human reproduction   **DEBATE**

Individualized ovarian stimulation in IVF/ICSI treatment: it is time to stop using high FSH doses in predicted low responders

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ABSTRACT: In IVF/ICSI treatment, the FSH starting dose is often increased in predicted low responders from the belief that it improves the chance of having a baby by maximizing the number of retrieved oocytes. This intervention has been evaluated in several randomized controlled trials, and despite a slight increase in the number of oocytes—on average one to two more oocytes in the high versus standard dose group—no beneficial impact on the probability of a live birth has been demonstrated (risk difference, −0.02; 95% CI, −0.11 to 0.06). Still, many clinicians and researchers maintain a highly ingrained belief in 'the more oocytes, the better'. This is mainly based on cross-sectional studies, where the positive correlation between the number of retrieved oocytes and the probability of a live birth is interpreted as a direct causal relation. If the latter would be present, indeed, maximizing the oocyte number would benefit our patients. The current paper argues that the use of high FSH doses may not actually improve the probability of a live birth for predicted low responders undergoing IVF/ICSI treatment and exemplifies the flaws of directly using cross-sectional data to guide FSH dosing in clinical practice. Also, difficulties in the de-implementation of the increased FSH dosing strategy are discussed, which include the prioritization of intermediate outcomes (such as cycle cancellations) and the potential biases in the interpretation of study findings (such as confirmation or rescue bias).

Key words: FSH dosing / predicted low responder / oocyte number / live birth / IVF/ICSI

Introduction

As part of IVF/ICSI treatment, exogenous FSH is used for ovarian stimulation in order to obtain oocytes and good-quality embryos for transfer (Macklon et al., 2006). A large inter- and intra-individual variation exists in the ovarian response to stimulation (Rustamov et al., 2017), and a considerable proportion (6–35%) of the women produce a low response (Oudendijk et al., 2012). This has been associated with reduced live birth rates (LBRs) in single-cycle, retrospective studies (Sunkara et al., 2011; Drakopoulos et al., 2016; Polyzos et al., 2018), although studies that have analysed multiple cycles suggest that not every low responder has reduced pregnancy prospects (Hendriks et al., 2008; Oudendijk et al., 2012; Moolenaar et al., 2013; Leijdekkers et al., 2019).

Individualized FSH dosing strategies have been proposed to decrease the variability in the ovarian response, with the objective to improve the effectiveness of IVF/ICSI treatment (Popovic-Todorovic et al., 2003b; Howles et al., 2006; La Marca et al., 2012; Yovich et al., 2012; Arce et al., 2013; Lan et al., 2013; Magnusson et al., 2017). These strategies rely on the putative dose–response relationship between the FSH dose and the ovarian response (Arce et al., 2014) and use biomarkers of the follicle cohort size to predict the response to stimulation (Broer et al., 2013a,b). Guided by these predictions, the FSH starting dose is often substantially increased in women with a predicted low response.

Currently, consensus about the beneficial effects of such a dosing strategy does not exist, due to differences in the interpretation of the published scientific evidence. This paper addresses the main issues
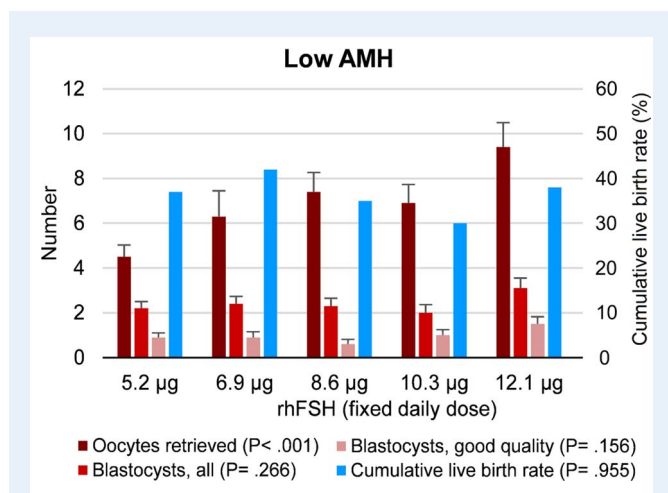
Figure 1 The effect of increased FSH doses (follitropin delta) on the number of oocytes, number of embryos and cumulative live birth rates in women with a predicted low response (AMH levels of 0.7–2.1 ng/mL). Adapted with permission from Arce et al. (2014). AMH, anti-Müllerian hormone; rhFSH, recombinant human FSH.

regarding the use of high FSH doses in predicted low responders and challenges the clinical value of this strategy in IVF/ICSI treatment.

The origin of FSH dose individualization in the predicted low responder

The ovarian response to stimulation relies mostly on the number of antral follicles present in the ovaries and potentially responsive to FSH (Macklon et al., 2006). This number declines with advancing female age, but a large variation exists between women of similar age (Broekmans et al., 2007). Using the antral follicle count (AFC) and serum anti-Müllerian hormone (AMH) levels, women with a reduced number of antral follicles can be identified with reasonable accuracy (Broer et al., 2013a). These so-called predicted low responders carry a substantial risk of a low response to ovarian stimulation, defined as the retrieval of less than four oocytes (Ferraretti and Gianaroli, 2014; Poseidon Group et al., 2016).

In several large cross-sectional studies, women with a low number of retrieved oocytes in response to a standard range of FSH dose were observed to have a lower LBR than women with a higher number of oocytes (Sunkara et al., 2011; Drakopoulos et al., 2016; Polyzos et al., 2018). Based on this observed correlation, a common assumption has gained ground that the probability of a live birth can be improved for the individual low responder by increasing the ovarian response to stimulation. Dose–response trials have indicated that the oocyte yield may be increased by using higher FSH doses (Fig. 1) (Sterrenburg et al., 2011; Arce et al., 2014), so that, in daily practice, predicted low responders are treated with doses far above the standard FSH dose of 150 IU/day (from 225 to 600 IU/day) in order to maximize the number of retrieved oocytes.

Still, the previously mentioned cross-sectional studies provide no information on whether such high FSH doses actually improve the chance of a live birth for the individual low responder. The observations only correlate the number of oocytes to the chance of a live birth but fail to inform on the effectiveness of interventions that alter the ovarian response. The fact that women with a higher number of oocytes have better pregnancy prospects does not automatically imply that the ovarian response is a 'key modifiable determinant' for the chance of a live birth in IVF/ICSI treatment. Factors related to both the ovarian response and the chance of a live birth, such as female age, may have a much more prominent role and are unaffected by FSH dosing. Therefore, even though a high FSH dose may effectively increase the oocyte yield, this may not translate into a similar positive effect on the LBR.

To answer the question of whether increasing the oocyte yield by using high FSH doses will actually lead to improved pregnancy chances, an interventional study design is required in which predicted low responders are randomly allocated to a high versus a standard FSH dose.

Comparative studies of FSH dosing in predicted low responders

Several randomized controlled trials (RCTs) have been performed on the effectiveness of FSH dose individualization. These RCTs can be categorized into two types: (i) trials that compare different FSH doses in a defined patient category (direct dose comparison studies) and (ii) trials that compare the use of an individualized FSH dosing algorithm to a standard dosing strategy (dosing algorithm studies). Both study types were recently summarized in an extensive systematic review (Lensen et al., 2018).

Direct dose comparison studies

In predicted low responders, eight RCTs directly compared a higher versus a lower FSH dose (see Table I) (Harrison et al., 2001; Klinkert et al., 2005; Berkkanoglu and Ozgur, 2010; Arce et al., 2014; Lefebvre et al., 2015; Bastu et al., 2016; Youssef et al., 2016; van Tilborg et al., 2017b). Only one of these trials was primarily powered to detect differences in cumulative LBR, including the results of both fresh and frozen embryo transfers (FET), for women with a predicted low (AFC 0–7) and suboptimal (AFC 8–10) response (van Tilborg et al., 2017b). This trial revealed no significant differences in cumulative LBR between the higher FSH dose (225 or 450 IU/day for predicted suboptimal and low responders, respectively) versus the standard FSH dose (150 IU/day) over 18 months of IVF/ICSI treatment (risk difference (RD), −0.02; 95% CI, −0.11 to 0.06). Moreover, the cost-effectiveness analysis revealed that the higher FSH dose increases the costs of treatment with a mean difference of €1099 per woman (95% CI, €562–€1591).

In this particular trial, small dose increments between cycles (maximum, 50 IU/day) were permitted if a woman had a poor response in the standard dose arm (van Tilborg et al., 2012). This occurred in 64% of the women between the first and second cycle, with a median increment of 50 IU/day (interquartile range, 50–50). Therefore, the

Table I Dose comparison studies in predicted low responders in IVF/ICSI treatment.

Publication	Definition low responder	Pregnancy outcome measure	Higher dose, n (%)	Lower dose, n (%)	RR (95% CI)
			225 or 450 IU	**150 IU**	
van Tilborg et al., 2017b	AFC ≤ 10	CLBR over 18 months (fresh + FET)	106/250 (42.4)	117/261 (44.8)	0.95 (0.78–1.15)
		First-cycle LBR (fresh + FET)	44/250 (17.6)	52/261 (19.9)	0.88 (0.62–1.27)
		First cycle LBR (fresh)	37/250 (14.8)	41/261 (15.7)	0.94 (0.63–1.42)
			300 IU	**150 IU**	
Klinkert et al., 2005	AFC ≤ 4	First cycle OPR (fresh)	1/26 (3.8)	2/26 (7.7)	0.50 (0.05–5.18)
			450 IU	**150 IU**	
Youssef et al., 2018*	Female age ≥ 35, or bFSH > 10 IU/L, or AFC ≤ 4, or Previous poor response[a]	First cycle OPR (fresh)	27/199 (13.6)	25/195 (12.5)	1.06 (0.64–1.76)
			400 IU	**300 IU**	
Harrison et al., 2001	bFSH > 8.5 IU/L	First-cycle CPR (fresh)	2/24 (8.3)	2/24 (8.3)	1.00 (0.15–6.53)
			450 IU	**300 IU**	
Bastu et al., 2016	ESHRE Bologna criteria (Ferraretti et al., 2011)	First cycle OPR (fresh)	4/31 (12.9)	5/31 (16.1)	0.80 (0.24–2.70)
			450 IU	**300 IU**	
Berkkanoglu and Ozgur, 2010**	AFC ≤ 11	First cycle LBR (fresh)	3/39 (7.7)	4/38 (10.5)	0.73(0.18–3.05)
			600 IU		
			4/42 (9.5)		0.90 (0.24–3.36)
			600 IU	**450 IU**	
Lefebvre et al.,2015	bFSH > 10 IU/L, or AMH < 1.0 ng/mL, or AFC ≤ 8, or Previous poor response[b]	First cycle LBR (fresh)	25/180 (13.8)	19/176 (10.8)	1.29 (0.74–2.25)
			6.9ug	**5.2 ug**	
Arce et al., 2014***	0.7–2.1 ng/mL	First cycle LBR (fresh + FET)	8/19 (42.1)	7/19 (36.8)	1.14 (0.52–2.52)
		First cycle LBR (fresh)	6/19 (31.6)	6/19 (31.6)	1.00 (0.39–2.55)
			8.6 ug		
			7/20 (35.0)		0.95 (0.41–2.20)
			7/20 (35.0)		1.10 (0.45–2.70)
			10.3 ug		
			6/20 (0.30		0.81 (0.33–1.99)
			5/20 (25.0)		0.79 (0.29–2.17)
			12.1 ug		
			8/21 (38.1)		1.03 (0.46–2.31)
			6/21 (28.6)		0.90 (0.35–2.33)

RR, relative risk; AFC, antral follicle count; CLBR, cumulative live birth rate; LBR, live birth rate; FET, frozen embryo transfer; OPR, ongoing pregnancy rate; bFSH, basal FSH; CPR, clinical pregnancy rate; AMH, anti-Müllerian hormone.

*This study compared 450-IU HMG in a GnRH agonist protocol to 150-IU FSH in a GnRH antagonist protocol.

**This study quasi-randomized patients according to the last number of their patient number.

***This five-arm study reported dosages of a new recombinant human FSH (follitropin delta, FE 999049) in micrograms, which cannot be directly translated into IU.

[a]Defined as ≤5 retrieved oocytes.

[b]Defined as <5 oocytes, <8 follicles or cycle cancellation on an FSH dose of ≥300 IU/day.

first complete cycle results may reflect the difference between the standard dose and the increased FSH dose the most clearly. This first cycle analysis, including the results of both fresh and FET cycles, revealed no significant difference in LBR (RD, −0.02; 95% CI, −0.08 to 0.05). Additionally, analysis of only the predicted low responders (AFC 0–7) revealed no significant differences in cumulative LBR over 18 months (RD, −0.06; 95% CI, −0.18 to 0.06). The first complete cycle analysis in this particular group, including the results of fresh and FET cycles, resulted in similar findings (RD, −0.03; 95% CI, −0.08 to 0.08).

None of the seven other direct dose comparison RCTs revealed a significant difference in pregnancy rates when using high FSH doses (Table I). Nonetheless, due to the small study samples, point estimates were imprecise and differences in either direction could not be ruled out based on these data. Unfortunately, all studies differed markedly with regard to their study population and FSH dose comparison, which hindered pooling of the results to increase precision. Still, although acknowledging the limitations of the studies, these RCTs provide the best scientific evidence to date, and none

of them support the use of high FSH doses in predicted low responders.

Dosing algorithm studies

In addition to the seven dose comparison RCTs, five dosing algorithm studies compared an individualized dosing strategy to a standard dose (Popovic-Todorovic et al., 2003a; Olivennes et al., 2015; Allegra et al., 2017; Nyboe Andersen et al., 2017; van Tilborg et al., 2017a). Only one small trial, which included mostly women with a good prognosis, revealed an increase in the ongoing pregnancy rate (relative risk, 1.50; 95% CI, 1.03–2.18) (Popovic-Todorovic et al., 2003a). Taken together in a meta-analysis, the trials demonstrated a pooled odds ratio of 1.04 (95% CI, 0.88–1.23) for a fresh cycle live birth (Lensen et al., 2018). However, in contrast to the dose comparison studies, dosing algorithm studies do not focus on the predicted low responders in particular but merely on the IVF/ICSI population as a whole. Therefore, as both higher and lower FSH doses are used in these trials, depending on the specific algorithm that is used, conclusions regarding the effectiveness of high FSH doses for predicted low responders cannot be drawn.

Statistical power of comparative studies

As none of the RCTs have shown an improvement in LBR after an increased FSH dose (Table I), the question arises as to whether we can now conclude that high FSH doses actually have no beneficial impact for predicted low responders. To answer this question, the issue of statistical significance needs to be addressed first. Commonly, *P* values are used as an arbitrary threshold of significance, and scientific conclusions are often based on whether effects are found to be statistically significant or not (Amrhein et al., 2019). However, the lack of statistical significance, as usually indicated by a *P* value > 0.05 or a CI that includes zero, does not necessarily mean that an effect is absent (Wasserstein et al., 2019). Therefore, instead of looking at statistical significance as a dichotomizing measure, the uncertainty and variation in study findings need to be better highlighted by a more detailed description of the point estimates and CIs (Amrhein et al., 2019).

When considering the data of the previously mentioned trial (van Tilborg et al., 2017b), the point estimate suggests a decrease in cumulative LBR of 2 percentage points with the high FSH dose (cumulative LBR of 44.8% vs 42.4%). Nonetheless, the 95% CI indicates that the high FSH dose may also result in a decrease in LBR of 11 percentage points or an increase of 6 percentage points. Therefore, in order to claim that the results show no important differences between the higher dose and the standard dose, all values inside this particular interval must be deemed as practically unimportant. Since such a claim is highly prone to contradicting clinical opinions, no uniform conclusions can be expected and an even larger trial may be needed to increase the precision of the point estimate.

Yet, at this moment, there is no proper evidence to justify the use of high FSH doses in predicted low responders. The findings of the largest dose comparison RCT even suggest a potential decrease in LBR when using a higher FSH dose (Table I). Moreover, it increases the costs of treatment (van Tilborg et al., 2017b). Therefore, as the use of high FSH doses could potentially harm women undergoing IVF/ICSI treatment, the standard FSH dose of 150 IU/day should be considered as the dominant strategy for predicted low responders.

The more oocytes, the better?

In predicted low responders, a high FSH dosage may increase the number of retrieved oocytes by, on average, one to two more oocytes and substantially reduces the rate of cycle cancellations for insufficient follicular growth (Youssef et al., 2016; van Tilborg et al., 2017b). Yet, as summarized in the previous paragraph, the randomized comparisons between a higher FSH dose and a standard FSH dose suggest that the increase in oocyte number and reduction in cycle cancellation rate do not actually improve the (cumulative) probability of a live birth. These findings may urge clinicians to refrain from cycle cancellations as a repeat cycle with a higher dosage will probably not improve the chance of a live birth. The common belief in 'the more oocytes, the better', that was derived from large cross-sectional studies (Sunkara et al., 2011; Drakopoulos et al., 2016; Polyzos et al., 2018), may thus require serious reconsideration.

Why an increased FSH dose does not improve LBR

More likely, the number of retrieved oocytes only partially mirrors the prognostic profile of an individual woman (Fig. 2). This prognostic profile is predominantly determined by a combination of well-known factors, such as the woman's age and the genetic quality of the oocytes (Munné et al., 1993; Hassold and Hunt, 2001; Broekmans et al., 2007), but also by unknown factors at, for instance, the sperm or endometrium level (Simon et al., 2014; Gallos et al., 2018; Liu et al., 2018). Women with a poor prognostic profile (e.g. advanced female age, reduced oocyte quality) often also have a reduced quantitative ovarian reserve and a lower number of retrieved oocytes. Using a higher FSH dose in order to increase the number of oocytes is unlikely to improve the probability of a live birth, as the main prognostic characteristics of the individual woman remain unaltered. Moreover, since predicted low responders by definition have a reduced number of antral follicles that are responsive to FSH, a higher FSH dose may not actually increase the oocyte yield for every woman.

Increased FSH doses and oocyte/embryo quality

The relationship between the number of oocytes and their quality may be expressed by the ploidy status of the embryo, as can be assessed through PGS (Twisk et al., 2006). Recent studies suggest that the chromosomal status of embryos mainly determines the success of implantation (Capalbo et al., 2014), although many more factors may be involved in the reproductive potential of embryos. In retrospective data, the embryo aneuploidy rate has appeared to be unrelated to the number of retrieved oocytes or embryos, within female age classes (Ata et al., 2012; Venetis et al., 2019). Women with a higher number of oocytes or embryos were thus observed to have a higher absolute number of euploid embryos (La Marca et al., 2017). Nonetheless, these were all observational studies that provide no valid information on whether an intervention that manipulates the ovarian response, such as increased FSH dosing, will actually improve this absolute number of good-quality/euploid embryos for an individual woman.

Several studies have aimed to investigate whether the FSH dose affects the embryo aneuploidy rate (Barash et al., 2017; Sekhon et al., 2017; Wu et al., 2018). These studies have revealed no significant
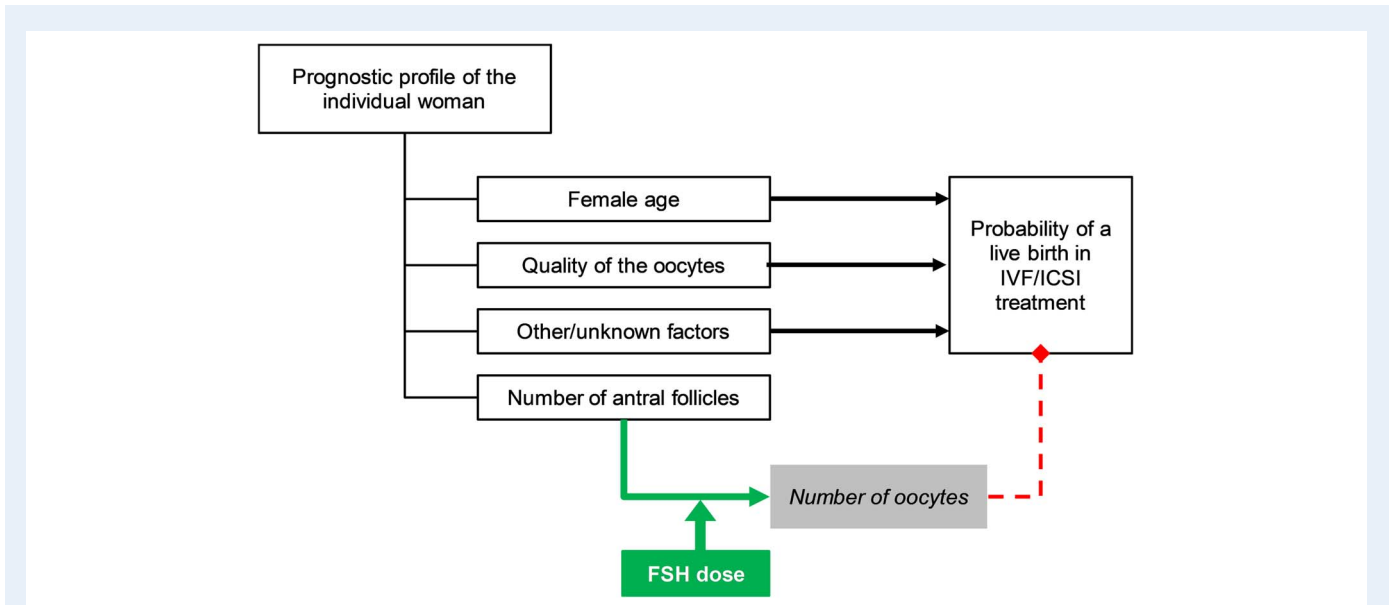
Figure 2 **Relationship between the prognostic profile of an individual woman, the number of oocytes and the probability of a live birth in IVF/ICSI treatment.**
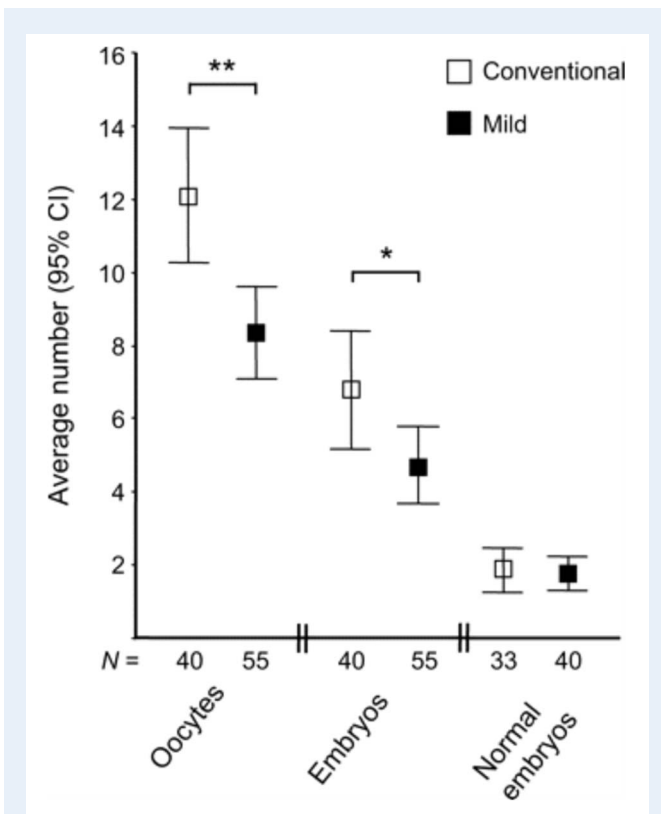

Figure 3 Relationship between the number of oocytes, embryos and chromosomally normal embryos on the basis of fluorescent in situ hybridization (FISH) results, following a conventional (225 IU/day) and mild (150 IU/day) ovarian stimulation protocol (from Baart et al., 2007). *$P < 0.05$, **$P < 0.01$.

association but were prone to confounding and selection bias due to their retrospective design. Prospective randomized studies that compared different FSH doses revealed that a higher FSH dose, although increasing the number of oocytes, reduced the proportion of high-quality/euploid blastocysts (see Figs. 1 and 3) (Baart et al., 2007; Arce et al., 2014). The higher FSH dose thereby resulted in similar absolute numbers of good-quality/euploid embryos and had no beneficial impact on LBR. These findings suggest that the surplus of oocytes, obtained by using an increased FSH dose, is of lower quality with a high proportion of nuclear immaturity and a compromised fertilization, development and implantation potential. This supports the notion that a certain hierarchy exists among antral follicles in their capability to respond to exogenous FSH, in which the most sensitive follicles at that time will develop with standard FSH exposure and provide the best quality oocytes (Kovalevsky and Patrizio, 2005; Patrizio et al., 2007; Patrizio and Sakkas, 2009; Martin et al., 2010; Doherty et al., 2014). Recruiting the few oocytes that have the potential to fertilize and develop into a competent embryo with a high implantation capacity therefore seems to be more important than striving for a maximal response with additional oocytes that do not fertilize or develop into good-quality embryos.

Why do we continue the high dosing strategy?

The prioritization of intermediate outcomes

Many clinicians seem reluctant to use a standard FSH dose of 150 IU/-day in predicted low responders. This is partly explained by the prioritization of intermediate outcomes, including the risk of a cycle cancellation or the occurrence of a low response. Some even suggest that a higher FSH dose is more beneficial than a standard dose, based on the fact that it improves intermediate outcomes while maintaining
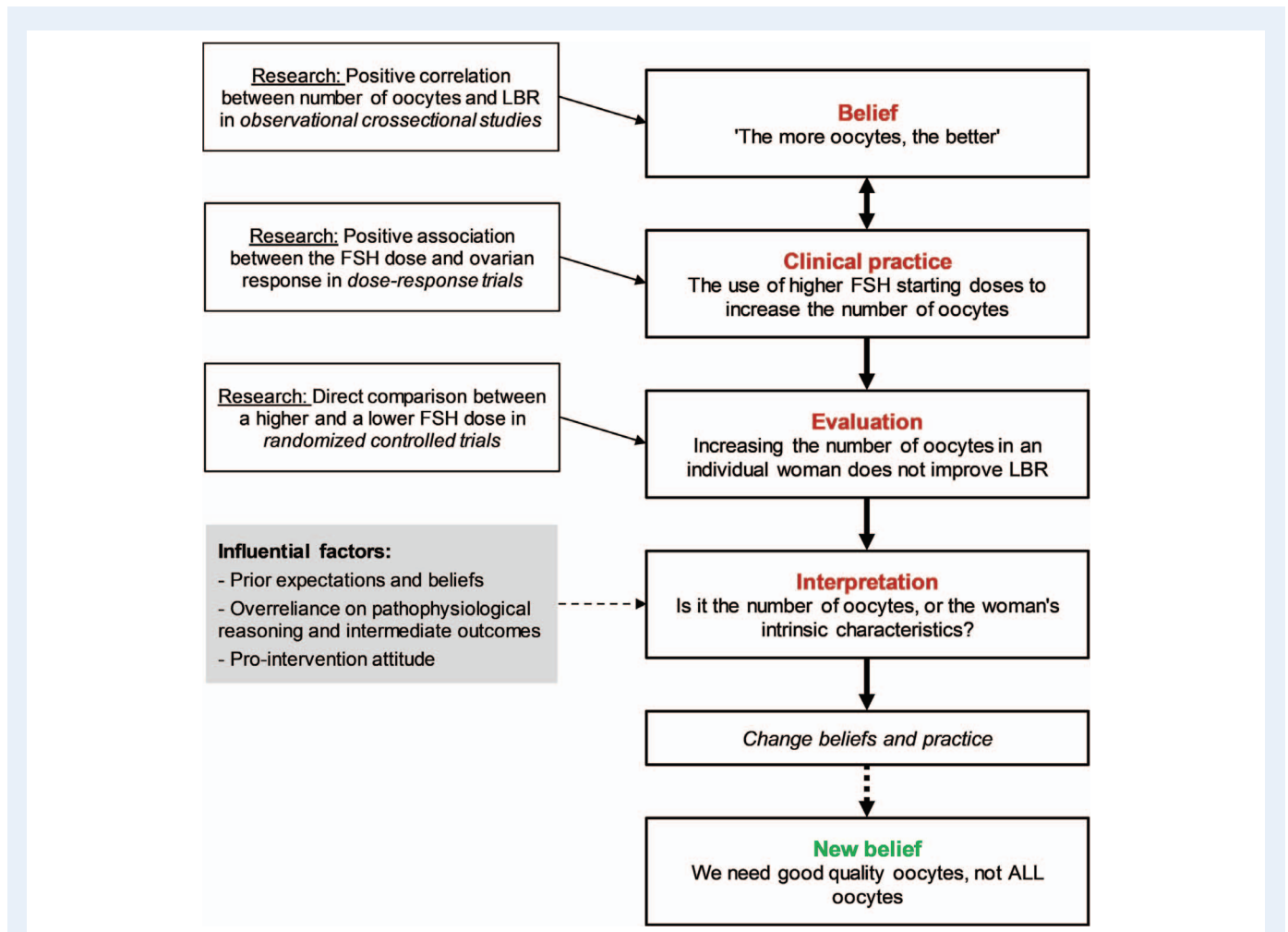
Figure 4 **Factors influencing the use of increased FSH starting doses in women with a predicted low response. LBR, live birth rate.**

the same level of cumulative LBR in predicted low responders (Nyboe Andersen *et al.*, 2017; La Marca *et al.*, 2018). From a certain perspective, improving intermediate outcomes is satisfactory for both the patient and the doctor. In women with a predicted suboptimal response (AFC 8–10), for example, the retrieval of four oocytes instead of eight could be perceived as a clinical failure, even when this has no negative impact on the chance of a live birth (Baart *et al.*, 2007; Arce *et al.*, 2014). By postponing any negative annotations until after the transfer of an embryo, the failure of treatment becomes distanced from directly modifiable treatment variables. This might beneficially impact the patient–doctor relationship and reduce the psychological stress during treatment, e.g. by lowering the risk of a cycle cancellation (Troude *et al.*, 2014). Ultimately, this could even improve the continuation of treatment (Olivius *et al.*, 2004; Rajkhowa *et al.*, 2006; Brandes *et al.*, 2009). However, from the dose comparison trial evaluating cumulative LBR (including the results of both fresh and FET cycles) across 18 months of treatment, which thereby also includes the impact of treatment discontinuation, no improvements of the cumulative LBR with high FSH doses were noted despite the improved intermediate outcomes (van Tilborg *et al.*, 2017b). Therefore, targeting expectations, by informing patients about their individual chances over multiple

cycles, may be a more appropriate method to help couples cope with failures after repeated attempts and alleviate the psychological stress during treatment (Dancet *et al.*, 2011; Holter *et al.*, 2014; McLernon *et al.*, 2016; Leijdekkers *et al.*, 2018).

The bias in the interpretation of research

Without prior demonstration of a benefit, the use of FSH doses > 150 IU/day has been readily integrated into IVF/ICSI treatment. De-implementation of this routine strategy now requires compelling studies demonstrating ineffectiveness (Scott and Elshaug, 2013). However, the threshold of research to be compelling is high and may be prone to several biases (see Fig. 4) (Kaptchuk, 2003). First, study results that contradict prior expectations are often less readily accepted than those confirming them (confirmation bias). Such contradicting results are prone to higher standards and selective finding of faults in the study design or execution (rescue bias). Additionally, an over-reliance on pathophysiological reasoning may cause a less skeptical attitude towards results that are supported by a bio-plausible mechanism and lead to the use of intermediate outcomes that do not necessarily translate into patient-important benefits (mechanism bias). Finally, clinicians

generally tend to choose action over inaction, even if the benefits of the action are small or even absent (pro-intervention bias) (Kaptchuk, 2003; Doust and Del Mar, 2004; Scott and Elshaug, 2013).

The appraisal of the results of the dose comparison RCTs on increased FSH dosing in predicted low responders is prone to these biases, mainly due to the strong belief in 'the more oocytes, the better' (Sunkara *et al.*, 2011; Drakopoulos *et al.*, 2016; Polyzos *et al.*, 2018). Opponents of the standard dosing strategy often use the lack of compelling evidence as an argument to give the use of higher FSH doses 'the benefit of the doubt' (La Marca *et al.*, 2018). This seems to indicate that a higher level of certainty is required to claim the lack of benefit, than that is needed to justify the continued use of the now routine and potentially harmful practice at the discretion of the clinician. The skepticism towards previous studies on FSH dosing raises the question of how much research is needed to stop the use of an unproven and costly treatment strategy (Haahr *et al.*, 2018; La Marca *et al.*, 2018; Mendoza-Tesarik and Tesarik, 2018; Nelson and Anderson, 2018; Sunkara and Polyzos, 2018; van Tilborg *et al.*, 2018).

How to proceed?

FSH starting doses > 150 IU/day should not be used as a standard dosing strategy in women with a predicted low response undergoing IVF/ICSI treatment, as they have no proven beneficial impact on the chance of a live birth and they increase the costs of treatment (van Tilborg *et al.*, 2017b). Clinicians and researchers who are not convinced by the evidence to date are challenged to limit the use of higher FSH doses to research settings, thereby generating the data that actually support the belief in 'the more oocytes, the better'.

Conclusion

In conclusion, using high FSH doses in predicted low responders undergoing IVF/ICSI treatment is based on feeble assumptions from retrospective cross-sectional studies about the importance of the number of oocytes in relation to the probability of a live birth. The highly ingrained belief in 'the more oocytes, the better' has induced the routine use of high FSH doses in predicted low responders, but is now contradicted by several comparative trials that have failed to show that a higher number of oocytes actually improve the probability of a live birth for an individual woman. Therefore, it is time to reconsider this belief and stop the use of high FSH starting doses in clinical practice.

Authors' roles

J.A.L., B.W.J.M., F.J.M.B. and H.L.T. were involved in the conception and design of the paper, and J.A.L. drafted the manuscript. All authors contributed in the discussion and revision of the manuscript.

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Conflict of interest

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