

REVIEW

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Dose adjustment of follicle-stimulating hormone (FSH) during ovarian stimulation as part of medically-assisted reproduction in clinical studies: a systematic review covering 10 years (2007–2017)

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Abstract

Background: Individualization of the follicle-stimulating hormone (FSH) starting dose is considered standard clinical practice during controlled ovarian stimulation (COS) in patients undergoing assisted reproductive technology (ART) treatment. Furthermore, the gonadotropin dose is regularly adjusted during COS to avoid hyper- or hypo-ovarian response, but limited data are currently available to characterize such adjustments. This review describes the frequency and direction (increase/decrease) of recombinant-human FSH (r-hFSH) dose adjustment reported in clinical trials.

Methods: We evaluated the proportion of patients undergoing ART treatment who received ≥ 1 r-hFSH dose adjustments. The inclusion criteria included studies (published Sept 2007 to Sept 2017) in women receiving ART treatment that allowed dose adjustment within the study protocol and that reported ≥ 1 dose adjustments of r-hFSH; studies not allowing/reporting dose adjustment were excluded. Data on study design, dose adjustment and patient characteristics were extracted. Point-incidence estimates were calculated per study and overall based on pooled number of cycles with dose adjustment across studies. The Clopper–Pearson method was used to calculate 95% confidence intervals (CI) for incidence where adjustment occurred in $< 10\%$ of patients; otherwise, a normal approximation method was used.

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Results: Initially, 1409 publications were identified, of which 318 were excluded during initial screening and 1073 were excluded after full text review for not meeting the inclusion criteria. Eighteen studies (6630 cycles) reported dose adjustment: 5/18 studies (1359 cycles) reported data for an unspecified dose adjustment (direction not defined), in 10/18 studies (3952 cycles) dose increases were reported, and in 11/18 studies (5123 cycles) dose decreases were reported. The studies were performed in women with poor, normal and high response, with one study reporting in oocyte donors and one in obese women. The median day that dose adjustment was permitted was Day 6 after the start of treatment. The point estimates for incidence (95% CI) for unspecified dose adjustment, dose increases, and dose decreases were 45.3% (42.7, 48.0), 19.2% (18.0, 20.5), and 9.5% (8.7, 10.3), respectively.

Conclusions: This systematic review highlights that, in studies in which dose adjustment was allowed and reported, the estimated incidence of r-hFSH dose adjustments during ovarian stimulation was up to 45%.

Keywords: Follicle-stimulating hormone (FSH), FSH dose adjustment, Recombinant-human FSH, Follitropin, Controlled ovarian stimulation (COS), In vitro fertilization (IVF), Medically-assisted reproduction, Assisted reproductive technology (ART) treatment, Systematic review

Background

There are many aspects of assisted reproductive technology (ART) treatment that can be individualized to optimize treatment outcomes, including controlled ovarian stimulation (COS), ovulation triggering and luteal phase support [1–3]. As with all medically-assisted reproduction treatments, the approach to patient care should be individualized according to the characteristics of each patient and monitored to ensure that the response is optimized with respect to efficacy and safety [4]. Evidence from routine care settings and randomized trials in which the individualized approach to reproductive medicine differs from a standardized approach may provide targeted evidence regarding the advantages or disadvantages of an individualized approach.

Individualization during COS can include the selection of down-regulation protocols (e.g. gonadotropin-releasing hormone [GnRH] agonist or antagonist), gonadotropin type, gonadotropin starting dose (with 100–225 IU generally considered the standard gonadotropin daily dose [5, 6]), gonadotropin dose adjustment during ovarian stimulation, type of trigger of final oocyte maturation, and type and duration of luteal phase support [7–9]. It is important to distinguish that individualization of the gonadotropin dose may be implemented at two different time points: at the start of each new treatment cycle ('starting dose selection'), or during the course of ovarian stimulation within a given cycle ('dose adjustment during treatment/cycle') [8, 10–13], even though it is unclear if this individualized approach is beneficial in terms of live birth rate according to the ESHRE guidelines for ovarian stimulation during ART treatment [14]. Likewise, dose individualization in patients with expected and unexpected high ovarian response may decrease the risk of ovarian hyperstimulation syndrome (OHSS) and cycle cancellation.

Starting dose selection

Starting dose selection is usually based on patient characteristics and established biomarkers for treatment response, including AMH and AFC, Day 3 follicle-stimulating hormone (FSH), age, body weight, response to any previous ovarian stimulation cycle (ovulation induction [OI] gonadotropin and/or ART treatment) and any specific diagnoses relating to subfertility (including polycystic ovary syndrome [PCOS], amenorrhea, thyroid stimulating hormone levels and conditions of the Fallopian tubes) [14–19]. Tailoring the FSH starting dose to the individual patient is considered to be standard clinical practice by some healthcare professionals, and a nomogram has been developed based on age, AMH and AFC to help clinicians calculate daily FSH starting doses [18].

Patients with reduced ovarian response after ovarian stimulation for ART can be categorized according to the POSEIDON criteria, based on age and expected euploidy rate, ovarian biomarkers (antral follicle count [AFC] and anti-Müllerian hormone [AMH]), and ovarian response if a previous stimulation has been performed [20]. Individualizing the gonadotropin dose according to whether a patient has expected low ovarian response (POSEIDON Groups 3 and 4; AFC < 5, AMH < 1.2 ng/ml) or unexpected low ovarian response (POSEIDON Groups 1 and 2; AFC ≥ 5, AMH ≥ 1.2 ng/ml) may mitigate against the risk of poor ovarian response (POR) and/or cycle cancellation [7–9, 21]. Cycle cancellation and/or the retrieval of no or very few viable oocytes owing to poor ovarian response may necessitate further COS cycles or discontinuation of the in vitro fertilization (IVF) procedure, which increases both the financial and emotional burden on patients [13] as well as time to live birth. However, based on the current evidence, the ESHRE guideline on ovarian stimulation was unclear whether a higher gonadotropin dose (> 150 IU) was recommended

for patients with predicted poor response, and a dose higher than 300 IU was not recommended for this patient group [14]. In addition, some studies suggest that higher gonadotropin doses during COS may be detrimental [22–25].

Excessive ovarian response to COS may also result in increased rates of cycle cancellation as well as an increased risk of OHSS [26]. There is significant evidence that, in patients predicted to have a hyper-response to FSH, decreasing the FSH starting dose may reduce the risk of OHSS [26]. In a recent study, women with a predicted hyper-response (AFC > 15) were randomized to an FSH daily dose of 100 IU ($n = 255$) or 150 IU ($n = 266$). There were no relevant differences in live birth rates between the groups, but the lower FSH dose was associated with a reduced incidence of mild and moderate OHSS, with no impact on severe OHSS [27]. Similarly, according to a pooled data analysis from four studies [28], live birth rates were similar in patients receiving adjustment of gonadotropin starting dose and those receiving standard starting dosing (OR 1.04 [95% CI 0.88, 1.23]) but a reduction in the incidence of moderate to severe OHSS (OR 0.58; 95% CI 0.34 to 1.00) was observed, suggesting a safety benefit.

Dose adjustment during treatment

There is good evidence that practitioners regularly adjust the gonadotropin dose during ovarian stimulation: dose adjustment was reported in up to 41% of cycles according to an analysis of routine clinical practice in the USA [29], probably because clinicians consider that adjusting the dose during COS represents individualized care to improve efficacy and safety during ART treatment.

Dose adjustment during treatment is usually based on ovarian response, measured by ultrasound assessment of follicular development and hormonal monitoring [14], with the aim of avoiding hypo- or hyper-ovarian responses, thereby optimizing outcome and safety and potentially also the endocrine profile, oocyte quality and endometrial receptivity. Doses for the majority of FSH preparations, including follitropin alfa and follitropin beta, can be adjusted at the start as well as during a treatment cycle. For example, for the reference recombinant follitropin alfa, a starting dose of 150–225 IU per day is indicated, with adjustment after 3–5 days of 75–150 IU not to exceed 450 IU/day [30]; and for the reference recombinant follitropin beta, a starting dose of 200 IU per day is recommended, with adjustment after ≥ 7 days of treatment, or after 6 days in patients with high response [31]. However, dose adjustment during treatment of some preparations is restricted by galenic formulation or specific usage instructions [9, 32]. Currently, dose adjustment with 12.5 IU increments are possible in specific formulations for follitropin alpha [33–38]. Furthermore, there is increasing evidence suggesting the benefit of

devices that allow small dose changes for reducing the risk of OHSS [39–41], although it needs to be confirmed whether using these devices would lead to improved clinical outcomes.

Dose adjustment may have particular benefits for specific patient groups. To maximize the ovarian potential, reduce the time to live birth and increase cumulative live birth rates, as many oocytes as possible need to be retrieved without putting the patient at risk for OHSS [42–44]. Patients with unexpected low ovarian response (Poseidon Groups 3 and 4) demonstrate an initial slow response to FSH stimulation in terms of estradiol levels and follicle growth [12]; therefore, increasing the FSH dose during treatment in these patients may increase the number of oocytes retrieved. However, trials reporting dose adjustment in poor responders are usually designed to assess individualization of the starting dose based on pretreatment assessment (e.g., AMH or AFC) in patients with expected poor response, making it difficult to assess the benefit of dose adjustment only during treatment in unexpected poor responders.

In patients with an unexpected hyper-response to FSH, decreasing the FSH dose during treatment may reduce the occurrence of OHSS; with moderate-to-severe OHSS estimated to arise in 0.5 to 5.0% of IVF cycles [45, 46]. However, similar to unexpected poor responders, most trials that report dose adjustment in hyper responders are designed to assess individualization of the starting dose in patients with expected hyper response, making it difficult to evaluate dose adjustments during treatment in patients with unexpected hyper-responses.

Aims

Although dose adjustment was reported in up to 41% of cycles according to an analysis of routine clinical practice in the USA [29], it is not known to what extent gonadotropin dose adjustment occur during the highly controlled research environment of a clinical trial. In some clinical trials, dose adjustment during ovarian stimulation may not be allowed, to reduce the variability of the intervention between patients. In other clinical trials, dose adjustment may be allowed, but the actual incidence of dose adjustment may not always be reported. The aim of this systematic review was to describe the frequency and direction (increase/decrease) of recombinant human (r-h) FSH dose adjustment reported in clinical trials that allowed dose adjustment within the study protocol, involving patients undergoing COS as part of IVF treatment.

Methods

Study protocol

The protocol used in this review is described below and has not been registered with any repositories. PubMed

was searched to identify publications reporting the proportion of patients undergoing COS for IVF receiving dose adjustment, covering a period of 10 years (6 Sept 2007 to 6 Sept 2017).

Literature search

The following search string was used: (((“follitropin alfa” OR “follitropin alpha” OR “follitropin beta” OR “follitropin delta” OR “follicle stimulating hormone” OR “follicle-stimulating hormone” OR FSH OR hfsh OR rhfsh OR rfsh OR “h-FSH” OR “rh-FSH” OR “r-hFSH” OR “r-h-FSH” OR “r-FSH” OR “u-FSH” OR ufsh OR “uh-FSH” OR “u-hFSH” OR “u-h-FSH” OR “gonal-f” OR gonal f OR gonal OR “SJ-0021” OR SJ0021 OR bembola OR folia OR ovaleap OR XM17 OR “XM-17” OR follitropin OR corifollitropin OR rekovelle OR “FE-999049” OR FE999049 OR elonva OR “FSH-CTP” OR “ML-8962” OR ML8962 OR “ORG-36286” OR ORG36286 OR “SCH-900962” OR SCH900962 OR follistim OR puregon OR “ORG-32489” OR ORG32489 OR Bravelle OR “HP-FSH” OR “HP-uFSH” OR “HP-u-FSH” OR “HP-uhFSH” OR “HP-u-hFSH” OR “HP-uh-FSH” OR menotropin))) AND ((“controlled ovarian stimulation” OR COS OR “controlled ovarian hyperstimulation” OR “ovarian stimulation” OR IVF OR “in vitro fertilization” OR “in vitro fertilisation” OR IUI OR “intrauterine insemination” OR “artificial insemination” OR ART OR “assisted reproductive” OR “assisted reproduction” OR “oocyte induction OR OI OR “oocyte retrieval”) OR (Reproductive Techniques [MeSH Terms])).

Study selection

The search was limited to a 10-year period (in order to reflect recent/current practice and to ensure that the number of articles to be screened was manageable) starting 6 Sept 2007, and filtered to include only studies written in English and conducted in humans. The inclusion criteria used to filter the results were: clinical trials (including prospective and retrospective studies) in women receiving ART treatment that allowed dose adjustment within the study protocol, with ≥ 1 dose adjustments of r-hFSH actually reported. Only studies that used r-hFSH were included in the data analysis (r-hFSH was selected in order to have a defined patient population; furthermore, evaluating all gonadotropins would have resulted in an unmanageable number of articles to screen); any comparator study arms using urinary FSH alone (i.e. without r-hFSH) were excluded. Only papers with primary reporting of results were included, whereby if data from a study were reported multiple times (i.e. secondary reporting), only the first publication reporting dose adjustment was included. The exclusion criteria used to filter the results were: congress abstracts; review articles; reports of studies that did not involve r-hFSH treatment;

studies that did not allow gonadotropin dose adjustment by protocol, studies that did allow dose adjustment but where no data on dose adjustment were reported.

Abstracts were initially screened by AJ to remove studies that were explicitly unrelated to the study question or that did not meet the inclusion or exclusion criteria. After initial screening, the full text of remaining articles was obtained and screened by AJ, DD, SL, WB, MM and TDH to identify relevant publications. Any disagreement was resolved by discussion.

Data collection

Data on study design, dose adjustment and patient characteristics were extracted during screening. The data extraction forms are included in Supplementary Table 1. Dose adjustment frequency data were recorded overall and also according to the direction of dose adjustment (i.e. increases/decreases in dose; or ‘unspecified’ for those studies that did not define the direction of the dose adjustment) according to how they were reported in the identified publications. The risk of bias in individual studies and across studies was not assessed, as this was a scoping review [47] in which the outcome evaluated should not be affected by subjective bias as no analysis or comparison between groups was considered.

Statistical analysis

Point estimates for incidences were reported per study and overall based on pooled number of cycles with dose adjustment across studies. The Clopper–Pearson method was used to calculate 95% confidence intervals (CI) for incidence where adjustment occurred in $< 10\%$ of patients; otherwise, a normal approximation method was used. Data were also analyzed according to the GnRH protocol (agonist vs antagonist).

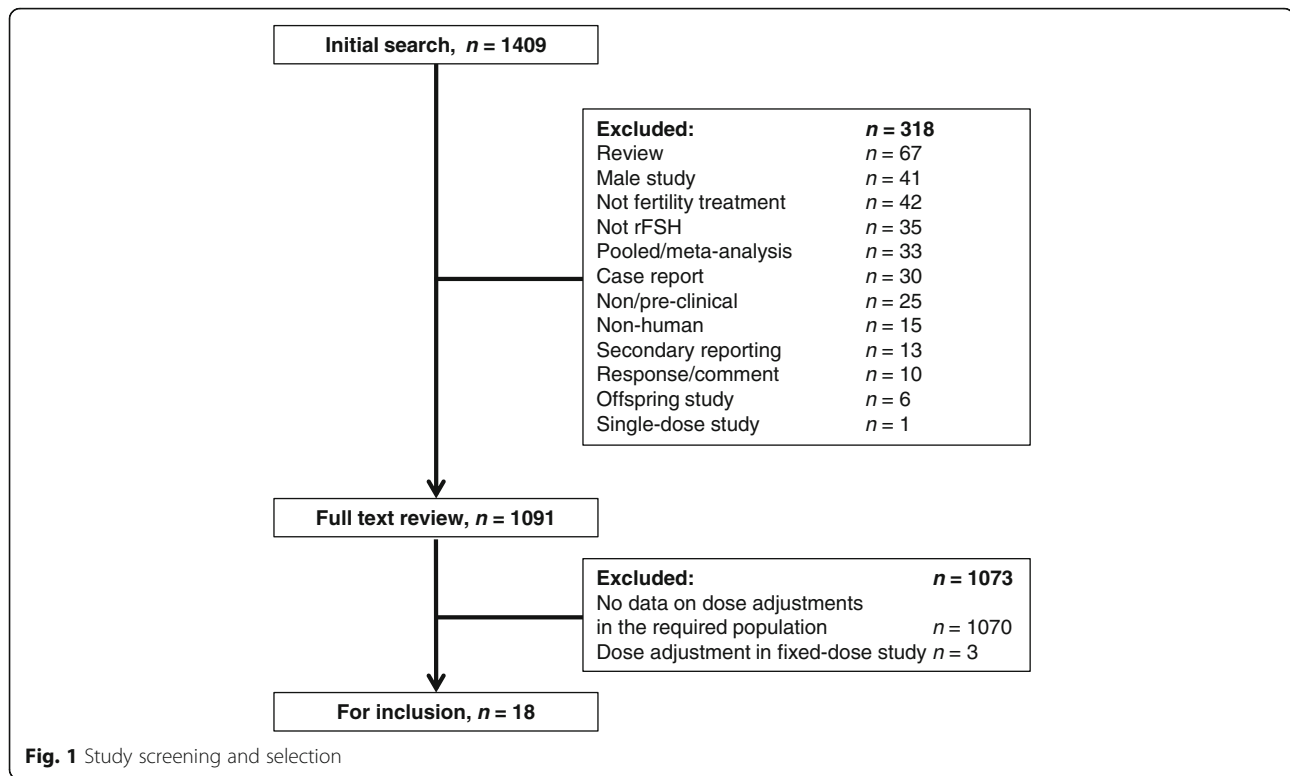
Results

Study selection

A total of 1409 publications were initially identified by the search, of which 318 studies were excluded during initial screening due to the fact they did not meet the inclusion criteria. A further 1073 studies were excluded following full-text review, as either no data on dose adjustment were available in the required population or dose adjustment were reported in fixed dose studies that did not allow dose adjustment in their study design (i.e. where adjusting the dose resulted in a protocol deviation). Eighteen out of the 1409 publications searched reported dose adjustment and were eligible for review [9, 40, 48–63]. Full screening details are shown in Fig. 1.

Study characteristics

In the 18 included studies, data were available for 6630 cycles. Five studies (1359 cycles) reported data for



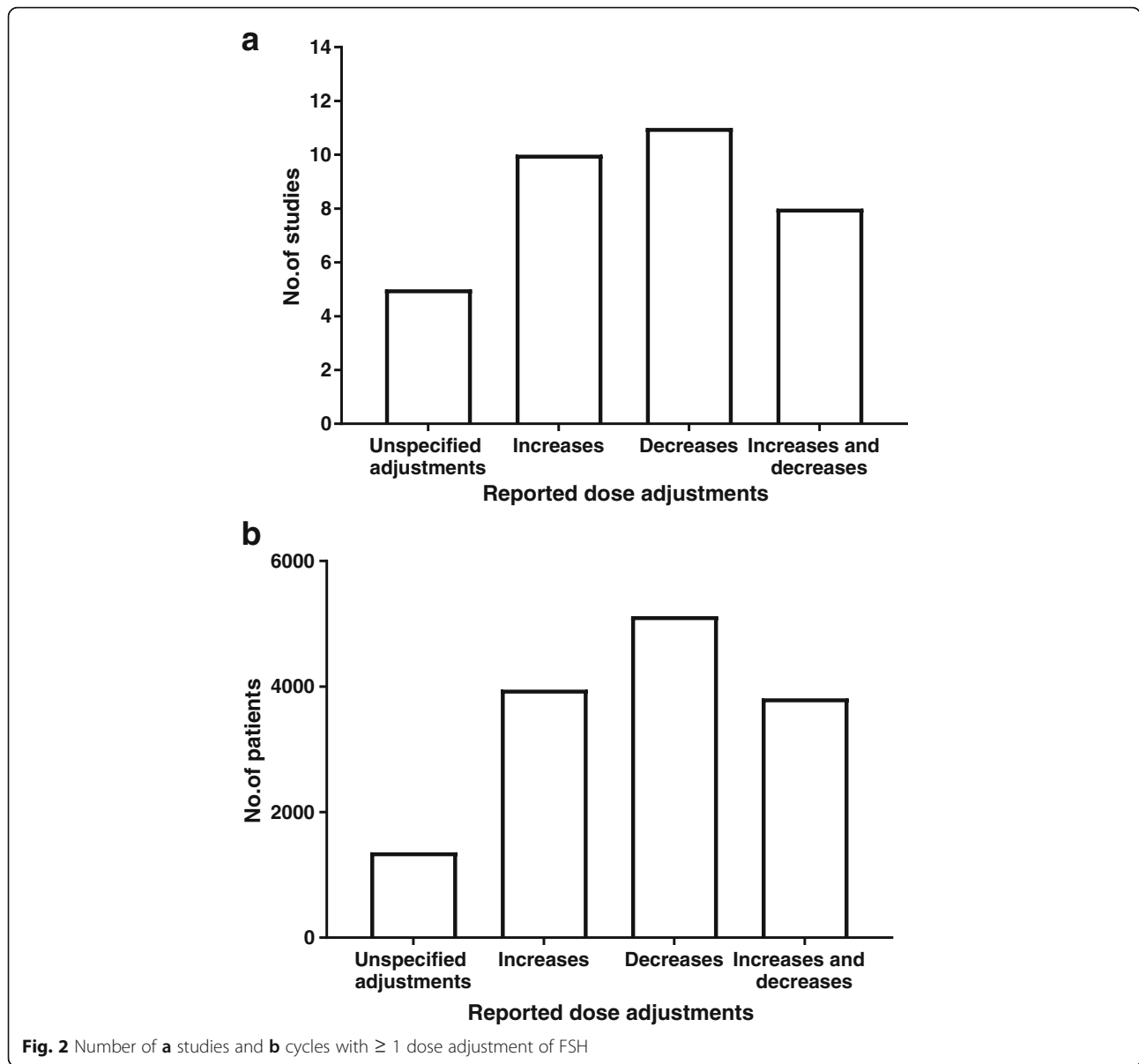
unspecified dose adjustments (increases or decreases; direction not defined), 10 studies (3952 cycles) reported dose increases, 11 studies (5123 cycles) reported dose decreases, and eight studies (3813 cycles) reported both dose increases and decreases (Fig. 2). Seven studies (1994 cycles) used GnRH agonists, eight studies (2411 cycles) used GnRH antagonists, and three studies either did not specify or used both agonists and antagonists. Ten studies were randomized controlled trials (RCTs) and three studies were done for marketing authorization purposes [54, 62, 63]. The studies were performed in patients with a predicted poor ($n = 2$), normal ($n = 3$) or high response ($n = 6$) (mean AFC [standard deviation (SD)] ranged from 5.3 [4.29] to 21.6 [12.0]; mean AMH [SD] ranged from 1.7 [2.06] to 27 [20]; Supplementary Table 1), with 7 studies not reporting AFC/AMH data to determine the predicted response. Two studies reported in non-standard populations (1 in oocyte donors [59] and 1 in obese women [52] [mean body mass index (BMI) (SD) 34.3 (3.6) kg/m²]). The median day that dose adjustment was permitted was on Day 6 after the start of treatment. 13 studies were conducted in Europe, two studies were international (Europe, USA, Canada, Brazil and Russia), one study was conducted in Brazil, one in the USA and one in Australia. Baseline patient characteristics, including age, BMI, AMH, AFC and serum FSH are summarized in Supplementary Table 2.

In the 18 studies, GONAL-f® (follitropin alfa, r-hFSH; Merck KGaA, Darmstadt, Germany) was the most frequently used FSH, followed by Puregon® (follitropin-b, r-hFSH, Merck Sharp & Dohme B. V, The Netherlands), being used in 13 and 6 studies, respectively, with some studies using both treatments. Two studies used biosimilars: one study used Bemfola® (follitropin alfa, Gedeon Richter Plc, Hungary) and one study used Ovaleap® (follitropin alfa, Theramex Ireland Limited, Ireland). The types of FSH used for treatment and any pre-treatment biomarkers measured are summarized in Supplementary Table 3.

Incidence of dose adjustment

Overall, the pooled point estimates for incidence (95% CI) for unspecified dose adjustment, dose increases, and dose decreases were 45.3% (42.7, 48.0), 19.2% (18.0, 20.5), and 9.5% (8.7, 10.3), respectively (Fig. 3).

When data were analyzed according to the GnRH protocol used, dose adjustment was more frequent with GnRH agonists than GnRH antagonists. The respective point estimates for incidence (95% CI) for unspecified dose adjustment, dose increases, and dose decreases were 58.6% (54.3, 63.0), 47.2% (44.0, 50.5), and 12.9% (11.0, 14.7) for GnRH agonists, and 39.5% (36.4, 42.6), 11.5% (8.0, 15.0), and 7.4% (5.9, 9.0) for GnRH antagonists (Fig. 4).



When looking at individual studies rather than pooled data, the lowest and highest point estimates for incidence (95% CI) in an individual study were 26.8% (13.3, 40.4) and 72.7% (64.0, 81.5), respectively, for an unspecified dose adjustment; 3.0% (0.8, 5.3) and 58.5% (45.2, 71.8), respectively, for dose increases; and 1.9% (-1.8, 5.5) and 53.4% (47.0, 59.8), respectively, for dose decreases. Point estimates for individual studies are shown in Table 1.

Discussion

In clinical trials in women receiving ART treatment that allowed dose adjustment within the study protocol, gonadotropin dose adjustment during treatment was reported in 45% of cycles evaluated (direction unspecified), with dose increases reported more frequently than dose

decreases (19% vs 10%, respectively). These results highlight that dose adjustment, when allowed according to study protocol, are used in published clinical trials of patients receiving ART treatment. It can be postulated that these dose adjustments occurred where healthcare professionals thought modification of the starting dose during treatment would result in improved outcomes. For example, in patients with unexpected poor ovarian response, increasing the gonadotropin dose may improve reproductive outcomes (by optimizing the number and quality of oocytes, resulting in good quality embryos) and reduce risks (such as reduced cycle cancellation rates), whereas in patients with unexpected hyper ovarian response, decreasing the gonadotropin dose may reduce the risk of OHSS.

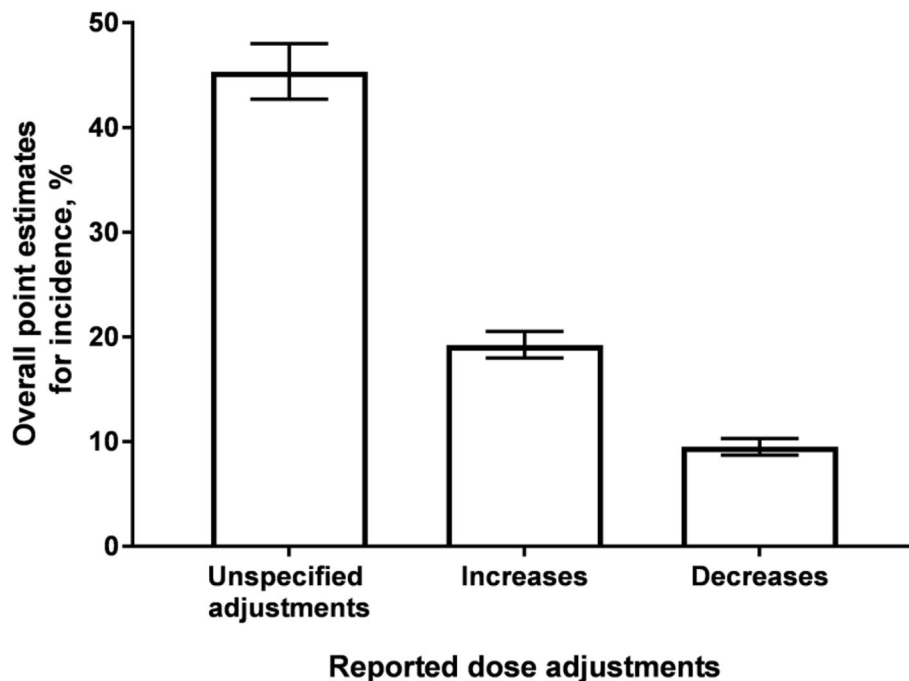


Fig. 3 Collective point estimates for incidence of dose adjustment based on data from pooled cycles

As only two studies in our systematic review reported dose adjustment in patients with predicted poor response (compared with three studies in patients with normal response, six studies in patients with hyper-response and seven studies of unknown response levels [AFC/AMH data not reported]), it could be postulated that the higher frequency of dose increases compared with dose decreases observed in our study were in patients with unexpected poor or insufficient response to ovarian stimulation. However, it is unclear whether dose adjustment during stimulation cycles per se or the final total dose of gonadotropin resulting from dose adjustment during ovarian stimulation affects the clinical and OHSS outcomes. The studies included in our systematic review were not specifically selected for the clinical outcomes; consequently, only three reported direct comparisons of outcomes in the constant dose versus the dose adjustment groups [9, 40, 59]. Of these studies, total dose was only reported in one study [9], but the results of this study have been challenged [3, 64, 65] as both treatment arms not only differed with respect to dose adjustment during ovarian stimulation, but also were different in the type of FSH preparation used, and in calculation and choice of FSH starting dose. Of the studies on which the ESHRE Guidelines on dose adjustment were based, only two reported the total dose [66, 67], and the total dose reflected the direction of adjustment (i.e., lower total dose when the dose was reduced [66] and higher total dose when the dose was increased

during ovarian stimulation [67], as can be expected). Therefore, additional studies are required to assess whether total dose or dose adjustment or both are important in affecting safety (OHSS risk) and efficacy (cycle cancellation risk and reproductive outcomes per started cycle).

Overall, of the 18 studies included in the systematic review, different GnRH analogs were used: eight used a long agonist, eight used an antagonist, one used a mixture and one was not specified. When the three studies in which direct comparisons of outcomes in the dose adjustment and constant dose groups were reported, one used an agonist (dose increases and decreases) [59], one used an antagonist (dose adjustment unspecified) [9] and one used agonist/antagonist (dose increases) [68]. A subanalysis examining dose adjustment according to the GnRH protocol used revealed that unspecified dose adjustment was more common in patients receiving a GnRH agonist than antagonist, being reported in approximately 59% versus 40% of cycles, respectively. Dose increases were also more frequent with GnRH agonists than antagonists (47% vs 12%, respectively), as were dose decreases (13% vs 7%, respectively). GnRH antagonists competitively bind to the GnRH receptor, causing immediate and rapid gonadotropin suppression, and their onset of action is significantly faster than that of GnRH agonists, which in contrast suppress gonadotropin release by desensitizing the pituitary receptors [69, 70]. In addition, GnRH antagonist suppression of gonadotropin

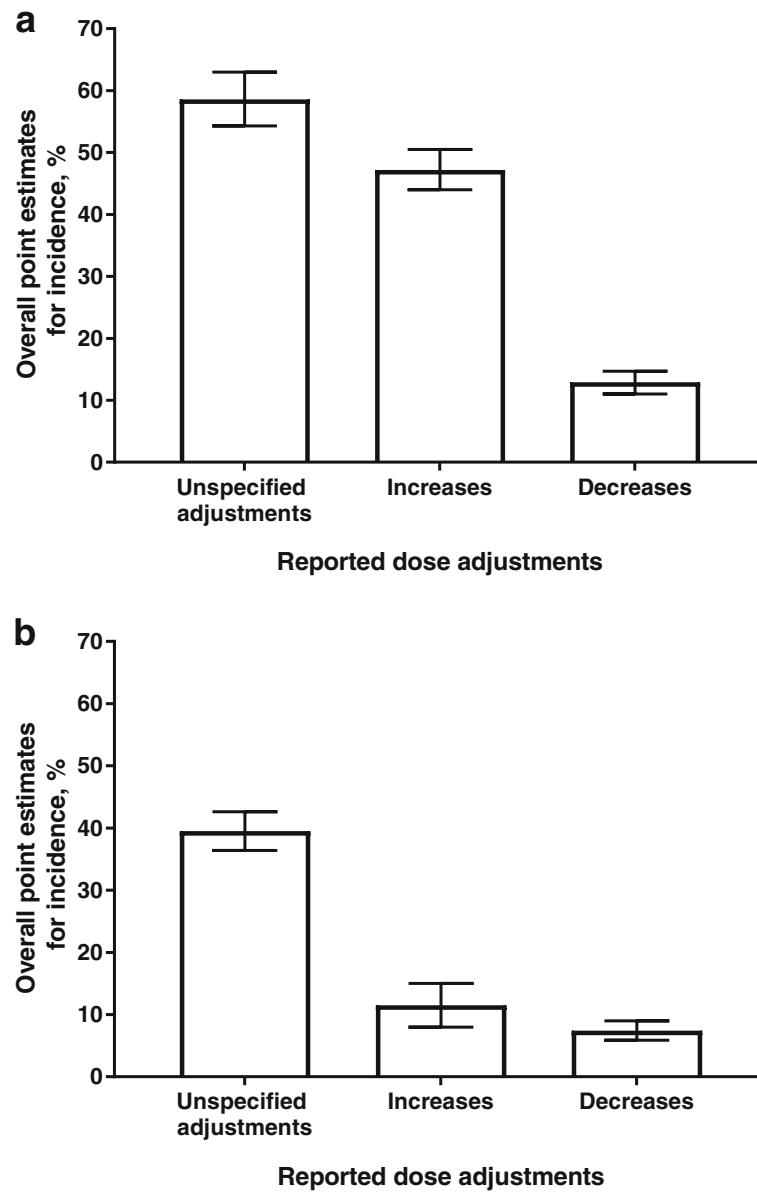


Fig. 4 Point estimates for incidence of dose adjustment according GnRH protocol: **a** agonist or **b** antagonist. Three studies did not specify the GnRH protocol used or used a mixture of agonists and antagonists, and these data were excluded from this subanalysis

secretion is rapidly reversible [71]. As a result, GnRH antagonist treatment is associated with a shorter duration of ovarian stimulation than with a GnRH agonist, as well as lower OHSS rates [72–75]. In a Cochrane review of 73 RCTs, Al-Inany et al. reported that antagonists were associated with a lower incidence of OHSS (odds ratio [OR] 0.61 [95% CI 0.51, 0.72]) and cycle cancellation due to a high OHSS risk (OR 0.47 [95% CI 0.32, 0.69]) compared with agonists [76]. Physicians may therefore be more likely to adjust the FSH dose in those patients receiving a GnRH agonist compared with a

GnRH antagonist, in order to reduce the OHSS risk, which is supported by the findings of this systematic review. Of the included studies, 16 used hCG triggering, one used an agonist trigger (antagonist down-regulation from Day 6) [9] and one used hCG/agonist trigger (in antagonist cycles with > 20 follicles; long down regulation flare cycle agonist/antagonist conversion with estrogen priming or antagonist, according to local practice) [68]) (data not shown). The GnRH agonist protocol, which is also associated with an increased risk of OHSS when compared to a GnRH antagonist protocol [77],

Table 1 Point estimates for incidence of unspecified dose adjustment, dose increase and dose decrease for individual studies included in the systematic review

Study	Study arm ^a	Unspecified dose adjustment (direction not specified), point estimate (%) for incidence (95% CI)	Dose increase, point estimate (%) for incidence (95% CI)	Dose decrease, point estimate (%) for incidence (95% CI)
Allegra 2017 [48]	Control (N = 99)	72.7 (64.0, 81.5)	–	–
	Nomogram ^b (N = 92)	60.9 (50.9, 70.8)	–	–
Buhler 2014 [49]	(N = 2074)	–	4.8 (3.9, 5.7)	3.7 (2.9, 4.5)
Magnusson 2017 [58]	AMH (N = 152)	54.6 (46.7, 62.5)	–	–
	Non-AMH (N = 155)	52.3 (44.4, 60.1)	–	–
Espinós 2017 ^c [52]	(N = 41)	26.8 (13.3, 40.4)	–	–
Nyboe Andersen 2017 [9]	r-hFSH (N = 661)	36.8 (33.1, 40.4)	–	–
Rettenbacher 2015 [62]	Bemfola (N = 220)	–	–	17.3 (12.3, 22.3)
	GONAL-f (N = 113)	–	–	14.2 (7.7, 20.6)
Strowitzki 2016 [63]	Ovaleap (N = 153)	–	35.9 (28.3, 43.6)	15.0 (9.4, 20.7)
	GONAL-f (N = 146)	–	43.2 (35.1, 51.2)	15.1 (9.3, 20.9)
Devroey 2012 [50]	r-hFSH (N = 375)	–	24.8 (20.4, 29.2)	2.1 (0.7, 3.6)
Durnerin 2008 [51]	Control (N = 49)	–	55.1 (41.2, 69.0)	2.0 (–1.9, 6.0)
	r-hLH pretreat (N = 53)	–	54.7 (41.3, 68.1)	3.8 (–1.4, 8.9)
Esteves 2009 [53]	r-hFSH (N = 236)	–	–	53.4 (47.0, 59.8)
Devroey 2009 [54]	r-hFSH (N = 750)	–	–	8.4 (6.4, 10.4%)
Freiesleben 2008 [55]	r-hFSH (N = 159)	44.0 (36.3, 51.7)	–	–
Kyrou 2009 [56]	r-hFSH (N = 230)	–	3.0 (0.8, 5.3)	7.0 (3.7, 10.2)
Lossl 2008 [57]	Androgen priming (N = 53)	–	58.5 (45.2, 71.8)	1.9 (–1.8, 5.5)
	Control (N = 50)	–	52.0 (38.2, 65.8)	2.0 (–1.9, 5.9)
Nakhuda 2010 ^d [59]	(N = 104)	–	10.6 (4.7, 16.5)	35.6 (26.4, 44.8)
Nyboe Andersen 2008 [60]	r-hFSH (N = 261)	–	51.7 (45.7, 57.8)	11.5 (7.6, 15.4)
	r-hFSH + r-hLH (N = 265)	–	48.7 (42.7, 54.7)	11.3 (7.5, 15.1)
Requena 2010 [61]	r-hFSH + HP-hMG (N = 46)	–	32.6 (19.1, 46.2)	–
	r-hFSH (N = 46)	–	32.6 (19.1, 46.2)	–
Yovich 2012 [40]	FSH dose < 100 IU (N = 47)	–	53.2 (38.9, 67.5)	–

AMH anti-Müllerian hormone, FSH follicle stimulating hormone, r-hFSH recombinant-human follicle stimulating hormone, r-hLH recombinant-human luteinizing hormone, HP-hMG highly purified human menopausal gonadotropin

^aOnly study arms using recombinant FSH were included in the data analysis; ^bFSH starting dose set using a nomogram based on age, serum Day 3 FSH and AMH; ^cStudy in obese women; ^dStudy in oocyte donors

cannot be used in conjunction with a GnRH agonist trigger. Furthermore, dose increases were reported more frequently than dose decreases in patients receiving GnRH agonists (47% vs 13%) and GnRH antagonists (12% vs 7%), in-line with the overall population, suggesting that more patients may have had unexpected poor or insufficient responses, resulting in physicians acting to increase the FSH dose in these patients.

Dose adjustment during treatment has been observed in an analysis of a routine care setting from a large US insurance database [29]. This analysis reported the occurrence of dose adjustment of r-hFSH and the characteristics of patients receiving r-hFSH for COS as part of IVF between July 2009 and December 2016. In this

analysis, 41% of 13,823 cycles from 23,582 patients undergoing IVF included ≥ 1 dose adjustments, with a greater proportion receiving dose decreases than dose increases (63 vs 57% of cycles). Patients who received dose adjustment were older, had a higher AFC and AMH, and a lower Day 3 FSH compared with those who did not receive a dose adjustment. Patients who received a dose adjustment were also more likely to have a diagnosis of diminished ovarian reserve and PCOS than those who received a fixed dose.

A lower proportion of patients received a dose adjustment in our review of clinical trials compared with the analysis of routine clinical practice in the USA [29] (with unspecified dose adjustments, increases and decreases

reported in 45, 19, and 10% of cycles in our study vs 41, 57, and 63%, respectively, in the US study). This is not surprising as more than half of the studies (10/18) our review identified were RCTs, which have highly selected patient populations based on their inclusion and exclusion criteria (for example, none of the RCTs identified in our review comprised patients with predicted poor response based on their AFC/AMH levels, whereas 10 to 20% of patients undergoing IVF are reported to have poor ovarian responses [78]); accordingly it can be anticipated that dose adjustment is more controlled and less freely available to physicians participating in RCTs compared with the routine care setting in the USA. Furthermore, the majority of studies included in our systematic review were from Europe (>70%), likely resulting in differences in clinical practices between our study and the US analysis [29].

Although the ovarian response markers used to evaluate the need for dose adjustment during treatment were not assessed in this analysis, dose adjustment during ovarian stimulation is usually based on ovarian response measured by ultrasound and/or hormonal monitoring. Estradiol levels and follicular size, as measured by ultrasound, are directly linked to progesterone production, with progesterone rise associated with a negative effect on pregnancy rates [79]. Adapting the stimulation dose during the late follicular phase according to the patient's response is sufficient to prevent this progesterone increase, as demonstrated by Lawrenz et al. [80] in a combined post-hoc analysis of the ENGAGE and PURSUE trials. In a subgroup analysis comparing the occurrence of premature progesterone rise in the women treated corifollitropin alfa with or without daily rFSH after Day 8, there was a significant increase in premature progesterone rise in those with additional rFSH compared with those without (20.8% vs 5.4%; $p < 0.001$), confirming that enhanced FSH stimulation towards the end of the follicular phase was responsible for the premature progesterone rise [80]. However, the ESHRE guidelines suggest that the addition of estradiol to ultrasound testing during ovarian stimulation does not appear to increase the probability of pregnancy or the number of oocytes retrieved, or to decrease the probability of OHSS compared with ultrasound alone [14]. It is important to note, however, that this recommendation was labeled by ESHRE as 'conditional' (*probably recommend*), for which ESHRE suggests that clinicians should recognize that different choices will be appropriate for individual patients, as opposed to recommendations labeled as 'strong' (*recommend*), for which ESHRE suggests most individuals should receive the intervention. Furthermore, this guidance was based on the Cochrane review by Kwan et al. [81], and there is a major concern over the validity of this recommendation for OHSS risk

management: only 781 women from 6 studies were included for analysis with ~4% OHSS rate, a point that Kwan et al. acknowledge, along with the need for a confirmatory large well-designed RCT. The addition of estradiol to ultrasound monitoring may be beneficial as precautionary good clinical practice and as a confirmatory test in women at high risk of OHSS [81], and it is common practice in many countries/regions to have routine monitoring with frequent ultrasound and/or estradiol measurements in women at high risk of OHSS [26, 82]. Furthermore, despite the conditional recommendation by ESHRE that an inclusion of an extended hormonal panel (estradiol, progesterone and luteinizing hormone [LH]) measures to ultrasound testing during ovarian stimulation does not appear to increase the probability of pregnancy or to decrease the probability of OHSS or cycle cancellation for high responders [14], this was based on studies with a small sample size which reported only a few cases of OHSS [83, 84]. Accordingly, a proviso that "the decision on timing of triggering in relation to follicle size is multi-factorial, taking into account the size of the growing follicle cohort, the hormonal data on the day of pursued trigger" was stipulated in the guidelines [14].

Few clinical trials have compared the effects of FSH dose adjustment during a treatment cycle with a fixed starting FSH dose; therefore, the actual effect of these dose adjustments on outcomes have not been fully investigated and cannot be determined from the data obtained by this systematic review. In a small RCT in patients with expected poor response, Klinkert et al. (2005) compared standard 150 IU rFSH dose ($n = 26$; 150 IU with the possibility of the dose being increased to 300 IU during treatment) with 300 IU rFSH dose ($n = 26$; 300 IU fixed dose). Nine patients (35%) in the standard rFSH (150 IU) group received dose adjustments due to an insufficient response, resulting in the dose being increased to 300 IU, but no improvement in ovarian responses were reported in these patients [85]. However, this was a small study and was not designed to assess dose adjustments during treatment, but rather to evaluate standard starting dose (150 IU) versus higher (300 IU) starting doses; therefore, it is impossible to draw conclusions concerning dose adjustments from this study. Previous studies assessing dose adjustment of human menopausal gonadotropin (hMG, containing FSH and LH activity) in patients with poor ovarian response [66] and in unselected patients [23, 86] have shown non-inferiority in terms of pregnancy rates compared with fixed hMG dose, suggesting limited benefit in adjusting the hMG dose during treatment. Based on this evidence, the ESHRE guidelines for ovarian stimulation for IVF/ICSI states that adjustment (increase or decrease) of the

gonadotropin dose in the mid-stimulation phase during ovarian stimulation is probably not recommended [14]. However, the recommendations based on such studies can be confounding, as evidence only indicates that there is no difference in assessed efficacy outcomes and does not consider additional relevant outcomes and risks that are relevant to patients (cycle cancellation, OHSS), costs or patient preferences. Indeed, in the studies on which these guidelines were based, no differences were reported for clinical outcomes (e.g., embryo number [23, 66, 67, 86], clinical pregnancy rates [23, 86, 87] or ongoing pregnancy rates [23]; live birth rates were not reported in any of the studies), although in a retrospective chart review of a mixed population [23], the number of oocytes retrieved was 9.7 (0.3) in the patients with a constant dose versus 13.4 (0.7) in the patients with dose decrease ($p < 0.001$). Furthermore, several of these studies also reported non-significant trends towards favorable outcomes in patients with dose adjustments compared with those with constant doses (e.g., higher implantation rates with dose increase [86] and with dose increase and decrease [23], higher clinical pregnancy rates with dose increase [86], lower cycle cancellation with dose decrease before coasting [87] and lower incidence of moderate OHSS with dose decrease before coasting [87]). In the two studies in our systematic review for which meaningful comparisons could be made, there was a significant difference in the mean (SD) number of oocytes retrieved (19.38 [1.18] for no dose change, 16.75 [2.5] with a dose increase and 26.89 [1.64] after dose decrease; $p < 0.001$) [59] and a trend towards higher oocyte numbers (8.5 [4.5] in constant dose group and 9.3 [6.3] in the dose increase group [40]), respectively. Only one case of severe OHSS was reported with dose increase, which was attributed to a violation of the PIVET algorithm [40]. Finally, the findings of the recent OPTIMIST trial could also be considered, as dose adjustment between cycles was permitted in both treatment arms to a maximum of 50 IU/ day, which could be considered as a proxy for dose individualization, as adjustments were not allowed to be made for any patients included in the study arms [21, 27]. Although no benefit of dose individualization based on AFC was reported for cumulative live birth outcomes in the poor responders, the reported data showed benefits of dose individualization on outcomes that are directly modifiable by dose adjustment (e.g., cycle cancellation, poor response, oocyte yield, number of fresh embryos and fresh transfer rate) [88, 89]. Therefore, larger properly designed studies are still needed to evaluate the differences in efficacy outcomes with dose adjustment during treatment compared with fixed gonadotropin dosing during ovarian stimulation. Coasting (withholding gonadotropin dose administration for ≥ 1 day) can also be considered as a form of dose reduction

during a stimulation cycle. In a systematic review of 493 patients in 12 studies, Delvigne and Rozenberg concluded that although the data were highly heterogeneous with respect to patient numbers and characteristics, as well as stimulation and coasting procedures, coasting decreased the risk of OHSS in high risk patients, although did not avoid the risk altogether [90]. A later Cochrane Review of 8 RCTs reported only low-level evidence based on data from 702 women at high risk of developing OHSS that coasting reduced moderate or severe OHSS more than no coasting [91]; however, only two of the included studies directly compared coasting with no coasting for the occurrence of OHSS [92, 93], both reporting lower rates of OHSS in the coasting groups than in the non-coasting groups. Despite this evidence, the American Society for Reproductive Medicine (ASRM) guidelines suggest there is insufficient evidence to recommend coasting for the prevention of OHSS. Furthermore, the effects of coasting on pregnancy outcomes are unclear [82].

Limitations of this systematic review included the fact that we specifically looked at r-hFSH in order to limit the scope of the search, which, even after restricting to r-hFSH, identified over 1400 publications for initial screening. Furthermore, we only included articles written in English, used data from a restricted time period, and only used PubMed for database searches. As this was a systematic review of published data, the effect of dose adjustment on outcomes could not be evaluated.

Conclusions

According to this systematic review, in studies in which r-hFSH dose adjustment was allowed and reported, the estimated incidence of r-hFSH dose adjustment during ovarian stimulation was up to 45%, with dose increases occurring more commonly than dose decreases. Dose adjustment was more frequent in patients receiving a GnRH agonist than a GnRH antagonist, and was reported in patients with a predicted poor, normal, or high response. In patients with poor ovarian response, increasing the FSH dose during ovarian stimulation may increase the number of oocytes retrieved and reduce the risk of cycle cancellation due to insufficient response; conversely, in patients predicted to have a hyper-response to FSH, decreasing the FSH dose may reduce the risk of OHSS and related risk for cycle cancellation. It may be hypothesized that healthcare providers consider dose adjustment during ovarian stimulation worthwhile for improving treatment outcomes and/or reducing risks, and this is reflected in clinical trial designs that allow dose adjustment. The incidence of this dose adjustment in routine clinical practice and its impact on clinical outcomes requires further evaluation.

Abbreviations

FSH: follicle-stimulating hormone; COS: controlled ovarian stimulation; ART: assisted reproductive technology; r-hFSH: recombinant-human FSH; CI: confidence interval; IVF: in vitro fertilization; GnRH: gonadotropin-releasing hormone; ICSI: intracytoplasmic sperm injection; ESHRE: European Society of Human Reproduction and Embryology; POR: poor ovarian response; OHSS: over hyperstimulation syndrome; AMH: anti-Müllerian hormone; AFC: antral follicle count; Ol: ovulation induction; PCOS: polycystic ovary syndrome; SD: standard deviation; BMI: body mass index; ASRM: American Society of Reproductive Medicine

Supplementary Information

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Additional file 1.

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Data availability statement

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck KGaA's Data Sharing Policy. All requests should be submitted in writing to Merck KGaA's data sharing portal <https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html>. When Merck KGaA has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck KGaA will endeavour to gain agreement to share data in response to requests.

Authors' contributions

All authors contributed to the conception and design of the analysis, as well as interpretation of data and critical review of this manuscript. All authors approved the manuscript for submission to the journal.

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Availability of data and materials

All data analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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