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ORIGINAL ARTICLE *Infertility*

Cumulative live birth rates in low-prognosis women

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STUDY QUESTION: Do cumulative live birth rates (CLBRs) over multiple IVF/ICSI cycles confirm the low prognosis in women stratified according to the POSEIDON criteria?

SUMMARY ANSWER: The CLBR of low-prognosis women is ~56% over 18 months of IVF/ICSI treatment and varies between the POSEIDON groups, which is primarily attributable to the impact of female age.

WHAT IS KNOWN ALREADY: The POSEIDON group recently proposed a new stratification for low-prognosis women in IVF/ICSI treatment, with the aim to define more homogenous populations for clinical trials and stimulate a patient-tailored therapeutic approach. These new criteria combine qualitative and quantitative parameters to create four groups of low-prognosis women with supposedly similar biologic characteristics.

STUDY DESIGN, SIZE, DURATION: This study analyzed the data of a Dutch multicenter observational cohort study including 551 low-prognosis women, aged <44 years, who initiated IVF/ICSI treatment between 2011 and 2014 and were treated with a fixed FSH dose of 150 IU/day in the first treatment cycle.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Low-prognosis women were categorized into one of the POSEIDON groups based on their age (younger or older than 35 years), anti-Müllerian hormone (AMH) level (above or below 0.96 ng/ml), and the ovarian response (poor or suboptimal) in their first cycle of standard stimulation. The primary outcome was the CLBR over multiple complete IVF/ICSI cycles, including all subsequent fresh and frozen-thawed embryo transfers, within 18 months of treatment. Cumulative incidence curves were obtained using an optimistic and a conservative analytic approach.

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MAIN RESULTS AND THE ROLE OF CHANCE: The CLBR of the low-prognosis women was on average ~56% over 18 months of IVF/ICSI treatment. Younger unexpected poor ($n = 38$) and suboptimal ($n = 179$) responders had a CLBR of ~65% and ~68%, respectively, and younger expected poor responders ($n = 65$) had a CLBR of ~59%. The CLBR of older unexpected poor ($n = 41$) and suboptimal responders ($n = 102$) was ~42% and ~54%, respectively, and of older expected poor responders ($n = 126$) ~39%. For comparison, the CLBR of younger ($n = 164$) and older ($n = 78$) normal responders with an adequate ovarian reserve was ~72% and ~58% over 18 months of treatment, respectively. No large differences were observed in the number of fresh treatment cycles between the POSEIDON groups, with an average of two fresh cycles per woman within 18 months of follow-up.

LIMITATIONS, REASONS FOR CAUTION: Small numbers in some (sub)groups reduced the precision of the estimates. However, our findings provide the first relevant indication of the CLBR of low-prognosis women in the POSEIDON groups. Small FSH dose adjustments between cycles were allowed, inducing therapeutic disparity. Yet, this is in accordance with current daily practice and increases the generalizability of our findings.

WIDER IMPLICATIONS OF THE FINDINGS: The CLBRs vary between the POSEIDON groups. This heterogeneity is primarily determined by a woman's age, reflecting the importance of oocyte quality. In younger women, current IVF/ICSI treatment reaches relatively high CLBR over multiple complete cycles, despite reduced quantitative parameters. In older women, the CLBR remains relatively low over multiple complete cycles, due to the co-occurring decline in quantitative and qualitative parameters. As no effective interventions exist to counteract this decline, clinical management currently relies on proper counselling.

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Key words: POSEIDON criteria / low prognosis / poor ovarian response / cumulative live birth / IVF/ICSI / anti-Müllerian hormone / female age / ovarian stimulation / ovarian reserve / Bologna criteria

Introduction

In IVF/ICSI treatment, one of the main challenges is the management of women with an impaired ovarian reserve or a reduced response to exogenous gonadotropins. These 'poor responders' generally have lower live birth rates and higher treatment discontinuation rates (Olivius *et al*., 2004; Busnelli *et al*., 2015; Polyzos *et al*., 2018). The definition of the poor responder has been standardized in the Bologna criteria (Ferraretti *et al*., 2011). However, questions have been raised about the capacity of these criteria to select homogenous populations for clinical trials (Ferraretti and Gianaroli, 2014; Papathanasiou, 2014). Considerable variation is seen in baseline characteristics and prognosis due to the several ways the Bologna criteria can be fulfilled. This heterogeneity is associated with differences in the underlying etiology, and may cause variation in the effectiveness of interventions (Papathanasiou, 2014). Therefore, analysis of the poor responder population as a whole as defined by the Bologna criteria might dilute potential treatment effects and could prevent the progress in clinical management for specific subpopulations.

In 2016, the POSEIDON group proposed a more subtle stratification of 'low-prognosis women' (Poseidon group *et al*., 2016). In this concept, women are categorized into four groups based on female age, ovarian reserve tests (anti-Müllerian hormone (AMH) or antral follicle count (AFC)), and the ovarian response in case of a previous stimulation (Table I). The proposed classification identifies women with an adequate ovarian reserve and a poor or suboptimal response to standard stimulation (unexpected poor or suboptimal responders) and women with an impaired ovarian reserve (expected poor responders). It attempts to differentiate between relevant subpopulations of women, in whom specific interventions might be beneficial. The POSEIDON criteria could thereby improve the homogeneity and comparability of clinical trials, decrease the dilution of potential treatment effects, and guide a more patient-tailored approach for low-prognosis women (Humaidan *et al*., 2016; Poseidon group *et al*., 2016).

Although a recent trial already used the POSEIDON criteria to select their study population (Xu *et al*., 2018), the actual prognosis of the low-prognosis women has not yet been properly investigated. Such information could help to validate the new POSEIDON concept and provides an initial insight in the necessity of new interventions for each group. Therefore, the current study aims to evaluate the cumulative live birth rate (CLBR) of the POSEIDON groups over multiple complete IVF/ICSI cycles, including all subsequent fresh

Table I The proposed POSEIDON groups of women with a low prognosis in IVF/ICSI treatment based on quantitative and qualitative parameters. AFC, antral follicle count; AMH, anti-Müllerian hormone; adapted from Poseidon group et al. (2016).

	Low-prognosis women in IVF/ICSI treatment	
	Younger	**Older**
Unexpected	**POSEIDON group 1** • Female age: <35 years • Ovarian biomarkers: AFC ≥ 5 and/or AMH ≥ 1.2 ng/ml • Ovarian response: **subgroup 1a**, poor (<4 oocytes); **subgroup 1b**, suboptimal (4–9 oocytes)	**POSEIDON group 2** • Female age: ≥35 years • Ovarian biomarkers: AFC ≥ 5 and/or AMH ≥ 1.2 ng/ml • Ovarian response: **subgroup 2a**, poor (<4 oocytes); **subgroup 2b**, suboptimal (4–9 oocytes)
Expected	**POSEIDON group 3** • Female age: <35 years • Ovarian biomarkers: AFC < 5 and/or AMH < 1.2 ng/ml	**POSEIDON group 4** • Female age: ≥35 years • Ovarian biomarkers: AFC < 5 and/or AMH < 1.2 ng/ml

POSEIDON group 1 and 2 are each divided in two subgroups (a and b), based on the first cycle ovarian response to standard FSH stimulation.

and frozen-thawed embryo transfers (FET), within 18 months of treatment.

Materials and Methods

Study design and population

Data of a recent Dutch multicenter prospective cohort study (OPTIMIST study), which included 1515 women between 2011 and 2014, were used for the analyses (NTR2657). Participants were aged <44 years, had regular menstrual cycles, and no significant abnormalities on transvaginal ultrasound. Women with polycystic ovarian syndrome, metabolic or endocrine abnormalities, or undergoing oocyte donation were excluded. All participants had their first IVF/ICSI cycle, or the first after a previous live birth. A more detailed study description was reported previously (van Tilborg et al., 2017a).

For the current study, we included low-prognosis women, who used a fixed FSH dose of 150 IU/day in the first cycle. Small dose adjustments between cycles were permitted, based on the response in the preceding cycle (van Tilborg et al., 2012). We categorized all women in the POSEIDON groups by using age, AMH, and the ovarian response in the first cycle (Poseidon group et al., 2016). We used AMH, as recent studies indicate that it may be a more accurate and robust biomarker than the AFC (Fleming et al., 2015; Iliodromiti and Nelson, 2015; Nelson et al., 2015a). Women with an adequate ovarian reserve and a normal response to stimulation (defined as 10–15 retrieved oocytes), whom are generally considered to have an optimal prognosis (Sunkara et al., 2011; Polyzos et al., 2018), were added to compare the CLBR to low-prognosis women.

AMH measurement

In the OPTIMIST study, blood sampling was performed prior to the start of stimulation in the early follicular phase, and AMH levels were determined in one batch by using the fully automatic Elecsys assay (Roche Diagnostics, Germany). As automated assays produce substantially lower values than the pre-existing enzyme linked immunosorbent assays (ELISA) (Gassner and Jung, 2014; Nelson et al., 2015b), and as the POSEIDON cut-off value of 1.2 ng/ml is based on studies evaluating the pre-existing assays (Humaidan et al., 2016), we adjusted the cut-off value to 0.96 ng/ml using the formula Elecsys = 0.087 + (0.729 ∗ Gen II ELISA) (Nelson et al., 2015b). This formula corresponds with our internal laboratory comparison of the Gen II ELISA with the Elecsys assay, which was carried out when the latter was implemented in our hospital at the beginning of 2018 (unpublished data).

Statistical analysis

The proportion of missing AMH values was 11.6%. As the missing values were related to logistic issues, they were considered to be missing completely at random and multiple imputation was performed (Sterne et al., 2009; Janssen et al., 2010) In this process, hundred imputed datasets were created using a multivariate imputation by chained equations algorithm (van Buuren and Groothuis-Oudshoorn, 2011). In each of the imputed datasets, women were classified in one of the POSEIDON groups, and results were pooled by assigning the women into the group that occurred in more than half (i.e. at least 51 out of 100) of the imputed datasets.

The primary outcome was the CLBR of the POSEIDON groups over multiple complete IVF/ICSI cycles, including all subsequent fresh and FET cycles, within 18 months of treatment. Additionally, we calculated the live birth rate (LBR) per consecutive cycle, per started stimulation, per oocyte retrieval, and per embryo transfer. All live births, irrespective of the mode of conception, were taken into account. Time to ongoing pregnancy leading to live birth was depicted by cumulative incidence curves, for which we used two approaches. First, a life table analysis (optimistic) assumed that the chances for couples who discontinue treatment would have been equal to couples who continue. Second, a competing risk approach (conservative) assumed that couples who discontinue treatment would have had zero chances of conceiving. The realistic curve is considered to lie between these two curves (Stolwijk et al., 1996). To measure whether signifi-

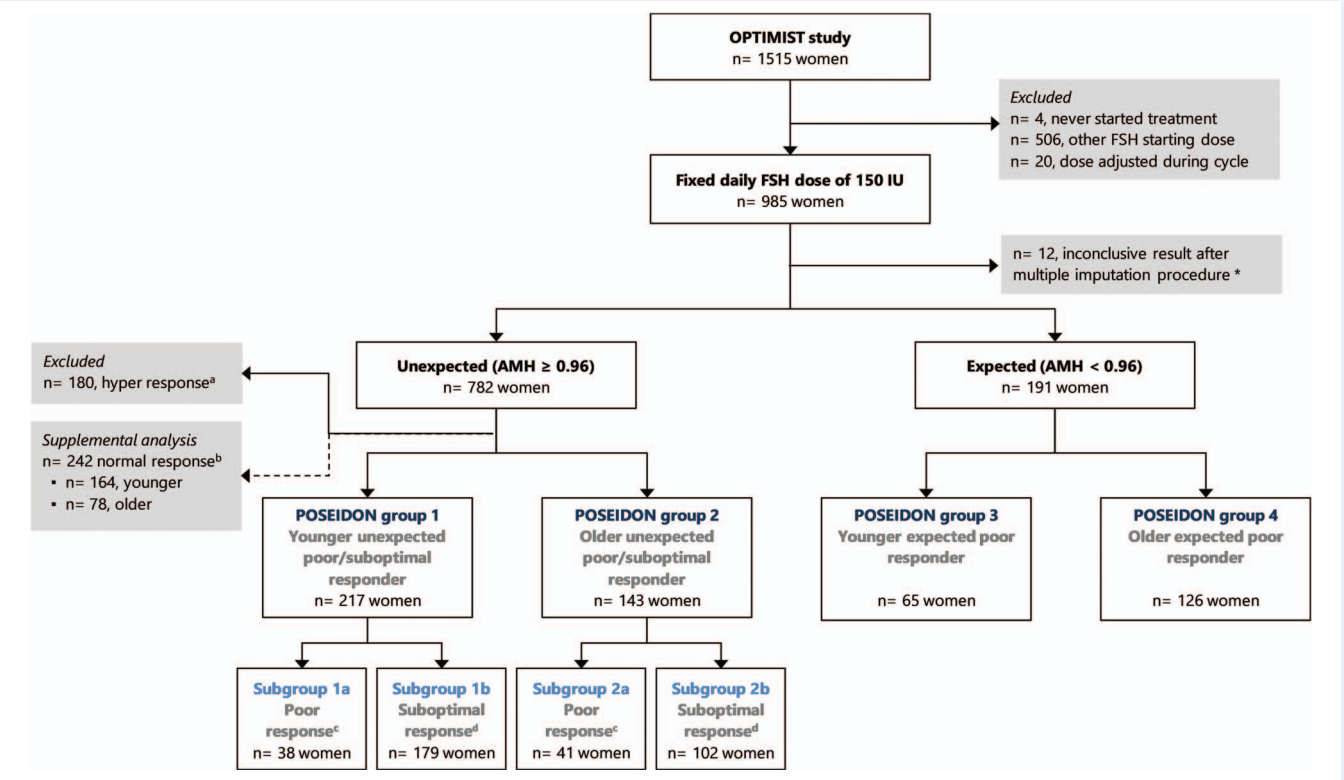

Figure 1 Flowchart of the study population of low-prognosis women according to the POSEIDON criteria (Poseidon group *et al.*, 2016). *These twelve women were not assigned to the same group in more than half of the hundred imputed datasets. [a]Hyper response, >15 retrieved oocytes or cycle cancellation for too many follicles according to the POSEIDON criteria. [b]Normal response, 10–15 retrieved oocytes according to the POSEIDON criteria. [c]Poor response, <4 retrieved oocytes or cycle cancellation for insufficient follicular growth according to the POSEIDON criteria. [d]Suboptimal response, 4–9 retrieved oocytes according to the POSEIDON criteria. AMH, anti-Müllerian hormone.

cant differences exist between the POSEIDON groups, a (pairwise) log-rank test was performed. *P*-values were adjusted using the Hommel correction for multiple testing (Hommel, 1988). A *P*-value of <0.05 was considered to indicate a statistically significant difference.

Statistical analyses were performed using R for Windows (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

Ethical approval was obtained by the Institutional Review Board of the University Medical Centre (MEC 10-273), and by the board of directors of the participating centres. All participants provided written informed consent.

Results

In the OPTIMIST study, 985 women received a fixed FSH dose of 150 IU/day in the first cycle. A total of 551 (55.9%) women met the POSEIDON criteria and were categorized in the pre-defined groups (Fig. 1). These women underwent 1128 fresh and 329 FET cycles during the 18 months of follow-up. Additionally, 164 younger and 78 older normal responders were included for supplemental comparison.

Baseline and treatment characteristics

Table II shows the baseline and treatment characteristics. By definition, POSEIDON groups 2 and 4 had a higher age than group 1 and 3, and AMH levels were higher in POSEIDON groups 1 and 2 compared to groups 3 and 4. Younger unexpected poor responders (subgroup 1a) had a higher body weight than the other (sub)groups. Primary infertility occurred more often in the younger POSEIDON groups (1 and 3), and they were most often treated for male factor infertility, whereas unexplained infertility occurred more frequently in the older groups (2 and 4).

The majority of low-prognosis women (75%) were treated with a GnRH agonist, and ICSI was most often performed in the younger POSEIDON groups (1 and 3). Unexpected suboptimal responders (subgroups 1b and 2b) had the lowest number of fresh and highest number of FET cycles. Unexpected poor responders (subgroup 1a and 2a) had the highest cancellation rates, and the FSH dose was increased (~60 IU/day) between cycle 1 and 2 in the majority of the expected or unexpected poor responders (subgroups 1a and 2a, groups 3 and 4). It should be noted that these features are likely to be related to

the characteristics that determined the assignment to the POSEIDON (sub)groups.

Cumulative live birth rates

In low-prognosis women, the average CLBR over 18 months of IVF/ICSI treatment was between 54% (conservative) and 57% (optimistic) (Table III). Figure 2 shows the cumulative incidence curves for each of the POSEIDON groups, and Table IV presents the results of the pairwise log-rank tests. The younger groups (1 and 3) had the highest CLBR over 18 months of treatment (Table III), and these groups also had the highest LBR per stimulation, oocyte retrieval, and embryo transfer. Within group 1, small differences were observed between the unexpected poor (subgroup 1a) and suboptimal responders (subgroup 1b). The older groups (2 and 4) had lower CLBR over 18 months of treatment. Within group 2, unexpected suboptimal responders (subgroup 2b) seemed to have higher CLBR than unexpected poor responders (subgroup 2a), although this difference was not statistically significant (Table IV). Older women with an impaired ovarian reserve (group 4) had the lowest CLBR, but still reached a rate between 37% (conservative) and 41% (optimistic) over 18 months of treatment (Table III). During the 18 months of follow-up, there were no large differences in the number of fresh treatment cycles between the POSEIDON groups with an average of 2 cycles per woman (Table II), yet women with the lowest prognosis (subgroup 2a and group 4) had a slightly higher number of fresh cycles (2.5 and 2.3 fresh cycles, respectively (Table II)).

Supplementary Figure S1 shows the cumulative incidence curves of the younger (<35 years) and older (≥35 years) normal responders. The CLBR for the younger normal responders was ~72%, and for the older normal responders ~58% over 18 months of treatment (Supplementary Table S1).

Discussion

This multicenter observational cohort study evaluated the CLBR of low-prognosis women according to the POSEIDON criteria and

Table II Baseline and treatment characteristics of low-prognosis women stratified according to the POSEIDON criteria (Poseidon group *et al.*, 2016).

		POSEIDON 1		POSEIDON 2		POSEIDON 3	POSEIDON 4
	All low-prognosis women (*n* = 551)	Subgroup 1a; younger unexpected poor responder (*n* = 38)	Subgroup 1b; younger unexpected suboptimal responder (*n* = 179)	Subgroup 2a; older unexpected poor responder (*n* = 41)	Subgroup 2b; older unexpected suboptimal responder (*n* = 102)	Younger expected poor responder (*n* = 65)	Older expected poor responder (*n* = 126)
Baseline characteristics							
Female age (years)	34.4 (4.5)	30.5 (2.7)	30.6 (2.8)	37.9 (2.0)	37.7 (2.1)	31.3 (2.7)	38.7 (2.2)
Infertility duration (years)	2.7 (1.8)	2.8 (2.0)	2.7 (1.5)	2.8 (2.0)	2.7 (2.1)	2.9 (1.4)	2.7 (2.1)
Body weight (kg)	71 (14)	81 (15)	70 (13)	74 (15)	67 (13)	72 (12)	71 (14)
Smoking (yes/no)	102 (18.5)	11 (29)	37 (20.7)	7 (17)	12 (11.8)	11 (17)	24 (19.0)
Primary infertility	319 (57.9)	30 (79)	123 (68.7)	18 (44)	45 (44.1)	47 (72)	56 (44.4)
Cause of infertility							
Unexplained	209 (37.9)	8 (21)	52 (29.1)	14 (34)	47 (46.1)	12 (19)	76 (60.3)
Tubal factor	49 (8.9)	2 (5)	12 (6.7)	7 (17)	13 (12.7)	9 (14)	6 (4.8)
Endometriosis	18 (3.3)	0 (0)	9 (5.0)	1 (2)	3 (2.9)	2 (3)	3 (2.4)
Male factor	297 (53.9)	30 (79)	116 (64.8)	21 (51)	44 (43.1)	42 (65)	44 (34.9)
AFC, median (IQR)	12 (6)	13 (5)	13 (4)	12 (3)	12 (5)	9 (5)	8 (5)
AMH, median (IQR)	1.32 (1.36)	1.98 (1.34)	2.00 (1.10)	1.31 (0.45)	1.95 (0.78)	0.69 (0.21)	0.55 (0.39)
Treatment characteristics							
ICSI	237 (43.0)	27 (71)	101 (56.4)	12 (29)	31 (30.4)	31 (48)	35 (27.8)
GnRH agonist	414 (75.1)	28 (74)	140 (78.2)	22 (54)	76 (74.5)	53 (82)	95 (75.4)
No. of fresh cycles/woman	2.0 (1.0)	2.1 (0.9)	1.8 (0.9)	2.5 (1.1)	2.0 (0.9)	2.0 (0.9)	2.3 (1.1)
No. of FET cycles/woman	0.6 (1.1)	0.3 (0.7)	0.7 (1.2)	0.6 (0.9)	1.0 (1.3)	0.5 (1.0)	0.3 (0.7)
First cycle cancellation	93 (16.9)	16 (42)	0	19 (46)	0	15 (23)	43 (34.1)
FSH dose increased between cycle 1 and 2	194/351 (55.3)	24/27 (89)	21/94 (22.3)	31/34 (91)	13/63 (20.6)	32/42 (76)	73/91 (80.2)
Amount of increase (IU/L)	56 (25)	61 (29)	51 (11)	57 (46)	57 (13)	54 (11)	57 (19)

Data are presented as mean (SD) or number (%) unless otherwise specified. AFC, antral follicle count (2–10 mm); AMH, anti-Müllerian hormone (ng/ml); IQR, interquartile range; FET, frozen-thawed embryo transfer.

Table III Cumulative ongoing pregnancy results within 18 months of IVF/ICSI treatment, resulting in a live birth for low-prognosis women stratified according to the POSEIDON criteria (Poseidon group *et al.*, 2016).

		POSEIDON 1		POSEIDON 2		POSEIDON 3	POSEIDON 4
	All low-prognosis women ($n = 551$)	Subgroup 1a; younger unexpected poor responder ($n = 38$)	Subgroup 1b; younger unexpected suboptimal responder ($n = 179$)	Subgroup 2a; older unexpected poor responder ($n = 41$)	Subgroup 2b; older unexpected suboptimal responder ($n = 102$)	Younger expected poor responder ($n = 65$)	Older expected poor responder ($n = 126$)
CLBR over 18 months[a]							
Optimistic (95%CI)	0.57 (0.53–0.61)	0.66 (0.46–0.79)	0.69 (0.61–0.76)	0.42 (0.25–0.56)	0.55 (0.44–0.64)	0.60 (0.46–0.71)	0.41 (0.31–0.49)
Conservative (95% CI)	0.54 (0.50–0.58)	0.63 (0.44–0.76)	0.67 (0.59–0.73)	0.41 (0.24–0.55)	0.52 (0.41–0.61)	0.58 (0.45–0.69)	0.37 (0.28–0.44)
LBR per cycle[a]							
Cycle 1	154/551 (28)	8/38 (21)	77/179 (43)	4/41 (10)	25/102 (25)	19/65 (29)	21/126 (17)
Cycle 2	95/351 (27)	7/27 (26)	31/94 (33)	9/34 (26)	19/63 (30)	14/42 (33)	15/91(16)
Cycle 3	44/176 (25)	8/14 (57)	11/37 (30)	3/20 (15)	9/31 (29)	4/20 (20)	9/54 (17)
Cycle 4	5/41 (12)	1/1 (100)	1/8 (13)	1/7 (14)	0/4 (0)	1/4 (25)	1/17 (6)
Cycle 5	0/7 (0)	0/0	0/0	0/2 (0)	0/0	0/0	0/5 (0)
Cycle 6	0/2 (0)	0/0	0/0	0/0	0/0	0/0	0/2 (0)
LBR per[a]							
Started stimulation	298/1128 (26)	24/80 (30)	120/318 (38)	17/104 (16)	53/200 (27)	38/131 (29)	46/295 (16)
Oocyte retrieval	298/955 (31)	24/61 (39)	120/310 (39)	17/74 (23)	53/191(28)	38/106 (36)	46/213 (22)
Embryo transfer	298/1185 (25)	24/61 (39)	120/408 (29)	17/86 (20)	53/286 (19)	38/124 (31)	46/220 (21)
Conception mode							
IVF/ICSI Fresh	236 (79)	22 (92)	96 (80)	13 (76)	39 (74)	34 (89)	32 (70)
IVF/ICSI FET	38 (13)	0 (0)	22 (18)	3 (18)	8 (15)	1 (3)	4 (9)
Spontaneous	21 (7)	1 (4)	2 (2)	1 (6)	6 (11)	3 (8)	8 (17)
Unknown	3 (1)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)

Data are presented as number (%), unless stated otherwise. CLBR, cumulative live birth rate; LBR, live birth rate; FET, frozen-thawed embryo transfer.

[a]Includes the results of subsequent fresh and frozen-thawed embryo transfers.

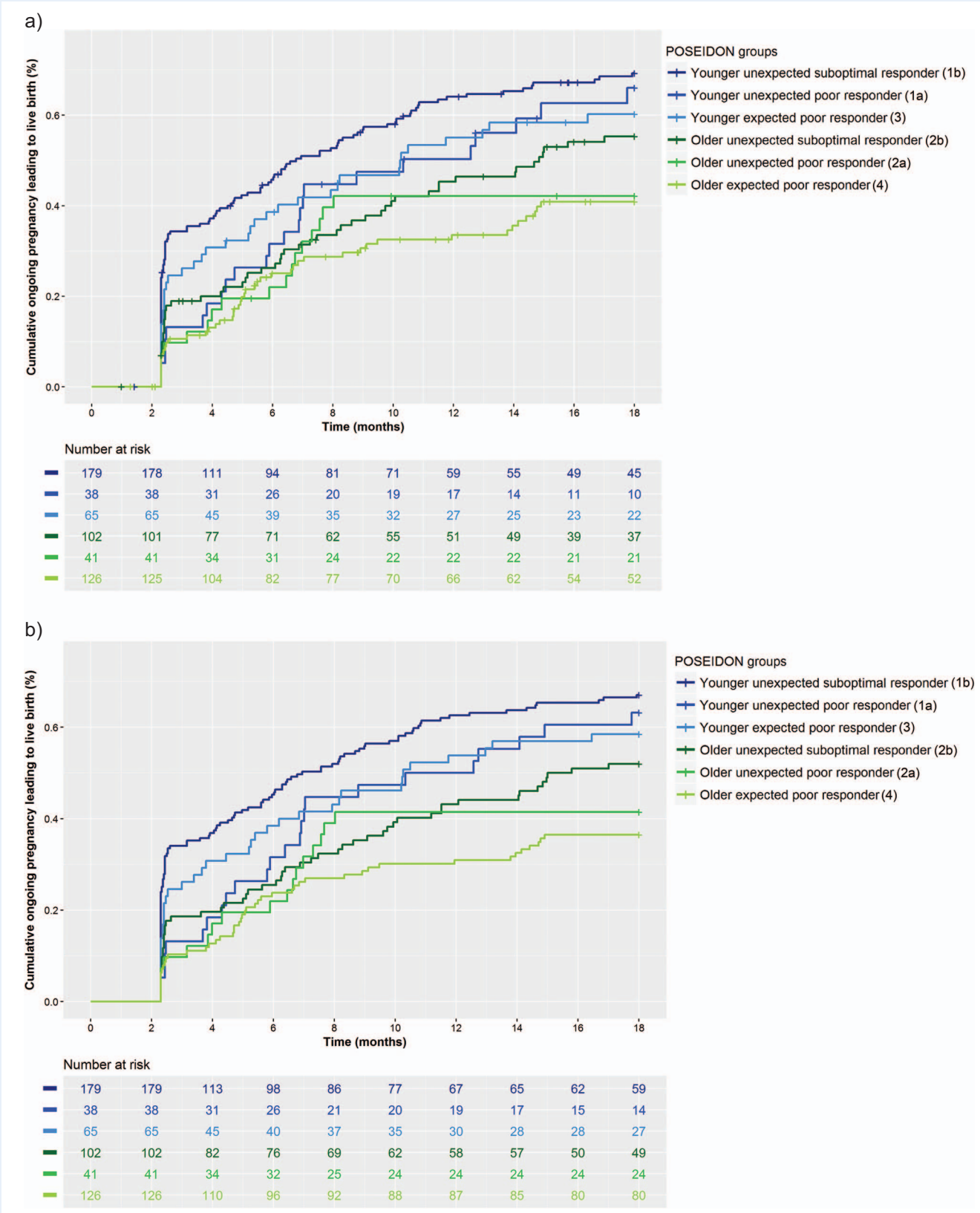

Figure 2 Cumulative live birth curves for low-prognosis women over 18 months of IVF/ICSI treatment. Women were stratified according to the POSEIDON criteria (Poseidon group *et al.*, 2016), and the curves were calculated by using (**a**) the life table analysis (optimistic approach) and (**b**) the competing risk method (conservative approach).

Table IV Pairwise log-rank comparisons of the 'optimistic' and 'conservative' cumulative incidence curves.

	Adjusted *P*-values (Hommel, 1988)				
	Young unexpected poor responder (1a)	**Young unexpected suboptimal responder (1b)**	**Older unexpected poor responder (2a)**	**Older unexpected suboptimal responder (2b)**	**Young expected poor responder (3)**
Optimistic					
Younger unexpected suboptimal responder (1b)	0.824	-	-	-	-
Older unexpected poor responder (2a)	0.504	**0.041***	-	-	-
Older unexpected suboptimal responder (2b)	0.988	0.051	0.860	-	-
Younger expected poor responder (3)	0.988	0.670	0.504	0.985	-
Older expected poor responder (4)	0.160	<**0.001***	0.988	0.448	0.075
Conservative					
Younger unexpected suboptimal responder (1b)	0.810				
Older unexpected poor responder (2a)	0.551	**0.048***			
Older unexpected suboptimal responder (2b)	0.810	**0.034***	0.810		
Younger expected poor responder (3)	0.979	0.720	0.551	0.800	
Older expected poor responder (4)	0.053	<**0.001***	0.979	0.285	**0.022***

*A p-value of < 0.05 is considered to indicate a statistically significant difference in CLBR over 18 months of IVF/ICSI treatment

reveals that ~56% has a live birth after 18 months of IVF/ICSI treatment. A considerable variation is seen between the POSEIDON groups, which is primarily attributable to a woman's age. Younger women had the highest CLBR, without a large impact of the first cycle ovarian response on the prognosis over 18 months. The CLBRs of older women were lower, especially for those with an impaired ovarian reserve, but still exceeded ~39%.

Explanation of findings

These findings are in line with several studies that demonstrated female age to be the main predictor of pregnancy in IVF/ICSI treatment (van Loendersloot *et al.*, 2010; Broer *et al.*, 2013; McLernon *et al.*, 2016). The distinct role of a woman's age on the reproductive capacity is explained by the age-related decline in oocyte quality, which coincides with a progressive decrease in the primordial follicle number (Broekmans *et al.*, 2009; Cimadomo *et al.*, 2018). As a consequence, the number of euploid embryos in IVF/ICSI treatment rapidly decreases after the age of 35 (Franasiak *et al.*, 2014; Demko *et al.*, 2016), which most likely explains the substantially lower CLBR in the older subgroups.

The variation in CLBR between the POSEIDON subgroups was secondarily attributable to the quantitative parameters. This is in line with studies that show that, within specific age categories, lower AMH levels and a reduced ovarian response are associated with a decreased probability of a live birth (Sunkara *et al.*, 2011; Hamdine *et al.*, 2015; Polyzos *et al.*, 2018). Yet, female age had a much more significant impact on the CLBR than the quantitative parameters, which is probably explained by the higher importance of the quality of the oocyte, as opposed to their number, in order to obtain a good quality embryo with a high implantation capacity (Baart *et al.*, 2007; Arce *et al.*, 2014).

Not all low-prognosis women had substantially reduced pregnancy prospects. The 18-month CLBR of the younger unexpected poor and suboptimal responders approached those of normal responders, who are generally considered to have optimal prospects in IVF/ICSI treatment. These findings are comparable to previous studies that evaluated CLBR of unexpected poor responders over multiple cycles (Klinkert *et al.*, 2004; Hendriks *et al.*, 2008; Oudendijk *et al.*, 2012; Moolenaar *et al.*, 2013). Although the pathophysiologic mechanism of the hypo-responsiveness is not fully understood in these younger women (Alviggi *et al.*, 2018), it is unlikely to be related to a reduced oocyte quality (Morin *et al.*, 2018), which probably explains the relatively high CLBR over multiple IVF/ICSI cycles.

As the CLBR is calculated over 18 months of treatment, the success rates over consecutive cycles determine the prognosis of each of the subgroups. Variation exists in the success rates of subsequent treatment cycles between the subgroups, which may be partly related

to differences in the effect of therapeutic adjustments between cycles. Still, the differences in baseline characteristics, including female age and ovarian reserve status, will mainly determine the LBR in the subsequent treatment cycles, as is illustrated by the persisting low LBR in subsequent cycles in older women with an impaired ovarian reserve.

Strengths

This study initiates the essential validation of the POSEIDON criteria and provides valuable information on long-term pregnancy prospects of the proposed groups. In recent years, embryo cryopreservation has become an integral part of IVF/ICSI treatment, and many couples have more than one fresh treatment cycle (Wong et al., 2014; McLernon et al., 2016). Therefore, evaluating CLBR over multiple complete cycles, instead of studying single fresh cycle results, provides a more comprehensive overview of the chance of success over an entire treatment period.

CLBRs are often overestimated due to the use of optimistic analytic approaches (Stolwijk et al., 1996). In this study, both an optimistic and a conservative approach were applied. This assured the robustness of the findings and carefully addressed the issue of treatment discontinuation, which is of particular importance in low-prognosis women.

The prospective design of the OPTIMIST study ensured reliable data collection with relatively low rates of missing values. Multiple imputation was applied to handle missing data, which is considered to be the preferred strategy for 'missings (completely) at random' to prevent biased estimates, to increase precision, and to avoid the waste of resources (Sterne et al., 2009; Janssen et al., 2010).

Limitations

The primary limitation of this study was the relatively small numbers in some of the subgroups, limiting the power to detect statistically significant differences and decreasing the precision of the estimates. Although this hindered the drawing of firm conclusions, our findings still provide the first meaningful indication of the proportion, characteristics, and prognosis of women in the POSEIDON groups.

Second, the majority of blood samples were obtained during downregulation with a GnRH agonist, which may have slightly affected serum AMH levels (Wang et al., 2007; Jayaprakasan et al., 2008; Su et al., 2013). However, as such a change most likely reflects a change in the follicle number and follicle size distribution, the accuracy to predict the ovarian response is unlikely to be compromised, as was confirmed by a previous study (Wang et al., 2007; Cai et al., 2018). In the POSEIDON classification, AMH is used as an ovarian response predictor to categorize women into expected and unexpected poor responders. As AMH maintains its predictive accuracy when measured during downregulation, the AMH values in the current study allowed for a valid and accurate classification of the low-prognosis women, and no large impact on the CLBR of the POSEIDON groups is expected.

Furthermore, all women started with a fixed FSH dose of 150 IU/-day, which may be considered as a low dose for women with an expected poor response. However, as previous studies revealed no beneficial impact of increased FSH doses on CLBR, it is unlikely that a higher starting dose would have altered our findings (van Tilborg et al., 2017b; Lensen et al., 2018). Also, small dose adjustments between cycles were permitted, which could have induced therapeutic differences between the subpopulations. Yet, as such dose adjustments closely reflect current practice, this allows for a greater generalizability of our findings.

Finally, the inclusion of multiple centers in the OPTIMIST study resulted in some between-center variation in treatment protocols among the included women, which may have influenced the success rates of treatment. Yet, as such variation mirrors the actual differences between infertility clinics, this also increases the representability of the results.

Implications

The recently introduced POSEIDON criteria identify low-prognosis women in IVF/ICSI treatment and combine quantitative and qualitative parameters to provide a more detailed stratification into homogenous groups (Poseidon group et al., 2016). This validation study shows the variation in CLBR between the proposed groups and reveals a primary role of female age, reflecting the importance of oocyte quality in the probability of a live birth.

For younger low-prognosis women, who generally have high-quality oocytes, the findings suggest that the quantitative parameters are of limited importance for their pregnancy prospects over multiple treatment cycles. Therefore, the question rises whether these women should be considered to have a low prognosis in clinical practice, especially as the present results suggest that current clinical management achieves relatively high CLBR over 18 months of treatment.

For older low-prognosis women, a higher oocyte yield may be needed to compensate for the decreased oocyte quality. However, the age-related decline is generally accompanied by a decreased size of the primordial follicle pool, which hinders the retrieval of a high number of oocytes (Broekmans et al., 2007). Therapeutic interventions that aim to improve the ovarian response, such as the use of increased doses of gonadotropins or co-treatment with growth hormone, dehydroepiandrosterone, or testosterone, have all failed to improve clinical outcomes in these women (Pandian et al., 2010; Nagels et al., 2015; Lensen et al., 2018). Also, no treatment options are available that target oocyte quality.

Therefore, the medical management of the older low-prognosis women remains particularly difficult and forms a challenge in IVF/ICSI treatment. Until new therapeutic interventions become available for this group, increasing awareness about the age-related decline in reproductive chances is needed to manage expectations and to inform younger women about fertility preservation options such as oocyte cryopreservation.

Conclusion

In conclusion, the CLBR of low-prognosis women is on average ~56% over 18 months of IVF/ICSI treatment, and varies considerably between the POSEIDON groups. The variation is primarily determined by female age, which reflects the importance of oocyte quality. In the younger groups, relatively high CLBRs are reached over 18 months of treatment, despite reduced quantitative parameters.

In the older groups, the CLBRs are substantially lower, and as no effective interventions exist to counteract the reduced oocyte quality, expectations should be managed before initiating treatment.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

T.C.v.T., H.L.T., B.W.J.M., and F.J.M.B. coordinated the OPTIMIST study. T.C.v.T., S.C.O., R.J.T.G., A.H., C.B.L., J.P.B., K.F., M.H.M., W.K.H.K., J.S.E.L., and all other members from the OPTIMIST study group collected the data. J.A.L., T.C.v.T., S.C.O., F.J.M.B., B.W.J.M., and H.L.T. were involved in study conception and study design. J.A.L. and M.J.C.E. performed the statistical analysis. J.A.L. drafted the manuscript. J.A.L., M.J.C.E., T.C.v.T., F.J.M.B., B.W.M., and H.L.T. interpreted the data. All authors participated to the discussion of the findings and revised the manuscript.

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Conflict of interest

J.A.L. is supported by a Research Fellowship grant and received an unrestricted personal grant from Merck BV. S.C.O., T.C.v.T., and H.LT. received an unrestricted personal grant from Merck BV. C.B.L. received research grants from Merck, Ferring and Guerbet. K.F. received unrestricted research grants from Merck Serono, Ferring, and GoodLife. She also received fees for lectures and consultancy from Ferring and GoodLife. A.H. declares that the Department of Obstetrics and Gynaecology, University Medical Centre Groningen received an unrestricted research grant from Ferring Pharmaceuticals BV, the Netherlands. J.S.E.L. has received unrestricted research grants from Ferring, Zon-MW, and The Dutch Heart Association. He also received travel grants and consultancy fees from Danone, Euroscreen, Ferring, AnshLabs, and Titus Healthcare. B.W.J.M. is supported by an NHMRC Practitioner Fellowship (GNT1082548) and reports consultancy work for ObsEva, Merck, and Guerbet. He also received a research grant from Merck BV and travel support from Guerbet. F.J.M.B. received monetary compensation as a member of the external advisory board for Merck Serono (the Netherlands) and Ferring Pharmaceutics BV (the Netherlands) for advisory work for Gedeon Richter (Belgium) and Roche Diagnostics on automated AMH assay development, and for a research cooperation with Ansh Labs (USA). All other authors have nothing to declare.

Appendix

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References

Alviggi C, Conforti A, Esteves SC, Vallone R, Venturella R, Staiano S, Castaldo E, Andersen CY, De PG. Understanding ovarian hyporesponse to exogenous gonadotropin in ovarian stimulation and its new proposed marker—the follicle-to-oocyte (FOI) index. *Front Endocrinol (Lausanne)* 2018;**9**:589.

Arce J-C, Nyboe Andersen A, Fernández-Sánchez M, Visnova H, Bosch E, García-Velasco JA, Barri P, de Sutter P, Klein BM, Faucer BCJM. Ovarian response to recombinant human follicle-stimulating hormone: a randomized, antimüllerian hormone-stratified, dose-response trial in women undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertil Steril* 2014;**102**:1633–1640.e5.

Baart EB, Martini E, Eijkemans MJ, Van Opstal D, Beckers NGM, Verhoeff A, Macklon NS, Fauser BCJM. Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. *Hum Reprod* 2007;**22**:980–988. Oxford University Press.

Broekmans FJ, Knauff EAH, te Velde ER, Macklon NS, Fauser BC. Female reproductive ageing: current knowledge and future trends. *Trends Endocrinol Metab* 2007;**18**:58–65.

Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. *Endocr Rev* 2009;**30**:465–493.

Broer SL, van Disseldorp J, Broeze KA, Dolleman M, Opmeer BC, Bossuyt P, Eijkemans MJC, Mol B-WJ, Broekmans FJM, Broer SL *et al*. Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach. *Hum Reprod Update* 2013;**19**:26–36.

Busnelli A, Papaleo E, Del Prato D, La Vecchia I, Iachini E, Paffoni A, Candiani M, Somigliana E. A retrospective evaluation of prognosis and cost-effectiveness of IVF in poor responders according to the Bologna criteria. *Hum Reprod* 2015;**30**:315–322.

van Buuren S, Groothuis-Oudshoorn K. MICE: Multivariate Imputation by Chained Equations in R. *J Stat Softw* 2011;**45**:1–67.

Cai J, Liu L, Zheng J, Zhang L, Jiang X, Li P, Sha A, Ren J. Differential response of AMH to GnRH agonist among individuals: the effect on ovarian stimulation outcomes. *J Assist Reprod Genet* 2018;**35**:467–473.

Cimadomo D, Fabozzi G, Vaiarelli A, Ubaldi N, Ubaldi FM, Rienzi L. Impact of maternal age on oocyte and embryo competence. *Front Endocrinol (Lausanne)* 2018;**9**:327.

Demko ZP, Simon AL, McCoy RC, Petrov DA, Rabinowitz M. Effects of maternal age on euploidy rates in a large cohort of embryos analyzed with 24-chromosome single-nucleotide polymorphism-based preimplantation genetic screening. *Fertil Steril* 2016;**105**:1307–1313.

Ferraretti AP, Gianaroli L. The Bologna criteria for the definition of poor ovarian responders: is there a need for revision? *Hum Reprod* 2014;**29**:1842–1845.

Ferraretti AP, La Marca A, Fauser BCJM, Tarlatzis B, Nargund G, Gianaroli L, ESHRE Working Group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Hum Reprod* 2011;**26**:1616–1624.

Fleming R, Seifer DB, Frattarelli JL, Ruman J. Assessing ovarian response: antral follicle count versus anti-Müllerian hormone. *Reprod Biomed Online* 2015;**31**:486–496.

Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, Scott RT. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. *Fertil Steril* 2014;**101**:656–663.e1.

Gassner D, Jung R. First fully automated immunoassay for anti-Müllerian hormone. *Clin Chem Lab Med* 2014;**52**:1143–1152.

Hamdine O, Eijkemans MJC, Lentjes EGW, Torrance HL, Macklon NS, Fauser BCJM, Broekmans FJ. Antimüllerian hormone: prediction of cumulative live birth in gonadotropin-releasing hormone antagonist treatment for in vitro fertilization. *Fertil Steril* 2015;**104**:891–898.e2.

Hendriks DJ, te Velde ER, Looman CWN, Bancsi LFJMM, Broekmans FJM. Expected poor ovarian response in predicting cumulative pregnancy rates: a powerful tool. *Reprod Biomed Online* 2008;**17**:727–736.

Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika* 1988;**75**:383–386. Oxford University Press.

Humaidan P, Alviggi C, Fischer R, Esteves SC. The novel POSEIDON stratification of 'low prognosis patients in assisted reproductive technology' and its proposed marker of successful outcome. *F1000Res* 2016;**5**:2911.

Iliodromiti S, Nelson SM. Ovarian response biomarkers. *Curr Opin Obstet Gynecol* 2015;**27**:182–186.

Janssen KJM, Donders ART, Harrell FE, Vergouwe Y, Chen Q, Grobbee DE, Moons KGM. Missing covariate data in medical research: to impute is better than to ignore. *J Clin Epidemiol* 2010;**63**:721–727. Elsevier.

Jayaprakasan K, Campbell BK, Hopkisson JF, Clewes JS, Johnson IR, Raine-Fenning NJ. Effect of pituitary desensitization on the early growing follicular cohort estimated using anti-Mullerian hormone. *Hum Reprod* 2008;**23**:2577–2583.

Klinkert ER, Broekmans FJ, Looman 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**:1247–1253.

Lensen SF, Wilkinson J, Leijdekkers JA, La Marca A, Mol BWJ, Marjoribanks J, Torrance H, Broekmans FJ. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI). *Cochrane Database Syst Rev* 2018;**2**:CD012693.

van Loendersloot LL, van Wely M, Limpens J, Bossuyt PM, Repping S, van der Veen F. Predictive factors in in vitro fertilization (IVF): a systematic review and meta-analysis. *Hum Reprod Update* 2010;**16**:577–589. Oxford University Press.

McLernon DJ, Steyerberg EW, te Velde ER, Lee AJ, Bhattacharya S. Predicting the chances of a live birth after one or more complete cycles of in vitro fertilisation: population based study of linked cycle data from 113 873 women. *BMJ* 2016;**355**:i5735.

Moolenaar LM, Mohiuddin S, Munro Davie M, Merrilees MA, Broekmans FJM, Mol BWJ, Johnson NP. High live birth rate in the subsequent IVF cycle after first-cycle poor response among women with mean age 35 and normal FSH. *Reprod Biomed Online* 2013;**27**:362–366.

Morin SJ, Patounakis G, Juneau CR, Neal SA, Scott RT, Seli E. Diminished ovarian reserve and poor response to stimulation in patients <38 years old: a quantitative but not qualitative reduction in performance. *Hum Reprod* 2018;**33**:1489–1498.

Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. *Cochrane Database Syst Rev* 2015;**11**:CD009749 available at http://www.ncbi.nlm.nih.gov/pubmed/26608695.

Nelson SM, Klein BM, Arce J-C. Comparison of antimüllerian hormone levels and antral follicle count as predictor of ovarian response to controlled ovarian stimulation in good-prognosis patients at individual fertility clinics in two multicenter trials. *Fertil Steril* 2015a;**103**:923–930.e1.

Nelson SM, Pastuszek E, Kloss G, Malinowska I, Liss J, Lukaszuk A, Plociennik L, Lukaszuk K. Two new automated, compared with two enzyme-linked immunosorbent, antimüllerian hormone assays. *Fertil Steril* 2015b;**104**:1016–1021.e6.

Olivius C, Friden B, Borg G, Bergh C. Why do couples discontinue in vitro fertilization treatment? A cohort study. *Fertil Steril* 2004;**81**:258–261.

Oudendijk JF, Yarde F, Eijkemans MJC, Broekmans FJM, Broer SL. The poor responder in IVF: is the prognosis always poor? A systematic review. *Hum Reprod Update* 2012;**18**:1–11.

Pandian Z, McTavish AR, Aucott L, Hamilton MP, Bhattacharya S. Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF). *Cochrane Database Syst Rev* 2010;**1**:CD004379.

Papathanasiou A. Implementing the ESHRE 'poor responder' criteria in research studies: methodological implications. *Hum Reprod* 2014;**29**:1835–1838.

Polyzos NP, Drakopoulos P, Parra J, Pellicer A, Santos-Ribeiro S, Tournaye H, Bosch E, Garcia-Velasco J. Cumulative live birth rates according to the number of oocytes retrieved after the first ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection:

a multicenter multinational analysis including ~15,000 women. *Fertil Steril* 2018;**110**:661–670.e1.

Poseidon group, Alviggi C, Andersen C, Buehler K, Conforti A, De Placido G, Esteves SC, Fischer R, Galliano D, Polyzos N, *et al.* A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept. *Fertil Steril* 2016;**105**:1452–1453.

Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;**338**:b2393.

Stolwijk AM, Hamilton CJ, Hollanders JM, Bastiaans LA, Zielhuis GA. A more realistic approach to the cumulative pregnancy rate after in-vitro fertilization. *Hum Reprod* 1996;**11**:660–663.

Su HI, Maas K, Sluss PM, Chang RJ, Hall JE, Joffe H. The impact of depot GnRH agonist on AMH levels in healthy reproductive-aged women. *J Clin Endocrinol Metab* 2013;**98**:E1961–E1966.

Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. *Hum Reprod* 2011;**26**:1768–1774.

van Tilborg TC, Eijkemans MJ, Laven JS, Koks CA, de Bruin JP, Scheffer GJ, van Golde RJ, Fleischer K, Hoek A, Nap AW, *et al.* The OPTIMIST study: optimisation of cost effectiveness through individualised FSH stimulation dosages for IVF treatment. A randomised controlled trial. *BMC Womens Health* 2012;**12**:29.

van Tilborg TC, Oudshoorn SC, Eijkemans MJC, Mochtar MH, van Golde RJT, Hoek A, Kuchenbecker WKH, Fleischer K, de Bruin JP, Groen H *et al.* Individualized FSH dosing based on ovarian reserve testing in women starting IVF/ICSI: a multicentre trial and cost-effectiveness analysis. *Hum Reprod* 2017a;**32**:2485–2495.

van Tilborg TC, Torrance HL, Oudshoorn SC, Eijkemans MJC, Koks CAM, Verhoeve HR, Nap AW, Scheffer GJ, Manger AP, Schoot BC *et al.* Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 1: the predicted poor responder. *Hum Reprod* 2017b;**32**:2496–2505.

Wang JG, Nakhuda GS, Guarnaccia MM, Sauer MV, Lobo RA. Müllerian inhibiting substance and disrupted folliculogenesis in polycystic ovary syndrome. *Am J Obstet Gynecol* 2007;**196**:77.e1–5.

Wong KM, Mastenbroek S, Repping S. Cryopreservation of human embryos and its contribution to in vitro fertilization success rates. *Fertil Steril* 2014;**102**:19–26.

Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X, Wang S. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. *Reprod Biol Endocrinol* 2018;**16**:29.