the
expression of VEGF and its receptors (Cullinan-Bove and
Koos, 1993; Hyder et al. 1996; Gargett et al. 2002). Gonado-
tropin administration increases the serum levels of E2. There-
fore, withholding gonadotropin during coasting reduces
ovarian stimulation, leading to a decline in serum E2 levels.