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The poor responder in IVF: is the prognosis always poor? A systematic review

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BACKGROUND: In IVF treatment a considerable proportion of women are faced with a low number of oocytes retrieved. These poor responders have reduced pregnancy rates compared with normal responders. However, this may not be applicable to all poor responders. This review aims at identifying patient characteristics and ovarian reserve tests (ORT) that will determine prognosis for pregnancy in poor responders.

METHODS: A systematic search was conducted in PubMed, Embase, Cochrane and SCOPUS databases in April 2010. Studies regarding patient characteristics or ORT in poor responders and their pregnancy prospects were included. All included papers were summarized in descriptive tables.

RESULTS: Nineteen studies were included. Pooled data of six studies comparing poor and normal responders demonstrated clearly lower pregnancy rates in poor responders (14.8 versus 34.5%). Ten studies indicated that older poor responders have a lower range of pregnancy

rates compared with younger (1.5–12.7 versus 13.0–35%, respectively). Four studies showed that pregnancy prospects become reduced when fewer oocytes are retrieved (0–7% with 1 oocyte versus 11.5–18.6% with 4 oocytes). Five studies concerning pregnancy rates in subsequent cycles suggested a more favourable outcome in unexpected poor responders, and if ≥2 oocytes were retrieved.

CONCLUSIONS: Poor responders are not a homogeneous group of women with regards to pregnancy prospects. Female age and number of oocytes retrieved in particular will modulate the chances for pregnancy in current and subsequent cycles. Applying these criteria will allow the identification of couples with a reasonable prognosis and balanced decision-making on the management of poor responders.

Key words: poor responder / IVF / pregnancy rate / number of oocytes / systematic review

Introduction

The birth of a normal healthy infant girl after replacement of a human embryo after IVF, reported by gynaecologist Steptoe and physiologist Edwards in the Lancet in 1978, resulted from the use of a single oocyte from a spontaneous ovarian cycle (Steptoe and Edwards, 1978; Healy *et al.*, 1987). Soon after this ground breaking event, controlled ovarian hyperstimulation (COH) was introduced, and the availability of a high number of oocytes boosted the pregnancy rates of IVF treatment (Healy *et al.*, 1987; Jennings *et al.*, 1996). However, after 40 years of experience there are still women who respond poorly to COH, resulting in only few oocytes at retrieval, a reduced number of embryos available for transfer and a poor pregnancy rate (Ulug *et al.*, 2003). The prevalence of poor responders is reported to vary between 5.6 and 35.1% (Biljan *et al.*, 2000; de Sutter and Dhont, 2003; Inge *et al.*, 2005; Veleva *et al.*, 2005; Hendriks *et al.*, 2008; Orvieto *et al.*, 2009), depending on differences in the definition of poor response.

In general, poor responders have a lower pregnancy rate compared with normal responders (Biljan *et al.*, 2000; de Sutter and Dhont, 2003; Galey-Fontaine *et al.*, 2005; Baka *et al.*, 2006; Timeva *et al.*, 2006; van der Gaast *et al.*, 2006; Saldeen *et al.*, 2007; Hendriks *et al.*, 2008; Zhen *et al.*, 2008), although reports on poor responders with reasonable prospects of pregnancy have also been published (Klinkert *et al.*, 2004; Hendriks *et al.*, 2008). The physiology behind ovaries responding poorly to hyperstimulation is the presence of a reduced number of FSH-sensitive follicles, most frequently linked to the condition known as diminished ovarian reserve. In some cases, however, poor response may be associated with suboptimal exposure to gonadotrophins, for example in obese women (Maheshwari *et al.*, 2007), or the presence of FSH receptor subtypes which render the follicles less sensitive to exogenous gonadotrophins (Simoni *et al.*, 2002).

Although declining ovarian reserve with age is associated with a reduction in oocyte quality, exemplified by poorer chances of implantation and higher rates of early pregnancy loss, a solid link between the remaining quantity of antral follicles and the quality of the oocytes held within these follicles seems missing. Hence, it can be assumed that not all poor responders are similar in terms of loss of oocyte quality and the question arises of whether patient characteristics can be identified that mark poor responders who still have an acceptable prognosis, both in the current cycle as well as in subsequent cycles. Once identified, these couples could be counselled on whether it is worthwhile to start or continue with IVF.

The aim of this literature review was therefore to identify the prognostic value of patient characteristics and ovarian reserve tests (ORT) for pregnancy in poor responders to COH in the current or subsequent cycle.

Methods

Literature search

A systematic search was conducted in PubMed, Embase, Cochrane and SCOPUS databases using synonyms for 'IVF', 'intracytoplasmic sperm injection' or 'assisted reproduction treatment' and 'poor response' or 'number of oocytes' and 'pregnancy rate'. A period of all years through to April 2010 was covered by the search. The search was conducted independently by two researchers (J.F.O and S.L.B.). No limits were used in the advanced search. If necessary and applicable, authors were contacted for any missing data. The Statement of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was followed as far as applicable, although the authors realized that the nature of the studies was likely to make adherence to this protocol difficult, as our aim was not to make a comparison between predefined groups but to investigate associations between predictive factors and the outcome.

Study selection

Studies were selected if the target population consisted of patients with a poor response to COH for IVF or ICSI and inclusion followed if two basic conditions were met. First, probability of pregnancy in the present cycle and/or subsequent cycles had to be reported or analysed. Second, the role of patient characteristics, such as age and/or BMI and/or ORTs and/or treatment characteristics, in the probability of a pregnancy occurring had to be documented. As ORTs, we preferred to study FSH, antral follicle count (AFC) and/or anti-Mullerian hormone (AMH) because these tests are superior to ovarian volume or any other test as a marker for ovarian reserve. However, ovarian volume as a predictive factor was still included in the search. All possible studies that could meet these two basic conditions were included in the search (see Fig. 1).

Currently, there is no international consensus regarding the definition of a poor response. Many definitions have been used since the 'poor responder' was first described in 1983 (Garcia *et al.*, 1983; Marrs *et al.*, 1983). Definitions vary from using the number of oocytes retrieved, the number of follicles at the end of COH, the peak estradiol (E_2) level after standard stimulation or a combination of these all. Every possible definition of poor response was included in this review so that a complete search, selection and analysis in this review could be performed. However, proxy definitions of poor response, such as prior elevated basal FSH or advanced female age, were not included in the present review as a considerable proportion of these so-called predicted poor responders will not demonstrate a poor response in the actual first cycle. Furthermore, all possible definitions used for the main outcome (pregnancy) in poor responders to COH were included. Reviews and case-reports did not meet the inclusion criteria and were excluded from the original search.

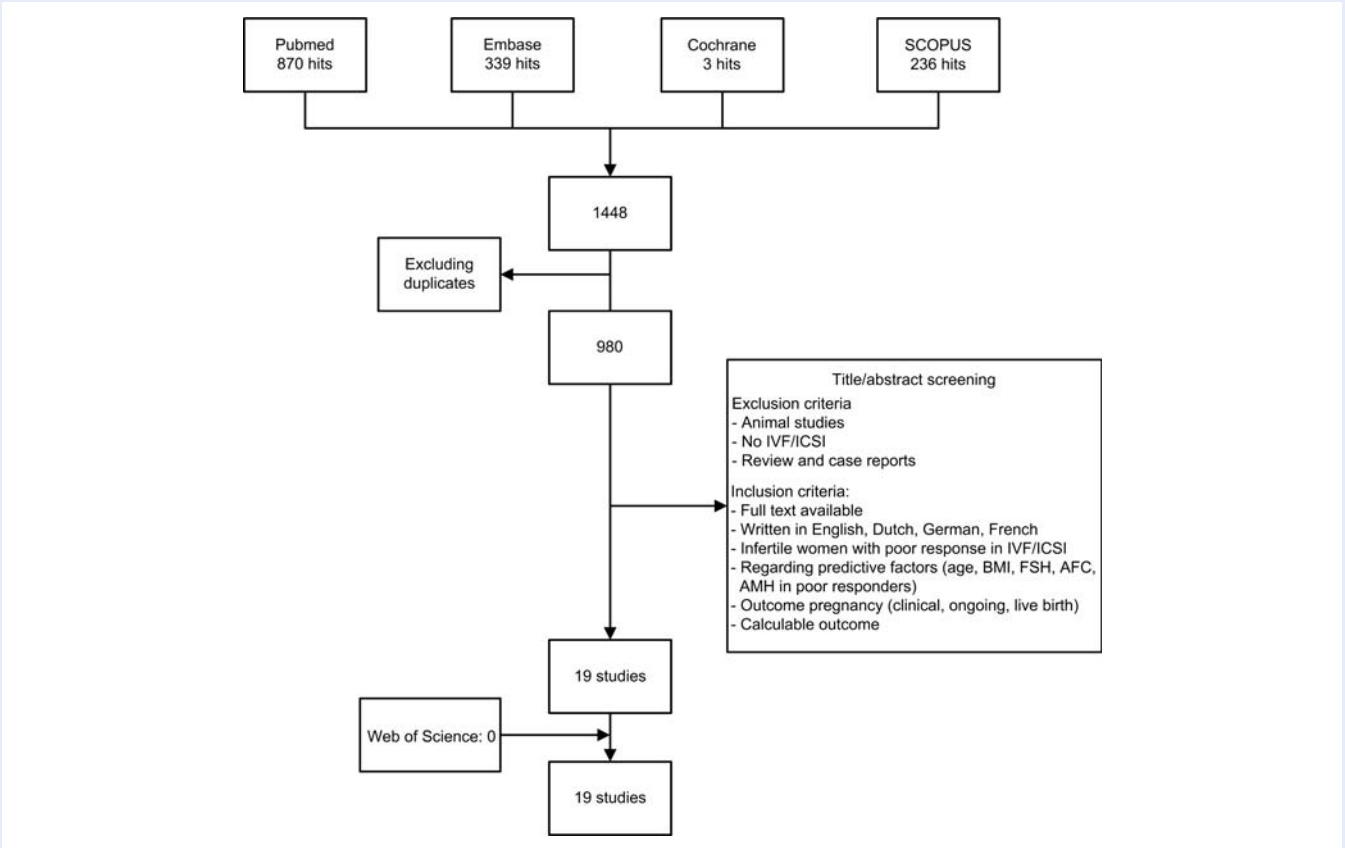

Figure 1 Search and selection strategy for systematic review of the literature to identify patient characteristics and ORT that will determine prognosis for pregnancy in poor responders in IVF. AFC, antral follicle count; AMH, anti-Mullerian hormone.

Study selection occurred in two stages. First, titles and abstract were screened by two researchers (J.F.O., F.Y.) in order to provide a selection of full-text papers likely to meet the predefined selection criteria (see Fig. 1). Second, final inclusion and exclusion occurred after examination of the full text by three independent researchers (J.F.O, F.Y and S.L.B). Any disagreement about inclusion was resolved by consensus or a fourth reviewer (F.J.M.B.).

Data extraction

Relevant data from all included studies were summarized in descriptive tables containing the study design, the number of included patients, the definitions applied and the patient characteristics or ORTs analysed (Table I).

Meta-analysis

The extracted data from the selected studies were converted into 2 × 2 tables for the predictive factor studied, patient characteristics or ORTs, versus pregnancy (yes or no), using the cut-off value for the predictive factors as stated in the studies. Odds ratios (OR) and measures of statistical uncertainty were calculated from the 2 × 2 tables. In case of similar cut-off values, statistical pooling was considered feasible, and inverse variance weighted pooling of the log (OR) was performed. When the differences between cut-off values were considered too large, no statistical pooling was performed.

Results

Systematic review

The initial database search resulted in 1448 hits. Duplicates were removed using Refworks, which resulted in 980 remaining articles. After reading the title and abstract a total of 19 full-text articles were detected. These articles reported on the prognosis of poor responders related to patient characteristics, compared with normal responders or concerning the pregnancy rate in the current cycle and the subsequent cycles (for overview of search strategy and results, see Fig. 1). These complete papers were read, and results were extracted and summarized. Six studies revealed the pregnancy rate for poor responders compared with normal responders, 10 studies showed the influence of female age on the pregnancy rate for poor responders and only one article reported the prognosis of poor responders and the influence of BMI. One study reported on the value of basal FSH as prognosticator of pregnancy. Four studies investigated the pregnancy rate by comparing classes of oocyte number obtained and five studies investigated the pregnancy rate for the present and consecutive cycles in first cycle poor responders. Three studies offering multivariable prediction models for outcome pregnancy were identified and considered suitable for data extraction (van Rooij *et al.*, 2003; Klinkert *et al.*, 2004; Hendriks *et al.*, 2008).

Table I Characteristics of the included studies.

Author	Year	Design	*n*	Definition poor response	Definition pregnancy	One or consecutive cycles	Predictive Factor studied	Compared with normal responders
Baka *et al.*	2006	RC	96c	≤3 oocytes or E2 level <500 pg/ml day of hCG injection or FSH < 20 IU/l	Clinical	One	Number of oocytes	No
Biljan *et al.*	2000	PC	828w	≤3 follicles US	Clinical	One	Age	Yes
Gaast, van der *et al.*	2006	RC	7422w	Not specified	Unclear	One	Number of oocytes	No
Galey-Fontaine *et al.*	2005	RC	163c	<5 follicles >14 mm + E2 <1000 pg/ml before HCG injection	Clinical	One	Age, FSH	No
Hanoch *et al.*	1998	RC	143c	E2 level <1000 pg/ml day of HCG injection	Clinical	One	Age	No
Hellberg *et al.*	2004	RC	1699w	<5 oocytes retrieved	Live birth	Consecutive	Number of oocytes	No
Hendriks *et al.*	2008	PC	222w	<4 oocytes or cancellation	Ongoing	Consecutive	ORT	Yes
Inge *et al.*	2005	RC	805c	≥1 oocyte and ≤5 oocytes	Live birth	One	Age	No
Klinkert *et al.*	2004	RC	225w	<4 oocytes or <3 follicles	Ongoing	Consecutive	ORT	No
Orvieto *et al.*	2009	RC	397w	<5 oocytes	Clinical	One	BMI	No
van Rooij *et al.*	2003	PC	93w	<4 oocytes	Ongoing	One	Age	No
Saldeen *et al.*	2007	RC	1706c	≤5 oocytes	Clinical	One	Age	Yes
Schimberni *et al.*	2009	RC	294w	previous cycle ≤1 follicle	Clinical	Consecutive		No
de Sutter *et al.*	2003	RC	9644c	≥1 oocyte and <5 oocytes	Ongoing	One	Age	Yes
Timeva *et al.*	2006	RC	1017c	≤5 oocytes	Clinical	One	Number of oocytes	Yes
Ulug *et al.*	2003	RC	209c	≤4 follicles >10 mm US	Clinical	One	Age, number of oocytes	No
Veleva *et al.*	2005	RC	45w	≤3 oocytes	Clinical	Consecutive	Poor response consistency	No
Yih *et al.*	2005	RC	4862c	≤4 oocytes	Clinical	One	Age	No
Zhen *et al.*	2008	RC	944c	<4 oocytes	Clinical	One	Age	Yes

n, number of women(w)/cycles(c). Study design: RC, retrospective cohort; PC, prospective cohort; US, ultrasound; E2, estradiol.

Cut-off values of age and FSH varied among the included studies as well as the definition of poor response. As a consequence of this, the results from these individual studies could not be compared and their data could not be aggregated. However, to point out a general tendency we pooled the data (without correcting for heterogeneity) concerning the comparison of poor responders and normal responders. For the analysis of predictive factors within the poor responder group, structured tabulations were performed in order to demonstrate the interpretations of the data.

We decided to refrain from contacting the authors for additional information as this would be more appropriate for an analysis of individual patient data and our aim was to give an overview of the current literature.

No publications were found regarding the prognosis for poor responders specified for smoking, AFC, AMH or ovarian volume. By cross-checking references from the articles utilizing the Web of Science, no additional studies were located. In Table I the studies selected for reading the full paper and subsequent data extraction are listed.

Prognosis for poor responders compared with normal responders

A literature overview of the pregnancy rate for poor responders compared with normal responders is shown in Table II, demonstrating that poor responders have a pregnancy rate varying from 7.6 to 17.5% compared with normal responders varying from 25.9 to 36.7%. After pooling the data, without a correction for heterogeneity, a total of 14 338 patients could be included. From the pooled data analysis the estimate for the pregnancy rate for poor responders was 14.8%, as opposed to 34.5% for normal responders. The effect of age on the difference in pregnancy prospects could be questioned. Unfortunately, this could not be taken into full account in this review, as individual patient data were lacking for multivariable analysis. However, a trend towards an older age for poor responders becomes apparent from the listed studies.

Female age

Ten studies were located regarding the prognosis of poor responders in subgroups based on female age (Table III). All 10 studies (Hanoch *et al.*, 1998; Biljan *et al.*, 2000; de Sutter and Dhont, 2003; Ulug *et al.*, 2003; van Rooij *et al.*, 2003; Galey-Fontaine *et al.*, 2005; Inge *et al.*, 2005; Yih *et al.*, 2005; Saldeen *et al.*, 2007; Zhen *et al.*, 2008) showed a decrease in pregnancy rate for the older poor responder and in five of these studies, these differences were statistically significant (Hanoch *et al.*, 1998; de Sutter and Dhont, 2003; Ulug *et al.*, 2003; Galey-Fontaine *et al.*, 2005; Zhen *et al.*, 2008). For example, de Sutter and Dhont (2003) compared the pregnancy rate between women of 36 years and younger with women older than 36 years and demonstrated a significant difference of $P < 0.0001$ (pregnancy rate of 23.0 versus 12.0%, respectively). Overall, the effect of female age on the prognosis in poor responders shows that older poor responders have lower pregnancy rates (ranging between 1.5 and 12.7%) compared with younger poor responders (ranging between 13.0 and 35%). Owing to the heterogeneity in age class distribution applied in the different studies, pooling of data for an overall meta-analysis could not be justified.

Table II Comparison of pregnancy rate in poor responders to normal responders.

Author	*n*	Definition poor response	Definition of pregnancy	PR/cycle poor responders (%)	PR/cycle normal responders (%)	*P*-value	Age in poor responders	Age normal responders	*P*-value
Biljan *et al.*	805w	≤3 follicles US	Clinical	14.3	33.0%	Not stated	37.3[a] 41.4[b]	34.5[a] 42.3[b]	0.003[a] NS[b]
Hendriks *et al.*	222w	<4 oocytes + cancellation	Ongoing	7.6	25.9	0.001	39	35	0.01
Saldeen *et al.*	1706c	≤5 oocytes	Clinical	9.0	32.6	<0.0005	35.9	33.7	<0.0001
Sutter, de *et al.*	9644c	≥1 oocyte and <5 oocytes	Clinical	17.5	35.3	<0.0001	Not stated	Not stated	
Timeva *et al.*	1017c	≤5 oocytes	Clinical	12.1	29.5	<0.05	Not stated	Not stated	
Zhen *et al.*	944c	<4 oocytes	Clinical	14.8	36.7	<0.05	36.6	33.3	<0.05
Pooled estimate	14 338			14.8	34.5				

n, number of women(w)/cycles(c) included; PR, pregnancy rate; NS, non-significance.
[a]Group <40 years.
[b]Group ≥40 years.

Table III Female age category and pregnancy rate per cycle started.

Article	*n*	Definition poor response	Female age	*P*-value	Note
			28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 >46		
Zhen *et al.*	472c	<4 oocytes	18.5% / 2.8%	<0.001	
Rooij, van *et al.*	47w	<4 oocytes	13.0% / 4.0%	NS	
Biljan *et al.*	42w	≤3 oocytes US	27.8% / 4.2%	>0.05	
Saldeen *et al.*	290c	≤5 oocytes	14.0% / 3.0%	NS	PR per ovarium pick up
Inge *et al.*	173c	≥1 oocyte and ≤5 oocytes	27.1% / 12.7%	NS	DR per cycle
Sutter, de *et al.*	1280c	≥1 oocyte and <5 oocytes	23.0% / 12.0%	<0.0001	
Galey-Fontaine *et al.*	163c	<5 foll. + E2 <1000 pg/ml before HCG	14.6% / 4.9%	<0.04	PR per retrieval
Ulug *et al.*	209c	≤4 follicles >10 mm US	19.5% / 7.2% / 1.5%	<0.04	PR per embryo transfer
Hanoch *et al.*	143w	E2 level <1000 pg/ml day of HCG injection	19.3% / 6.0% / 6.5%	0.004	
Yih *et al.*	525w	≤4 oocytes	35% / 21% / 17% / 11%	NS	PR per retrieval

n, number of women(w)/cycles(c) included; PR, pregnancy rate; DR, delivery rate; US, ultrasonographically; SD, standard deviation; NS, not stated; E2, estradiol.

Table IV Number of oocytes retrieved and pregnancy rate per first cycle started.

Article	*n*	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	*P*-Value	Note
Baka *et al.*	96c	0.0	15.2	12.5			0.41	*P*-value on 3 oocytes versus 1
Gaast, van der *et al.*	7422w	7.0	11.5	15.6	18.6	21.7	NS	Data extracted from figure
Timeva *et al.*	1017c	0.0	10.8	8.7	11.5	22	<0.05	
Ulug *et al.*	209c	2.3	4.3	11.5	15.9		<0.05	PR per embryo transfer

n, number of women(w)/cycles(c) included; PR, pregnancy rate; NS, not stated.

Body mass index

Only one study was found concerning pregnancy rates for poor responders and the influence of BMI. Orvieto *et al.* (2009) described the pregnancy rate in subgroups for BMI below or above 30 kg/m^2. A significant decrease in pregnancy rate was found for the poor responders with a BMI $>$ 30 kg/m^2 versus a BMI $<$ 30 kg/m^2 (4.5 versus 23%, respectively). The age distribution of the patients in the two subgroups was similar (32.4 SD $\pm$ 5.5 years versus 32.7 SD $\pm$ 4.5 years, for BMI $>$ 30 and BMI $<$ 30, respectively).

Basal FSH

Galey-Fontaine *et al.* (2005) compared the pregnancy rates for poor responders according to the basal FSH level. In the analysis of 163 poor responders with either normal or elevated basal FSH levels (cut-off 12.0 IU/l), a significant decrease in pregnancy rates for women with an elevated basal FSH versus those with normal FSH (4.0 versus 14.8%, respectively) was demonstrated. After correction for female age category ($<$ versus $\geq$36 years), the effect of elevated basal FSH on the prospects in this poor responder group was still significant.

Number of oocytes retrieved

Four papers summarized the outcome of IVF in poor responders in subgroups based on the actual number of oocytes retrieved (Table IV). Three groups investigated the predictive value of the number of oocytes retrieved for poor responders with one, two and three oocytes retrieved (Ulug *et al.*, 2003; Baka *et al.*, 2006; Timeva *et al.*, 2006): women with one oocyte retrieved showed a very low pregnancy rate in all three studies (0, 0 versus 2.3%, respectively), while in cases with two oocytes retrieved higher numbers of pregnancies (15.2, 10.8 versus 4.3%, respectively) were observed. The same was true for cases with three oocytes, showing a further increase in pregnancy prospects, with the exception of the study by Timeva *et al.* (2006) and Baka *et al.* (2006). Timeva *et al.* (2006) and Ulug *et al.* (2003) also reported on four oocytes retrieved, which resulted in even better results (11.5 versus 15.9%, respectively) and finally Timeva *et al.* (2006) also included women with five oocytes retrieved, with a pregnancy rate of 22%.

Several studies (Yih *et al.*, 2005; Timeva *et al.*, 2006; van der Gaast *et al.*, 2006) investigated the predictive value of the number of oocytes retrieved, including all women undergoing IVF/ICSI, with regard to pregnancy rate. The authors assumed that there is an optimal range of oocytes for achieving pregnancy. According to the results of van der Gaast *et al.* (2006) 13 oocytes at retrieval resulted in the highest pregnancy rate of 28%. Furthermore, they showed a clear correlation in pregnancy rate for poor responders depending on the number of oocytes retrieved; however, data could not be accurately obtained from the graph shown.

Performance in subsequent cycles

Five studies have described the pregnancy rate for poor responders in the current and subsequent cycles (Table V). Hendriks *et al.* (2008) and Klinkert *et al.* (2004) analysed the pregnancy rate for the expected poor responder compared with the unexpected poor responder in three consecutive cycles.

In both Hendriks *et al.* (2008) and Klinkert *et al.* (2004) a decrease in pregnancy rate was observed for expected poor responders in the subsequent cycles from 7 to 9% in the second cycle to 0% in the third subsequent cycle, with a cumulative pregnancy rate in the second and third cycle of 11.5–19%. This contrasted to unexpected poor responders, who showed an increasing pregnancy rate from 11 to 22% in the second cycle to 21–25% in the third cycle, with a cumulative rate of 25.9–47% in the third cycle. Moreover, Schimberni *et al.* (2009) investigated the pregnancy rate for poor responders, defined as a cancelled cycle in the previous cycle, who underwent a series of natural cycle IVF treatment. An increasing pregnancy rate was seen until the third cycle (9.5–12%), however, after the third cycle the chance of becoming pregnant falls to 10.2% in the fourth, until 7.2% in the fifth cycle, with an overall cumulative pregnancy rate of 16.7%.

Hellberg *et al.* (2004) studied the birth rate in 1699 women with two subsequent IVF cycles, 898 of whom had three successive IVF cycles. The number of oocytes retrieved in the first IVF cycle was used to predict the outcome in the second or third treatment cycle. When one to two oocytes were retrieved in the first cycle, the birth rate in the second cycle was 9.5%. The retrieval of three to four oocytes resulted in birth rates of 16.5% in the second cycle. Moreover, irrespective of the number of oocytes retrieved in the second cycle, a decline in birth rate (mean 7.3%) was demonstrated in the third cycle when originally one to three oocytes were retrieved in the first cycle.

Finally Veleva *et al.*, (2005) reported on the predictive value of a poor response in the first cycle on pregnancy rates in two subsequent cycles. In 54% of the women, an initial low response was followed by a normal response in at least one cycle. However, with a pregnancy rate of only 10.1% per cycle, they concluded that a poor response was an indicator of a poor prognosis. In the studied population, consisting

Table V Poor responder and pregnancy rate in subsequent cycles.

Author	*n*	Cycles		PR per cycle (cumulative PR)		Definition pregnancy	Note
				Expected poor responder (EPR)	Unexpected poor responder (UPR)		
Hendriks *et al.*	79w	3	Cycle 1 Cycle 2 Cycle 3	8% 7% (11.5%) 0% (11.5%)	7% 11% (14.8%) 21% (25.9%)	Ongoing	(un)expected poor responder: 'tri-variable-model' [12 × FSH (IU/l)] − [14 × AFC (*n*)] − [1 × inhibin B (pg/ml)]
Klinkert *et al.*	225w	3	Cycle 1 Cycle 2 Cycle 3	11% 9% (19%) 0% (19%)	9% 22% (29%) 25% (47%)	Ongoing	EPR: ≥41 years FSH ≥ 15 IU/l UPR: <41 years and FSH < 15 IU/l
				Poor responder in cycle 1			
Schimberni *et al.*	294w	≥5	Cycle 2 Cycle 3 Cycle 4 Cycle 5	9.7% (12.9%) 12.0% (15.0%) 10.2% (16.3%) 7.1% (16.7%)		Clinical	Natural cycle IVF after cycle 1 Poor responder if in previous cycle ≤1 follicle
Hellberg *et al.*	1699w	2	Cycle 2	1–2 oocytes cycle 1 3–4 oocytes cycle 1	9.5% 16.5%	Live birth	Poor responder if <5 oocytes retrieved
Veleva *et al.*	45w	3	Cycle 2 a/o Cycle 3 Cycle 2 a/o Cycle 3	Poor response Normal response	10.1% (*n* = 43w) 16.7% (*n* = 2w)	Clinical	

n, number of women(w)/cycles(c) included; PR, pregnancy rate; AFC, antral follicle count.

mostly of women <40 years of age, a consistent low ovarian response was observed in only 2.5%, with a live birth rate of 16.7% per cycle of two cases stimulated three times. As only data on three cycles completed have been analysed in retrospect, selection bias is likely to have influenced the observations.

Discussion

Main findings

This systematic literature review is the first to summarize the available evidence regarding the prognostic value of various patient characteristics and ORTs to predict the pregnancy rate in the current or subsequent cycle for poor responders after COH for IVF/ICSI in cycle one. The review confirms that poor responders have a diminished pregnancy rate compared with normal responders but also demonstrates that several factors modulate the prognosis in this patient group, with possible implications for clinical practice.

The aim of this review was to determine patient characteristics that differentiate poor responders with pregnancy prospects close to zero from those poor responders who still have a reasonable prognosis. In clinical practice, this latter category of poor responders should not be judged based solely on their poor response and no limitations in number of IVF treatment cycles should be applied. In contrast, balanced decision-making on the management of poor responders that could be identified as having poor pregnancy prospects is desirable. The question is whether additional cycles are justified or continuation of treatment should be discouraged. Unfortunately, this review does not allow us to make this clear differentiation between favourable and unfavourable poor responders. The clinical value may lie in the possibility to counsel couples on the different prospects.

Not all women who respond poorly to COH have poor pregnancy prospects. The reduced prospects in poor responders for pregnancy may partly be attributed to the effect of female age, as in several studies reported in this review the poor responders are of higher age than control normal responders. The gradual decline in oocyte quality with advancing age in parallel to follicle number reduction, will explain the effect of poor response on reproductive capacity (Broekmans *et al.*, 2009). However, a full in-depth analysis into this subject appeared not to be possible and comparison of data for individual patients may be the only way to fully asses the role of female age in the comparison of normal versus poor responders.

Among the factors predicting pregnancy outcome within the poor responder group, female age appeared to play a distinct role. The trend that older poor responders have a lower pregnancy rate compared with younger poor responders is exemplified by the fact that in half of the studies a significant difference in pregnancy rate between age groups was noted. Not one publication contradicted this observation. Much like for the role of age in the difference in pregnancy rates between normal and poor responders, the age effect on oocyte quality may explain the effect of age within the poor response group. Several studies have shown that quantitative measures of ovarian reserve will relate to measures of quality but more so in older women. For example, poor response to stimulation was predictive of both pregnancy loss and the occurrence of a trisomic pregnancy after IVF (Haadsma *et al.*, 2010a, b). However, ORTs, such as the AFC and AMH, failed to be predictive of pregnancy loss in an infertile population, in contrast to the steady relationship of female age with pregnancy loss (Haadsma *et al.*, 2009). This indicates that the

relationship between quantity of follicles and quality of oocytes is far from elucidated, with age being a driver behind decline in oocyte quality but partly independent of changes in quantity.

A second factor of relevance for prognosis in poor responders was the degree of poor response. As a result of the lower number of oocytes, there are fewer embryos to transfer and subsequently a lower prospect for pregnancy, in addition to the assumed overall negative effect of poor ovarian capacity on oocyte quality. An increased number of oocytes improves the prospects for pregnancy, varying from close to zero with one oocyte up to almost 15% when four oocytes had been retrieved. In the present review, the role of female age could not be analysed from the existing data, thereby leaving open the possibility that the effect of number of oocytes is mainly explained by age effects. In general, more oocytes will increase the chances for obtaining high-quality embryos, an effect that has been shown to be independent of age. Such independence has also been demonstrated for the poor responder group separately (Saldeen *et al.*, 2007). Larger datasets using individual patient data from published literature may allow for additional analyses of this subject. It should be noted, however, that there seems to be an optimal range for the number of oocytes retrieved: in addition to low numbers, the retrieval of high numbers of oocytes has consistently been associated with less favourable, although not poor, pregnancy prospects (van der Gaast *et al.*, 2006; Sunkara *et al.*, 2011).

The present review has also demonstrated that patient characteristics other than age and ORTs have not been investigated properly as yet. Obese poor responders might have a lower pregnancy rate than non-obese poor responders, as the results in this review supported current views on the role of body weight in female reproduction (Lintsen *et al.*, 2005; Koning *et al.*, 2010). However, as the evidence for a role of body weight in poor responders is only based on one paper, it is not possible to reach a final conclusion (Orvieto *et al.*, 2009). Likewise, for the only ORT studied (basal FSH level), evidence was found that it affects pregnancy rates in poor responders, based on only one study. The literature has previously shown a link between a raised basal FSH and a reduced reproductive capacity (Broekmans and Klinkert, 2004), which also fits the concept of the expected poor responder where, combined with an abnormal FSH test result prognosis is clearly decreased (Klinkert *et al.*, 2004).

The systematic review on the prospects in subsequent cycles has yielded a limited number of studies. The question was raised what prognosis can be expected for women with a poor response in their first cycle, if they would continue treatment. Is it worthwhile proceeding for these women? From the limited studies available it emerges that some poor responders may still have reasonable prospects, depending greatly on their ovarian reserve status and age (Hellberg *et al.*, 2004; Klinkert *et al.*, 2004; Veleva *et al.*, 2005; Hendriks *et al.*, 2008; Schimberni *et al.*, 2009). Larger studies are necessary to support the concept of the expected poor responder, who may have a prognosis so poor that further treatment should be avoided.

Limitations

Results obtained in this review could have been influenced by some limitations in the search strategy. First of all there was no international consensus for the definition of a poor response. Different definitions and cut-off values were used, varying from $\leq$2 oocytes at retrieval to $\leq$5 oocytes at retrieval, $\leq$4 follicles $>$10 mm to $<$6 follicles just before retrieval (Ulug *et al.*, 2003), a previous cancelled cycle (Schimberni *et al.*, 2009), E_2 level $<$1000 pg/ml on the day of HCG injection (Hanoch *et al.*, 1998), basal FSH level $>$10 IU/l, FSH stimulation with $>$450 l U or a combination of any of these (Galey-Fontaine *et al.*, 2005; Baka *et al.*, 2006; Hendriks *et al.*, 2008). Consequently, various patient groups were included in our search, affecting the homogeneity of the data and thereby the generalizability of the findings. As a result, articles were selected only when the authors used a low number of oocytes retrieved or when the mean number of oocytes was low, as this definition of poor responder is the one most commonly used. Milder ovarian stimulation protocols, with individualized dosing or the use of GnRH antagonist LH peak prevention, are currently promoted in order to decrease adverse effects (Verberg *et al.*, 2009; Olivennes, 2010): such an approach will result in a more modest number of oocytes at retrieval, with the inclusion of more cases that will formally yield a poor response but with in fact optimal implantation rates (Verberg *et al.*, 2009). Obviously, in such responders the addition of the word 'poor' may be considered a misnomer. Also, various cut-off values were applied for age categories, which have prevented a more robust overall analysis of the effect of the characteristics on pregnancy prospects.

Second, no studies were found regarding AMH and AFC in the prediction of outcome in poor responders. Therefore, only the predictive value of FSH was reported. Studies regarding AMH and AFC in outcome prediction in poor responders are highly desirable, as these tests have been shown to be superior over FSH in the prediction of response in an IVF population. If the AMH and AFC tests would help to identify so-called expected poor responders, estimation of the prognosis may become more meaningful, as demonstrated previously (Hendriks *et al.*, 2008). Outcome results on pregnancy were reported in many different ways, and presented as rate per cycle, per retrieval, per embryo transfer or per implantation, and as clinical pregnancy, ongoing pregnancy rate or live birth. Conversion could be performed with some of the results but ultimately pooling of data were greatly jeopardized. Still, comparisons within the studies were valid as the same units of outcome were applied.

The results were further influenced by the inclusion or exclusion of cancelled cycles, or cycles with no eggs retrieved. Excluding these cases may lead to overestimation of the performance of poor responders, and currently there are no means of correcting for this phenomenon. Moreover, the cut-off value utilized in determining when to cancel a cycle differed greatly, varying from $<$3 mature follicles visualized ultrasonographically (Biljan *et al.*, 2000; Veleva *et al.*, 2005; Hendriks *et al.*, 2008) to up to no more than five follicles present and an E_2 level $<$1000 pg/ml (Yih *et al.*, 2005). As a result of these considerations, the conclusions in this review must be used with the assumption that cancelled cycles would have produced the same results as those cases that did undergo final maturation triggering and ovum retrieval in comparable circumstances of follicle growth.

Clinical implications

The clinical value of the present findings may lie in the counselling of couples that face a poor response to COH for whom, in general,

the prospects are clearly different from cases with a normal response to hyperstimulation. However, this may be less obvious in younger women with three or four oocytes obtained and previously normal results in ORTs. Such poor response may be accidental and unrelated to a loss in oocyte quality. The question then will be which approach will be preferable. Ready cancellation of the cycle and repeating the stimulation with higher dosages of FSH may be driven by the hope for a normal response, with possibly better prospects. Proceeding to the follicle aspiration and dealing with the limited number of oocytes available that may still show sufficient quality in younger patients may be justifiable. In presumed poor ovarian reserve patients (abnormal ovarian reserve, high age) proceeding to retrieval may be the best way, as prognosis may not be altered anyway. Studies on the management of predicted or observed poor responders so far have not delivered the solid evidence for a preferred strategy. As such, proceeding to follicle aspiration may be justified in cases with a so called unexpected poor response.

If the poor response is observed after the oocyte retrieval, the same factors may direct our counselling on the question of whether additional cycles are justified. Female age and ovarian reserve status in concert deliver the tools for correct decision-making, as a subgroup with still favourable prognosis can be identified. Nevertheless, robust studies on the management of predicted or actual poor responders are greatly needed, with a focus on the cost effectiveness of various strategies.

In summary, this literature review demonstrates that poor responders are not a homogeneous group and that the prognosis for these patients may vary greatly depending on patient characteristics, such as age or the actual number of oocytes obtained. These factors may help in decision-making regarding continuation of treatment. Continued research using individual patient data from the published literature will enable more firm conclusions to be reached on the role of predictive factors in the poor responder in IVF.

Authors' roles

Each author has contributed in a substantial way to the work described in the manuscript and its preparation. J.F.O, F.Y. and S.L.B. were responsible for search and selection of articles, assessment of eligible articles, data extraction and tabulation and writing and revising of the manuscript. M.J.C.E. is responsible for statistical analysis and writing and revising the manuscript. F.J.M.B. made contributions to the concept, interpretation of data, revising the manuscript and final approval of the version to be published.

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Conflict of interest

F.J.M.B. is a member of the external advisory board for Ferring Pharmaceuticals, Hoofddorp, the Netherlands. He receives no monetary compensation.

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