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.
**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 their study population (Xu *et al.*, 2018), the actual prognosis of low-prognosis women has not yet been properly investigated. Such information could help to validate the new POSEIDON concept and provide 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 cycles per woman within 18 months of follow-up.

**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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**Trial Registration Number**: Not applicable.

**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
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 substanti-
POSEIDON criteria and cumulative live birth rates

POSEIDON criteria and cumulative live birth rates

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. Hyper response, >15 retrieved oocytes or cycle cancellation for too many follicles according to the POSEIDON criteria. Normal response, 10–15 retrieved oocytes according to the POSEIDON criteria. Poor response, <4 retrieved oocytes or cycle cancellation for insufficient follicular growth according to the POSEIDON criteria. Suboptimal response, 4–9 retrieved oocytes according to the POSEIDON criteria. AMH, anti-Müllerian hormone.

significant 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

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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>
<thead>
<tr>
<th>Table II Baseline and treatment characteristics of low-prognosis women stratified according to the POSEIDON criteria (Poseidon group et al., 2016).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POSEIDON 1</strong>&lt;br&gt;Subgroup 1a; younger unexpected poor responder</td>
</tr>
<tr>
<td>All low-prognosis women (n = 551)</td>
</tr>
<tr>
<td>Female age (years)</td>
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<tr>
<td>Infertility duration (years)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
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<tr>
<td>Smoking (yes/no)</td>
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<tr>
<td>Primary infertility</td>
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<tr>
<td>Cause of infertility</td>
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<tr>
<td>Unexplained</td>
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<tr>
<td>Tubal factor</td>
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<tr>
<td>Endometriosis</td>
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<tr>
<td>Male factor</td>
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<tr>
<td>AFC, median (IQR)</td>
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<td>AMH, median (IQR)</td>
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</table>

Baseline characteristics

<table>
<thead>
<tr>
<th>Treatment characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICSI</td>
</tr>
<tr>
<td>GnRH agonist</td>
</tr>
<tr>
<td>No. of fresh cycles/woman</td>
</tr>
<tr>
<td>No. of FET cycles/woman</td>
</tr>
<tr>
<td>First cycle cancellation</td>
</tr>
<tr>
<td>FSH dose increased between cycle 1 and 2</td>
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<tr>
<td>Amount of increase (IU/L)</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th></th>
<th>POSEIDON 1</th>
<th></th>
<th>POSEIDON 2</th>
<th></th>
<th>POSEIDON 3</th>
<th></th>
<th>POSEIDON 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All low-prognosis women (n = 551)</td>
<td>Subgroup 1a; younger unexpected poor responder (n = 38)</td>
<td>Subgroup 1b; younger unexpected suboptimal responder (n = 179)</td>
<td>Subgroup 2a; older unexpected poor responder (n = 41)</td>
<td>Subgroup 2b; older unexpected suboptimal responder (n = 102)</td>
<td>Younger expected poor responder (n = 65)</td>
<td>Older expected poor responder (n = 126)</td>
</tr>
<tr>
<td><strong>CLBR over 18 months</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Optimistic (95%CI)</td>
<td>0.57 (0.53–0.61)</td>
<td>0.66 (0.46–0.79)</td>
<td>0.69 (0.61–0.76)</td>
<td>0.42 (0.25–0.56)</td>
<td>0.55 (0.44–0.64)</td>
<td>0.60 (0.46–0.71)</td>
<td>0.41 (0.31–0.49)</td>
</tr>
<tr>
<td>Conservative (95% CI)</td>
<td>0.54 (0.50–0.58)</td>
<td>0.63 (0.44–0.76)</td>
<td>0.67 (0.59–0.73)</td>
<td>0.41 (0.24–0.55)</td>
<td>0.52 (0.41–0.64)</td>
<td>0.58 (0.45–0.69)</td>
<td>0.37 (0.28–0.44)</td>
</tr>
<tr>
<td><strong>LBR per cycle</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cycle 1</td>
<td>154/551 (28)</td>
<td>8/38 (21)</td>
<td>77/179 (43)</td>
<td>4/41 (10)</td>
<td>25/102 (25)</td>
<td>19/65 (29)</td>
<td>21/126 (17)</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>95/351 (27)</td>
<td>7/27 (26)</td>
<td>31/94 (33)</td>
<td>9/34 (26)</td>
<td>19/63 (30)</td>
<td>14/42 (33)</td>
<td>15/91 (16)</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>5/41 (12)</td>
<td>1/1 (100)</td>
<td>1/8 (13)</td>
<td>1/7 (14)</td>
<td>0/4 (0)</td>
<td>1/4 (25)</td>
<td>1/17 (6)</td>
</tr>
<tr>
<td>Cycle 5</td>
<td>0/7 (0)</td>
<td>0/0</td>
<td>0/0</td>
<td>0/2 (0)</td>
<td>0/0</td>
<td>0/0</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>Cycle 6</td>
<td>0/2 (0)</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td><strong>LBR per</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Started stimulation</td>
<td>298/1128 (26)</td>
<td>24/80 (30)</td>
<td>120/318 (38)</td>
<td>17/104 (16)</td>
<td>53/200 (27)</td>
<td>38/131 (29)</td>
<td>46/295 (16)</td>
</tr>
<tr>
<td>Oocyte retrieval</td>
<td>298/955 (31)</td>
<td>24/61 (39)</td>
<td>120/310 (39)</td>
<td>17/74 (23)</td>
<td>53/191 (28)</td>
<td>38/106 (36)</td>
<td>46/213 (22)</td>
</tr>
<tr>
<td>Embryo transfer</td>
<td>298/1185 (25)</td>
<td>24/61 (39)</td>
<td>120/408 (29)</td>
<td>17/86 (20)</td>
<td>53/286 (19)</td>
<td>38/124 (31)</td>
<td>46/220 (21)</td>
</tr>
<tr>
<td><strong>Conception mode</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVF/ICSI Fresh</td>
<td>236 (79)</td>
<td>22 (92)</td>
<td>96/80 (60)</td>
<td>13 (76)</td>
<td>39 (74)</td>
<td>34 (89)</td>
<td>32 (70)</td>
</tr>
<tr>
<td>IVF/ICSI FET</td>
<td>38 (13)</td>
<td>0 (0)</td>
<td>22 (18)</td>
<td>3 (18)</td>
<td>8 (15)</td>
<td>1 (3)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>21 (7)</td>
<td>1 (4)</td>
<td>2 (2)</td>
<td>1 (6)</td>
<td>6 (11)</td>
<td>3 (8)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

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

*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).
POSEIDON criteria and cumulative live birth rates

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

<table>
<thead>
<tr>
<th></th>
<th>Optimistic</th>
<th>Conservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger unexpected suboptimal responder (1b)</td>
<td>0.824</td>
<td>0.810</td>
</tr>
<tr>
<td>Older unexpected poor responder (2a)</td>
<td>0.504</td>
<td>0.551</td>
</tr>
<tr>
<td>Older unexpected suboptimal responder (2b)</td>
<td>0.988</td>
<td>0.810</td>
</tr>
<tr>
<td>Younger unexpected suboptimal responder (1b)</td>
<td>&lt;0.001*</td>
<td>0.053</td>
</tr>
<tr>
<td>Older unexpected poor responder (2a)</td>
<td>0.448</td>
<td>0.160</td>
</tr>
<tr>
<td>Older unexpected suboptimal responder (2b)</td>
<td>0.075</td>
<td>0.988</td>
</tr>
</tbody>
</table>

* 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 arises 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

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Conflict of interest
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Appendix


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