

Clinical outcomes in relation to the daily dose of recombinant follicle-stimulating hormone for ovarian stimulation in *in vitro* fertilization in presumed normal responders younger than 39 years: a meta-analysis

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BACKGROUND: The optimal ovarian stimulation dose to obtain the best balance between the probability of pregnancy and the risk of complications, while maximizing cost-effectiveness of *in vitro* fertilization (IVF) treatment, is yet to be established.

METHODS: A systematic search of the electronic databases PubMed, EMBASE and Cochrane library, from 1984 until October 2009 for randomized controlled trials comparing different doses of recombinant FSH in IVF, was performed.

RESULTS: Ten studies (totaling 1952 IVF cycles) were included in the present meta-analysis, comprising patients younger than 39 years with regular menstrual cycle, normal basal FSH levels and two normal ovaries. Comparison was made between studies using a daily dose of 100 versus 200 IU recFSH, and between 150 versus 200 IU recFSH or higher. Although oocyte yield was greater in the >200 IU/day dose group, pregnancy rates were similar compared with lower dose groups. The risk of insufficient response to ovarian stimulation was greatest in the 100 IU/day dose group. The risk of developing ovarian hyperstimulation syndrome was greater in the >200 IU/day dose group. The number of embryos available for cryopreservation was lowest in the 100 IU/day group, but similar comparing the 150 IU/day and the >200 IU/day dose groups.

CONCLUSIONS: This meta-analysis suggests that the optimal daily recFSH stimulation dose is 150 IU/day in presumed normal responders younger than 39 years undergoing IVF. Compared with higher doses, this dose is associated with a slightly lower oocyte yield, but similar pregnancy and embryo cryopreservation rates. Furthermore, the wide spread adherence to this optimal dose will allow for a considerable reduction in IVF costs and complications.

Key words: RCT / IVF / recFSH / ovarian stimulation / meta-analysis

Introduction

In the UK, one in six couples is faced with the problem of infertility (Cahill and Wardle, 2002) and almost 45 000 cycles of *in vitro* fertilization (IVF) treatment are carried out annually. In order to compensate for inefficiencies in the process, and to allow for the selection of embryos for intrauterine transfer or cryopreservation, ovarian stimulation is usually performed by administering exogenous gonadotrophins (Macklon *et al.*, 2006). This approach results in the generation of multiple oocytes from a single treatment cycle, as opposed to the normal menstrual cycle which usually results in the ovulation of a single oocyte (Fauser and Van Heusden, 1997).

For ovarian stimulation, recombinant follicle-stimulating hormone (recFSH) preparations are currently administered in dosages ranging from 100 to 600 IU/day (Nargund *et al.*, 2007; Malizia *et al.*, 2009). The induced multiple follicular development carries the risk of premature luteinization. Co-treatment with gonadotrophin-releasing hormone (GnRH) agonist or antagonist is normally instituted to prevent an untimely rise in the luteinizing hormone (LH) (Huime and Lambalk, 2001). The costs of the gonadotrophins represent a significant proportion (up to 30%) of the costs for an entire IVF treatment cycle (Wechowski *et al.*, 2009). Therefore, a reduction in the amount of recFSH-administered would significantly affect the costs of an IVF treatment.

At present, the optimal starting dose for ovarian stimulation leading to the highest possibility of achieving a pregnancy, while minimizing the chances for major patient discomfort and complications, is not known. Studies reporting the dose-effect relationship for this type of medication are scarce, and current practice is largely based on empirical considerations. The aim of the current systemic review is to identify the optimal daily starting dose of recFSH taking into account ovarian response, pregnancy chances, rate of cycle cancellation and the incidence of the potentially life-threatening complication of ovarian hyperstimulation syndrome (OHSS). Published randomized comparative dosage trials were searched in order to identify the recFSH dose with the best clinical efficacy, cost-effectiveness and safety profile.

Methods

Search strategy, selection criteria and data collection

In this meta-analysis, the Quality of Reporting of Meta-analyses (QUOROM) guidelines were adhered to. Prior to performance of the literature search, a number of inclusion criteria were established. Only randomized controlled trials were considered eligible. The reported methods of allocation concealment were critically assessed: (i) allocation was adequate, (ii) allocation was unclear and (iii) allocation was inadequate. In order to be included, it was necessary that the trials compared different starting dosages of recFSH for ovarian stimulation in women aged between 18 and 40 years undergoing IVF/ICSI treatment. We performed an electronic search of MEDLINE and EMBASE for English and non-English language publications from 1984 until October 2009. The following Medical Subject Headings (MeSH) search terms were used: 'IVF', 'ICSI', 'ART', 'ovarian stimulation', 'recFSH', 'gonadotrophin' and 'RCT'.

The MeSH strategy yielded 2404 publications in MEDLINE, EMBASE and the Cochrane library. Of those publications, 2356 (including duplicates) were excluded because it was clear from the title that they did

not fulfil the selection criteria. From the remaining 48 articles, 25 could be excluded on the basis of the abstracts. Two reviewers (M.D.S. and S.M.V.-V.) independently reviewed the remaining 23 articles and extracted data from each study using a standardized form. Discrepancies were resolved by discussion and consensus. Finally, the bibliographies of identified studies were hand searched. Figure 1 summarizes the flowchart of article selection and inclusion. When clarification was required regarding an individual study, the first or senior author of the respective article was contacted. The parameter was stated not estimable if no further information could be obtained.

Statistical analysis

Since most of the studies compared either a dose of 100 IU/day versus higher, or 150 IU/day versus higher, two comparisons were made. Comparison A addressed 100 IU/day recFSH versus 200 IU/day recFSH, and comparison B 150 versus 200–250 IU/day recFSH. Further pooling of these groups was considered inappropriate since there was an overlap in dose (a high dose in one study could be the lower dose in another study).

When the outcome of interest was a continuous variable (e.g. number of oocytes), the difference in mean value between the two groups was calculated together with the standard error. These differences were pooled across studies, resulting in a weighted mean difference (WMD). Pooling was performed using the inverse of the variance as weight. For dichotomous outcome parameters (e.g. cancellation), the odds ratios (ORs) per study were calculated and pooled. Pooling was performed using the Mantel–Haenszel method. Statistical pooling was performed for the following outcome parameters: number of oocytes retrieved, clinical pregnancy rate, cancellation rate due to low response, amount of gonadotrophins in IU, OHSS rate and number of cryopreserved embryos.

The 95% confidence intervals (CIs) were calculated for the WMD and pooled ORs, respectively, using the random effects method. The random effect method is preferred because it remains valid even if true heterogeneity between studies is present, therefore we will only present random effects estimates. Statistical heterogeneity between studies was tested for all the outcome parameters and quantified by the I^2 statistic. This describes the percentage of the variability in the effect estimates that is due to heterogeneity rather than sampling variation. A value $>50\%$ is considered as moderate/high heterogeneity (Higgins *et al.*, 2003). In case of statistically significant heterogeneity, univariate meta-regression was performed using the random effects method described by van Houwelingen *et al.* (2002), on the following study characteristics: mean age, mean BMI, duration of infertility, percentage of primary infertility and use of a GnRH analogue. All parameters were reported per started cycle, except for the number of oocytes which were calculated per ovum pick up and the number of frozen embryos which were stated per embryo transfer. All analyses were performed in Review Manager 5.

Results

We identified 11 relevant dosage RCTs reporting data on 1967 women undergoing a single IVF cycle. All trials had parallel design and in most studies the treatment was adequately concealed prior to allocation eight studies allocation score A (Out *et al.*, 1999, 2000, 2001, 2004; Latin-American Puregon IVF Study Group, 2001; Wikland *et al.*, 2001; Hoomans *et al.*, 2002; Tan *et al.*, 2005) and three studies allocation score B (de Jong *et al.*, 2000; Pruksananonda *et al.*, 2004; Cavagna *et al.*, 2006). All but three studies were double-

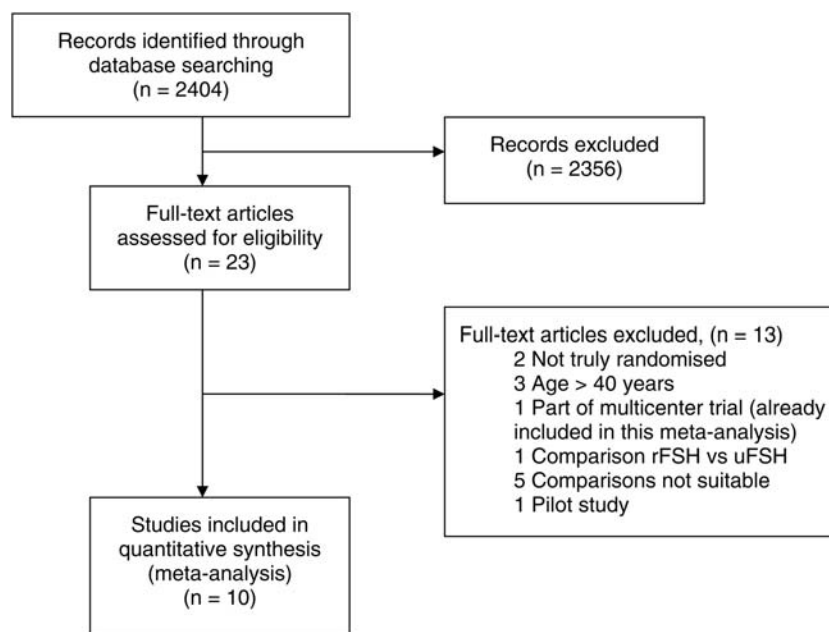


Figure 1 Flow chart of search strategy.

blinded (de Jong et al., 2000; Wikland et al., 2001; Cavagna et al., 2006).

For comparison A (100 versus 200 IU/day recFSH) six studies met the criteria for inclusion in the analysis. Unfortunately, as it was the only study eligible for comparison A which compared 100 versus 150 IU/day and used the GnRH antagonist as co-treatment, we had to exclude one pilot study (de Jong et al., 2000) because of the small numbers of patients (15 in total). Therefore, comparison A involved 960 women in total. The remaining five studies were analyzed in comparison B (150 versus 200–250 IU/day recFSH), involving 992 women. Table I summarizes the inclusion and exclusion criteria per included RCT. All the RCTs included presumed normal responders in their studies (age younger than 39 year, normal basal FSH, regular menstrual cycle and two normal ovaries). Table II summarizes the characteristics of the included studies and the participants. In all studies the upper limit of included ages was at least 35 years.

The main outcome parameters are summarized in Figs 2–7. Figure 2 shows the number of oocytes obtained per oocyte retrieval. In comparison A, the 100 IU/day recFSH group yielded significantly fewer oocytes compared with the higher dose group (mean difference -3.56 ; 95% CI $-4.86, -2.27$; $P < 0.0001$). In comparison B, the 150 IU/day recFSH users obtained 1.7 oocytes fewer than those applying higher dosages (mean difference -1.67 ; 95% CI $-2.53, -0.81$; $P = 0.0001$).

In comparison A, the higher dose group obtained more cryopreserved embryos per embryo transfer (mean difference 1.40 ; 95% CI $-2.32, -0.47$; $P = 0.003$). No difference as observed for comparison B in the number of frozen embryos obtained (mean difference -0.05 ; 95% CI $-0.49, -0.39$; $P = 0.82$) (Fig. 3).

Figure 4 demonstrates the difference in the total amount of recFSH administered between the lower and the higher dose groups. The

mean difference in both comparisons is very similar, but the CI differs (comparison A: mean difference -813.72 IU/day; 95% CI $-860.26, -767.17$; $P < 0.0001$ comparison B: mean difference -671.98 IU/day; 95% CI $-896.85, -447.10$; $P < 0.0001$).

In both comparison groups A and B, the pregnancy rates per started IVF/ICSI cycle did not differ between lower and higher dosages [comparison A: OR 0.95 (calculated pooled estimates 19.5 and 20.3%, respectively), 95% CI 0.69–1.30, $P = 0.74$; comparison B: OR 1.14 (calculated pooled estimates 26.8 and 24.2%, respectively), 95% CI 0.85–1.51, $P = 0.38$] (Fig. 5).

Cancellation due to low ovarian response to stimulation in comparison A (Fig. 6) was observed to be more frequent in the 100 IU/day recFSH dose group [OR 5.02 (calculated pooled estimates 16.4 and 3.8%, respectively); 95% CI 2.19–11.51; $P = 0.0001$]. There was no difference in cancellation rate for low response in comparison B [OR 1.10 (calculated pooled estimates 4.4 and 4.0%, respectively); 95% CI 0.59–2.05; $P = 0.76$].

Figure 7 illustrates the risk of OHSS in relation to dose. In comparison A, the risk was reduced in the 100 IU/day recFSH dosage dose group by a factor of almost two [OR 0.58 (calculated pooled estimates 1.9 and 3.4%, respectively); 95% CI 0.18–1.90; $P = 0.37$]. In comparison B, the risk for OHSS was 33% lower in the 150 IU/day recFSH group compared with the higher dosage group [OR 0.67 (calculated pooled estimates 2.6 and 3.8%, respectively); 95% CI 0.33–1.37; $P = 0.27$]. However, for both comparison groups these ORs were not significantly different.

Heterogeneity across comparisons was found for the parameters number of oocytes (comparison A $I^2 = 65\%$), number of frozen embryos (comparison A $I^2 = 80\%$) and total amount of recFSH (comparison B $I^2 = 96\%$).

In meta-regression on the parameter number of oocytes, none of the study characteristics explained the heterogeneity. For the

Table I Inclusion-and exclusion criteria for all the included RCTs.

Study	Inclusion criteria*	Exclusion criteria
Comparison A (100 versus 200 IU/day)		
Out et al. (1999)	Age: 18–39 BMI: 18–29 Cycle: 24–35 Cause of infertility potentially solvable by IVF or ICSI Good physical and mental health	Infertility caused by endocrine abnormalities such as hyperprolactinemia, PCOS, absence of ovarian function Previous ovarian stimulation cycles after which less than three oocytes were retrieved Chronic cardiovascular, hepatic, renal or pulmonary disease History of or current abuse of alcohol or drugs Administration of non-registered investigational drugs within 3 months prior to screening
Out et al. (2001)	Age: 18–37 BMI: 18–29 Cycle: 24–35 Male infertility solvable by ICSI Presence of two ovaries Good physical and mental health	Female cause of infertility except mild endometriosis or mechanical factor Previous IVF or ICSI cycle(s) after which less than three oocytes were retrieved Previous IVF or ICSI cycle(s) with hospitalization due to OHSS More than four previous IVF/ICSI cycles Total fertilization failure in previous IVF or ICSI cycle LH/FSH ratio at screening ≥ 3 Chronic cardiovascular, hepatic, renal or pulmonary disease History of or current abuse of alcohol or drugs Administration of non-registered investigational drugs within 3 months prior to screening
Hoomans et al. (2002)	Age: 18–39 BMI: 18–29 Cycle: 24–35 Cause of infertility potentially solvable by IVF or ICSI Good physical and mental health	Infertility caused by endocrine abnormalities such as hyperprolactinemia, PCOS, absence of ovarian function Previous IVF or ICSI cycle(s) after which less than three oocytes were retrieved Previous IVF or ICSI cycle(s) with hospitalization due to severe OHSS Chronic cardiovascular, hepatic, renal or pulmonary disease History of or current abuse of alcohol or drugs Administration of non-registered investigational drugs within 3 months prior to screening
Pruksananonda et al. (2004)	Age: 25–38 BMI: 18–29 Cycle: 24–35 Good physical and mental health Cause of infertility potentially solvable by IVF or ICSI	Infertility caused by endocrine abnormalities such as hyperprolactinemia, PCOS, absence of ovarian function Previous IVF or ICSI cycle(s) after which less than three oocytes were retrieved
Tan et al. (2005)	Age: 18–39 BMI: 18–29 Cycle: 24–35 Normal early follicular serum FSH concentration Cause of infertility potentially solvable by IVF or ICSI Good physical and mental health	Infertility caused by endocrine abnormalities such as hyperprolactinemia, PCOS, absence of ovarian function Previous IVF or ICSI cycle(s) after which less than three oocytes were retrieved Chronic cardiovascular, hepatic, renal or pulmonary disease History of or current abuse of alcohol or drugs Administration of non-registered investigational drugs within 3 months prior to screening
Comparison B (150 versus 200–250 IU/day)		

Continued

Table 1 Continued

Study	Inclusion criteria*	Exclusion criteria
Out et al. (2000)	Age: 30–39 BMI: 18–29 Cycle: 24–35 Cause of infertility potentially solvable by IVF or ICSI Good physical and mental health	Infertility caused by endocrine abnormalities such as hyperprolactinemia, PCOS, absence of ovarian function One ovary or history of ovarian resection Severe endometriosis (Grade III) Previous ovarian hyperstimulation cycles in which less than three oocytes were retrieved Chronic cardiovascular, hepatic, renal or pulmonary disease History of or current abuse of alcohol or drugs Administration of non-registered investigational drugs within 3 months prior to screening
Wikland et al. (2001)	Age: 20–39 BMI: <30 Cycle: 25–32 Two normal ovaries Normal uterine cavity Infertility treatment due to tubal, male or idiopathic factors or mild endometriosis	Not more than three previous ART attempts No ovarian stimulation 3 months prior to study entry Previous history of severe OHSS Previous failure of IVF or ICSI treatment due to poor response to gonadotrophin therapy (fewer than three mature follicles) ICSI failure History of abnormal gynecological bleeding of undetermined origin Any contraindication to pregnancy Presence of clinically significant systemic disease
Latin-American Puregon IVF study group (2001)	Age: 30–39 BMI: 18–29 Cycle: 24–35 Cause of infertility solvable by IVF or ICSI Good physical and mental health	Infertility caused by endocrine abnormalities such as hyperprolactinemia, PCOS Absence of ovarian function One ovary or history of ovarian resection Severe endometriosis (Grades III and IV) Previous ovarian hyperstimulation cycles in which less than three oocytes were retrieved Previous hospitalization due to OHSS Chronic cardiovascular, hepatic, renal or pulmonary disease History of or current abuse of alcohol or drugs Administration of non-registered investigational drugs within 3 months prior to screening
Out et al. (2004)	Age: 18–39 BMI: 18–29 Cycle: 24–35 Weight: 50–90 kg	History of/or current endocrine abnormality Elevated early follicular phase FSH and/or LH concentration Any clinically significant abnormal laboratory value One ovary Any ovarian and/or abdominal abnormality that would interfere with adequate ultrasound investigation Contra-indications for use of gonadotrophins Use of hormonal preparations within 1 month prior to date of signing consent Alcohol or drugs abuse, or history thereof Administration of investigational drugs within 3 months prior to screening
Cavagna et al. (2006)	Age: 18–35 BMI: 19–29 Cycle: 24–35 FSH < 10 mIU/ml	Endocrine abnormalities Previous ART cycle with poor response Systemic chronic disease

*Age in years, BMI in kg/m² and menstrual cycle in days.

Table II Characteristics of included RCTs, involving a total of 1952 subjects.

Study	Design ^a	Comparison	Study protocol ^b	Population characteristics ^c			
				Mean age	Mean BMI	Mean duration of infertility	Number of primary infertility (%)
Comparison A (100 versus 200 IU/day)							
Out et al. (1999)	Allocation A	100 versus 200 IU/day	Agonist	32.7 (3.41) versus 32.4 (3.05)	22.9 (2.87) versus 23 (2.83)	5.25 versus 5	62 versus 75
	Multicenter	n = 101 versus n = 98	Fixed				
	n = 199						
Out et al. (2001)	Allocation A	100 versus 200 IU/day	Agonist	27.5 (4.2) versus 27.5 (3.7)	22.7 (3.1) versus 23.2 (3.1)	3.9 (2.7) versus 4.1 (3)	69 versus 70
	Multicenter	n = 91 versus n = 88	Fixed				
	n = 179						
Hoomans et al. (2002)	Allocation A	100 versus 200 IU/day	Agonist	31.6 (3.6) versus 32.1 (3.8)	22.2 (2.9) versus 22.3 (2.9)	5.2 (2.8) versus 5.9 (3.5)	NA
	Multicenter	n = 163 versus n = 167	Fixed				
	n = 330						
Pruksananonda et al. (2004)	Allocation B	100 versus 200 IU/day	Agonist	34.7 (3.14) versus 33.7 (6.87)	20.2 (1.97) versus 20.7 (2.22)	6 (3.2) versus 5.4 (2.3)	NA
	Single center	n = 30 versus n = 30	Fixed				
	n = 60						
Tan et al. (2005)	Allocation A	100 versus 200 IU/day	Agonist	33.3 (3.1) versus 33.4 (3.3)	NA	4.7 (3.2) versus 4.8 (3.2)	80 versus 76
	Multicenter	n = 97 versus n = 95	Fixed 4 days, then flexible				
	n = 192						
Comparison B (150 versus 200–250 IU/day)							
Out et al. (2000)	Allocation A	150 versus 200 IU/day	Agonist	35.1 (2.6) versus 34.5 (3.2)	23.8 (2.8) versus 23.5 (3.4)	7 (4.1) versus 7.69 (5.3)	60 versus 65
	Multicenter	n = 67 versus n = 71	Fixed				
	n = 138						
Wikland et al. (2001)	Allocation A	150 versus 225 IU/day	Antagonist	32.7 (3.9) versus 32.2 (3.9)	22.9 (2.6) versus 22.9 (2.5)	3.6 (1.7) versus 3.7 (2.1)	43 versus 30
	Bicenter	n = 58 versus n = 59	Fixed 5 days, then flexible				
	n = 117						
Latin-American Puregon IVF study group (2001)	Allocation A	150 versus 250 IU/day	Agonist	35.1 (3.1) versus 35.3 (2.9)	22.9 (2.7) versus 23.1 (2.7)	5.4 (3.3) versus 5.2 (3.5)	53 versus 61
	Multicenter	n = 201 versus n = 203	Fixed				
	n = 404						

Continued

Table 11 Continued

Study	Design ^a	Comparison	Study protocol ^b	Population characteristics ^c			Number of primary infertility (%)
				Mean age	Mean BMI	Mean duration of infertility	
Out et al. (2004)	Allocation A	150 versus 200 IU/day	Antagonist	32.7 (3.6) versus 32.2 (3.5)	23.5 (2.9) versus 23.5 (2.7)	4.6 (2.7) versus 4.6 (2.5)	51 versus 62
	Multicenter	n = 131 versus n = 126	Fixed 5 days, then flexible				
Cavagna et al. (2006)	Allocation B	150 versus 200 IU/day	Agonist	31.4 (2.8) versus 31.7 (2.8)	NA	6.1 (2.5) versus 6.7 (3.3)	73 versus 75
	Single center	n = 40 versus n = 36	Fixed				
		n = 76					

NA, information not available.

^aRCT, randomized control trial. Concealment of allocation: (A) adequate and (B) unclear.

^bUse of GnRH analogue (agonist or antagonist), and use of recFSH fixed during treatment or flexible (increase or decrease of the dose after certain days).

^cMean (SD) or median (range).

parameter number of frozen embryos, the body mass index (BMI) was the characteristic which could explain this heterogeneity. Women with a lower BMI showed a greater dose-related difference in the number of embryos available for freezing, and this was similarly evident in both the comparison groups.

In comparison B, heterogeneity in the total amount of recFSH was explained by the study characteristic age. The first two studies (Out et al., 2000; Latin-American Puregon IVF Study Group, 2001) have a mean age around 35 years and the rest of the studies (Wikland et al., 2001; Out et al., 2004; Cavagna et al., 2006), around 32 years. The studies with the ‘older’ patients have a larger difference in total amount of recFSH (Fig. 4).

Discussion

Until now, no consensus regarding the optimal starting dose of FSH for ovarian hyperstimulation in IVF/ICSI treatment cycles in presumed normal responders exists. Sufficiently powered dose–response studies providing useful information in relation to the preferred effective starting dose of exogenous gonadotrophins are scarce. Despite this lack of information, many clinicians have strong beliefs as to what constitutes the best dose regimen for their patients. However, this is based largely on personal experience and limited empirical research. Therefore, practices vary throughout the world and even between IVF centers within the same country. These differences in patient management may have major implications for IVF pregnancy rates, drug costs, complication rates and possibly also for patient discomfort.

The current meta-analysis represents a first attempt to provide objective information regarding the relationship between the applied daily FSH dose for ovarian stimulation in presumed normal responders in IVF/ICSI and the outcomes, cost and complications of the treatment. This study demonstrates that the average number of oocytes retrieved per pick-up is increased when higher FSH doses over 100 IU/day are given, whereas pregnancy rates do not differ across the dosage range tested (Fig. 8). Moreover, the number of frozen embryos available for subsequent transfer does not improve with dosages exceeding 150 IU/day, suggesting that cumulative pregnancy rates (including additional cryo embryo transfer cycles) will not become superior.

Pharmacodynamic studies of recFSH have shown that the response to a 225 IU daily dose varies mainly according to the women’s age and her ovarian reserve status (Karlsson et al., 1997). This finding implies that a limitation exists under given circumstances in the number of follicles that can be stimulated to ongoing development. The comparison between 150 IU/day and higher dosages revealed that the increase in number of oocytes harvested is limited. This may indicate that the dose eliciting optimal stimulation of the ovaries in most patients may be somewhere between 150 and 200 IU/day. Using a dosage of 100 IU/day leads to a more pronounced reduction in oocyte number compared with higher doses, suggesting that in this dose range a dose–response relationship does exist. With current starting dosages of 150 IU/day or more in most centers, optimal or near optimal stimulation of the ovaries will usually be obtained.

In recent years, so-called ‘mild’ stimulation regimens have been proposed, aimed at harvesting more modest numbers of oocytes (Nargund et al., 2007). Initial studies suggest that in comparison with conventional stimulation, milder ovarian stimulation protocols

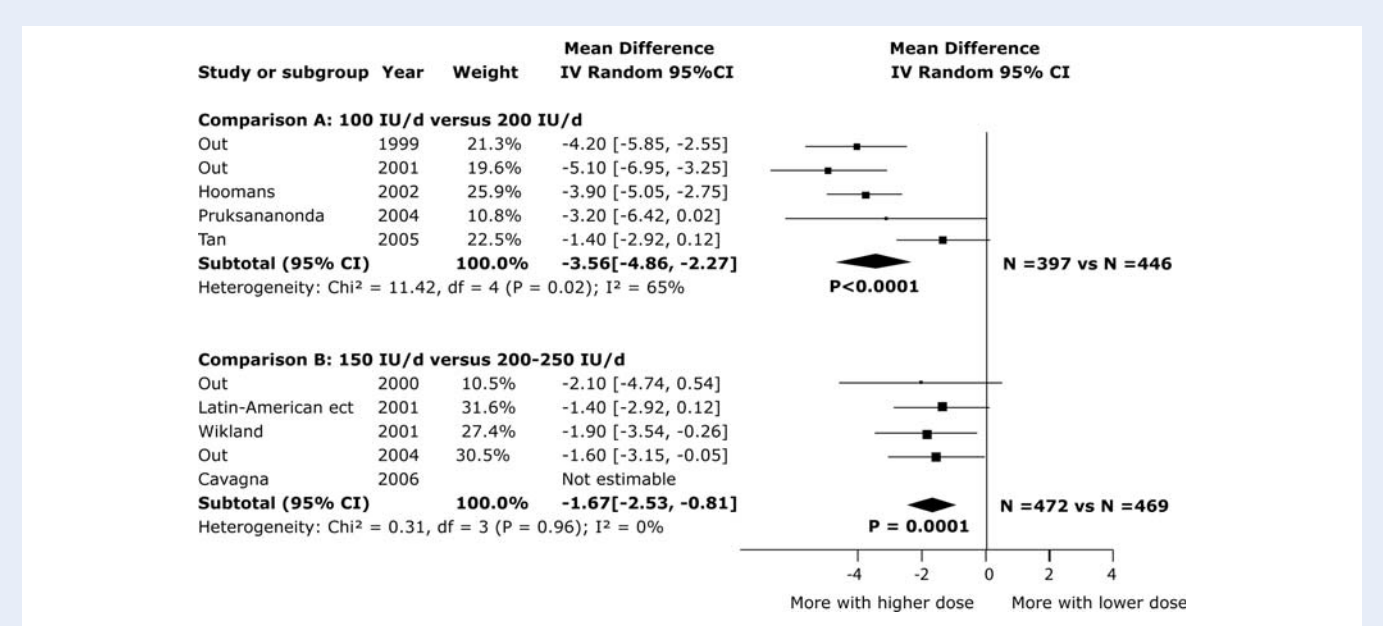


Figure 2 Forest plot of mean difference of number of oocytes per oocyte pick-up. Forest plot: the area for each square is proportional to the weight of the corresponding study. The diamond represents the pooled WMD, and its width represents its 95% CI. A horizontal line represents each study, with its effect size and 95% CIs. The solid vertical line corresponds to no difference. df, degrees of freedom.

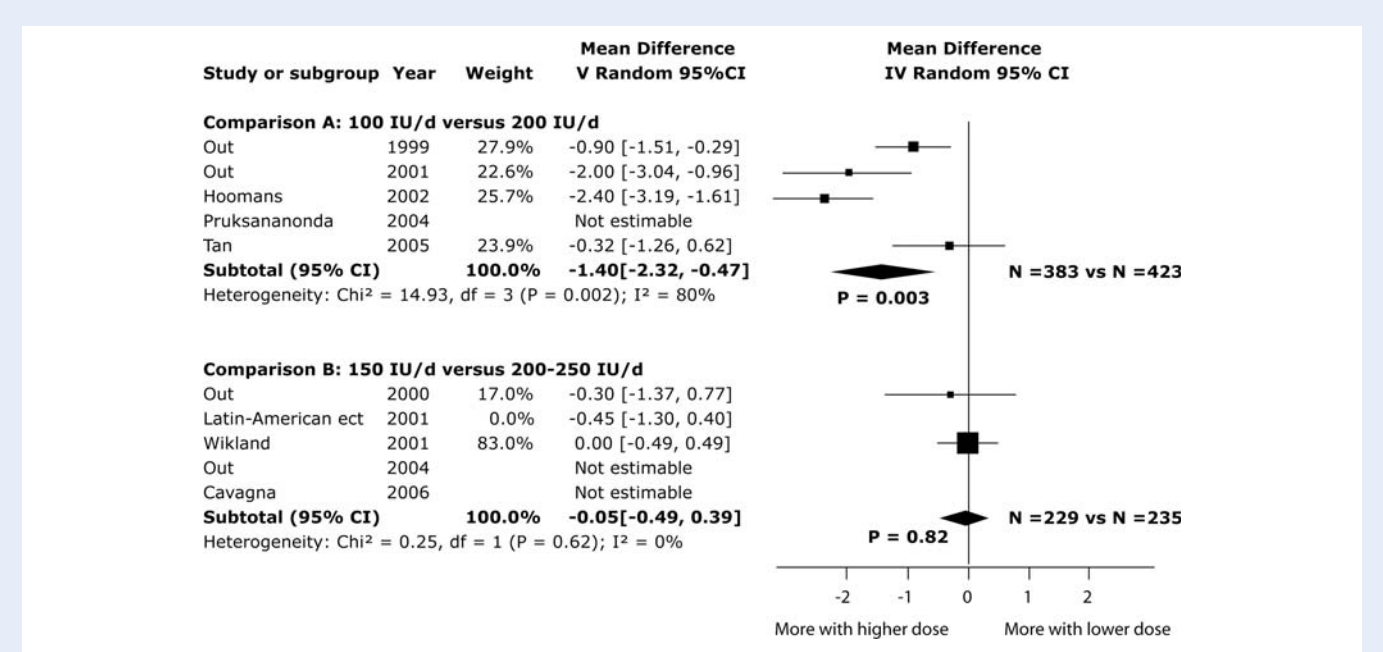


Figure 3 Forest plot of mean difference of number of cryopreserved embryos.

are associated with medical, health, economic and psychological benefits (Heijnen *et al.*, 2007). The present meta-analysis demonstrates that even in conventional GnRH agonist stimulation regimes the use of lower daily dosages of recFSH (i.e. 100 IU/day) produces more modest ovarian responses without undesirable effects on pregnancy rates. Consistent with these findings, a recent study in which recFSH dose adaptations were based on individualized patient profiles, ranging from 75 up to 225 IU/day, revealed that in ~30% of patients,

a dose of 100 IU/day or less is sufficient to obtain moderate oocyte numbers with high pregnancy rates (Olivennes *et al.*, 2009). Milder ovarian responses may create equal numbers of good quality embryos compared with conventional stimulation approaches (Hohmann *et al.*, 2003; Baart *et al.*, 2007). The current paradigm of a standard dose which will work for the majority of women is therefore being increasingly questioned (Fauser *et al.*, 2008). In the current meta-analysis, data were pooled in two comparison groups (A: 100

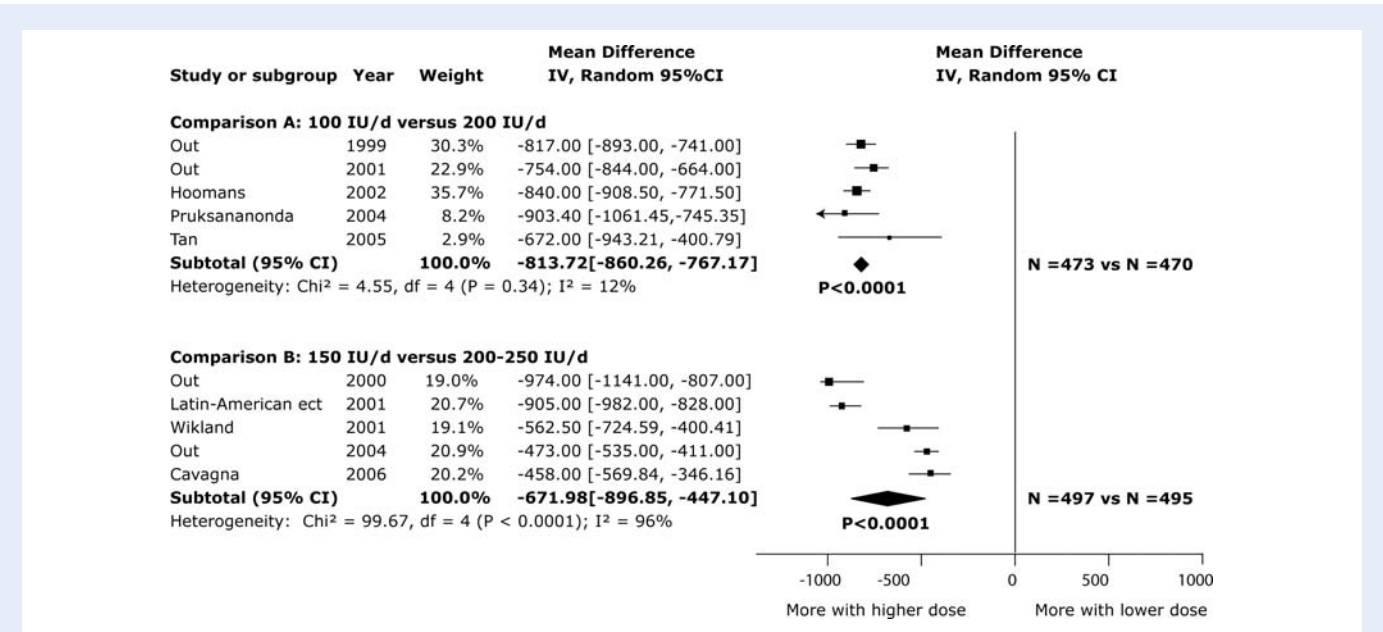


Figure 4 Forest plot of mean difference of total amount of recFSH (IU).

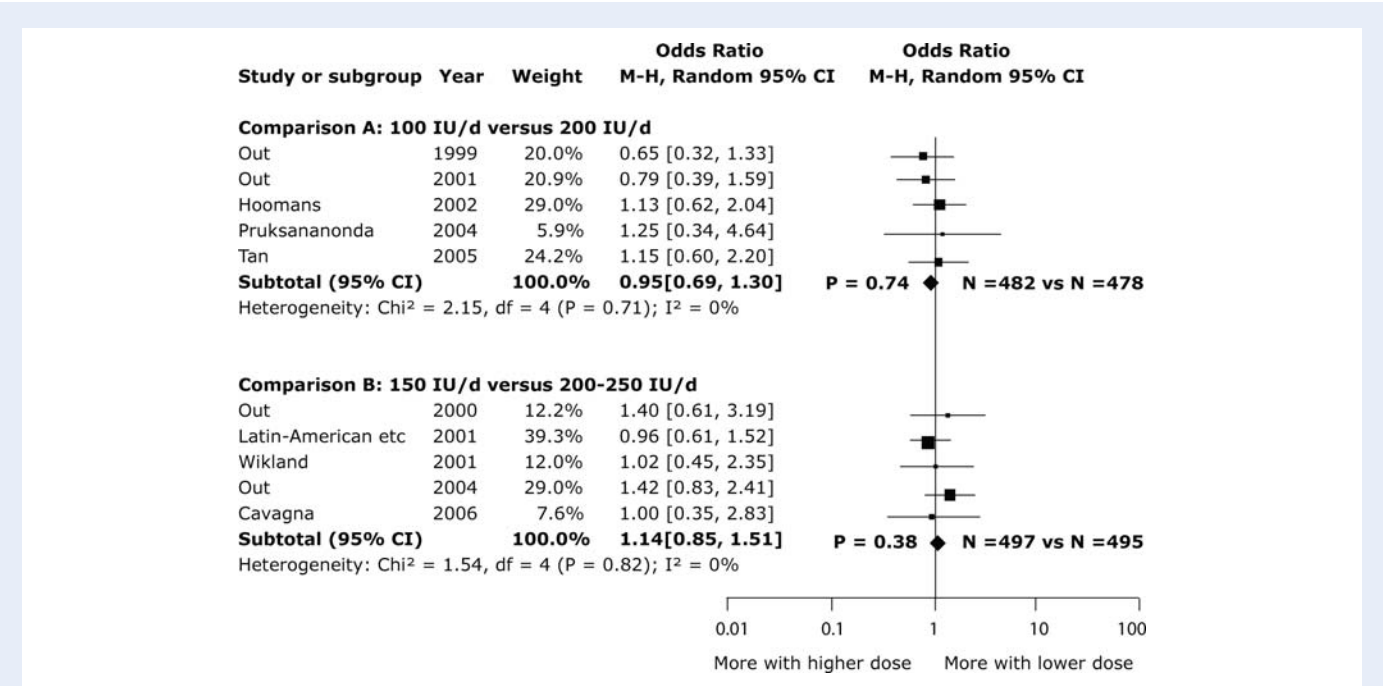


Figure 5 Forest plots of ORs of clinical pregnancy rates.

versus 200 IU/day; B: 150 versus 200–250 IU/day). Besides the dosages, the studies were different in the use of GnRH agonist and antagonist co-treatment. We demonstrated that for the analysis of total amount of recFSH, number of oocytes and number of cryopreserved embryos, heterogeneity could be explained by age and BMI. The validity of pooling studies with different co-treatment characteristics may be questioned. However, re-analysis excluding the studies with GnRH antagonist as co-treatment (Wikland et al., 2001; Out

et al., 2004) demonstrated no differences in pooled results of all outcome parameters compared with the original analysis. A potentially negative outcome of giving a lower dose of recFSH is the risk of low response resulting in cycle cancellation. However, we have previously shown in this meta-analysis that the pregnancy rates following low dosage use are similar to conventional dosages. This indicates that doctors should not be unduly concerned if a low response is observed and can proceed to aspiration of the oocytes

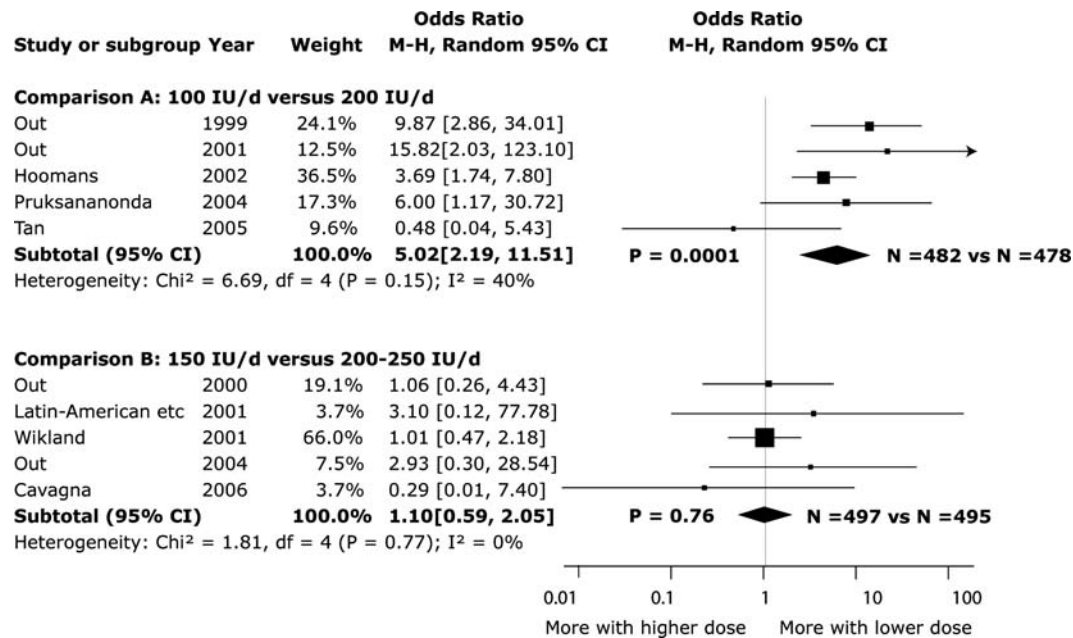


Figure 6 Forest plots of ORs of cycle cancellation rates due to low ovarian response to stimulation.

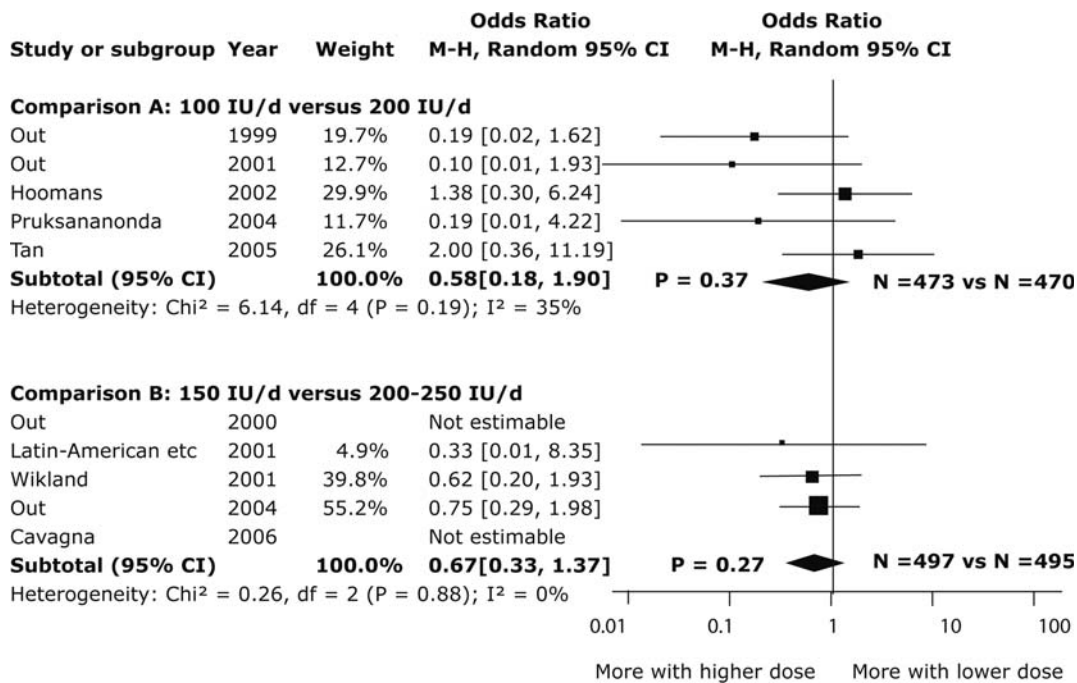


Figure 7 Forest plots of ORs of OHSS rates.

even when few follicles are present. When using 150 IU/day the probability of low response is not different from higher dosages, indicating that in general, 150 IU/day is likely to represent the optimal dosage.

Extreme responses to ovarian stimulation introduce the risk of developing the OHSS (Delvigne and Rozenberg, 2002; Aboulghar and Mansour, 2003). Although early diagnosis and treatment may

minimize the risk of catastrophic events (such as thromboembolism and multiple organ failure) preventing the occurrence of OHSS remains the cornerstone of proper management. Alongside refraining from human chorionic gonadotrophin for triggering of final oocyte maturation or the cryopreservation of all embryos obtained in very high responder patients, avoiding extreme ovarian response should

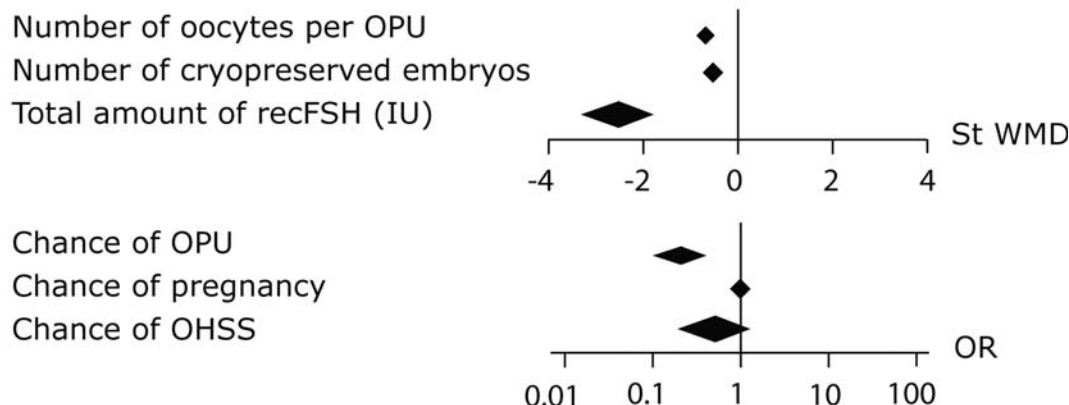
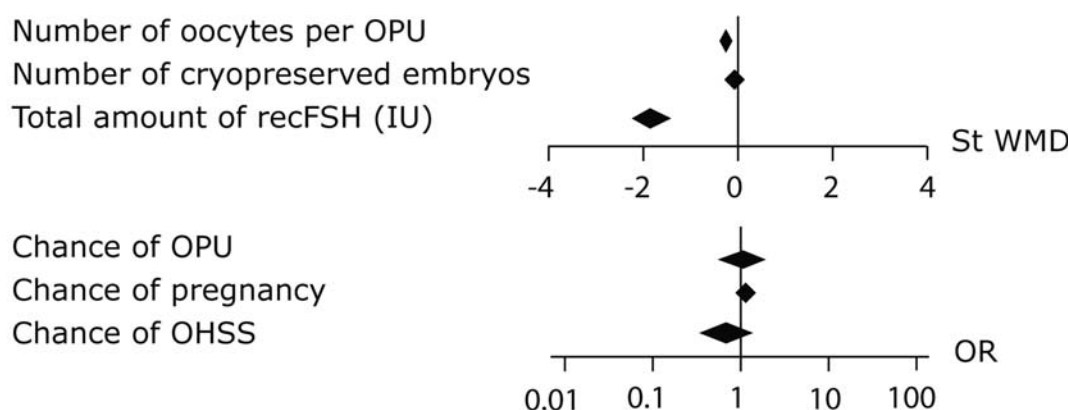
A 100 IU/d versus 200 IU/d**B 150 IU/d versus 200-250 IU/d**

Figure 8 Summary all parameters; **(A)** Comparison A: 100 versus 200 IU/day; **(B)** Comparison B: 150 versus 200–250 IU/day. St WMD, standardized weighted mean difference; OR, odds ratio; OPU, ovum pick up; OHSS, ovarian hyperstimulation syndrome.

be regarded as the primary approach in the prevention of OHSS. The tendency for lower OHSS rates in lower dose groups, as demonstrated in the present meta-analysis, further supports the approach of submaximal ovarian stimulation.

Reduction in total recFSH dose would also considerably cut the cost of IVF treatment. As the total duration of stimulation (on average 12 days) is not affected by dosage changes, the use of a standard dose of 150 IU/day, instead of 225 IU/day, would reduce per-cycle costs of gonadotrophin medication by ~30% (Wechowski et al., 2009). This would imply that every set of two IVF treatment cycles will save the amount of recFSH sufficient for a third stimulation cycle. The use of GnRH antagonist as co-treatment might lead to an even lower consumption of recFSH, mainly by a reduction in the duration of stimulation due to relatively high endogenous FSH concentrations early during the stimulation cycle (Fauser and Van Heusden, 1997; Baart et al., 2007; Heijnen et al., 2007).

Significant strengths of the current meta-analysis are that it was performed according to the QUOROM guidelines, that almost 2000 IVF

cycles were involved in the analysis, that heterogeneity was addressed and was explained by meta-regression. We had to split the dosage comparisons into two groups. An advantage of this split was that we could assess the dose at which there was no more gain of a higher dose and thus determine the optimal starting dose. Limitations of this study are that the patient groups were more restricted in age and BMI than is seen in everyday practice. Furthermore, the most relevant clinical end-point, cumulative live birth, was not available in most studies. We therefore had to restrict the analysis to ongoing pregnancy rates. The effect of OHSS is overestimated since in some studies no distinction was made between mild, moderate and severe OHSS. Another limitation of this meta-analysis is that all included studies had the number of oocytes as primary outcome parameter. Therefore none of the studies were powered for differences in pregnancy rates. The pooling of data, however, has allowed for drawing valid conclusions on the effect of FSH dosage level on the clinical pregnancy rates. Finally, all underlying studies applied a so-called 'one-size fits all' approach, with no possibilities for patient-

tailored adjustments based on individual patient characteristics (Popovic-Todorovic *et al.*, 2003b).

In conclusion, this meta-analysis suggests that the optimal starting dose of recFSH for IVF/ICSI is 150 IU daily in presumed normal responders younger than 39 years. This dose is associated with a more modest oocyte yield, but an equal pregnancy rate compared with higher doses. Further benefits of this dose include a possible reduction in the risk for OHSS, in the face of sufficient numbers of oocytes to allow for cryopreservation of surplus embryos. In the future, the use of patient-tailored approaches may further optimize the risk-benefit balance, increasing the proportion of women exhibiting an adequate ovarian response while further reducing the need for intense monitoring of ovarian response (Popovic-Todorovic *et al.*, 2003a; Fauser *et al.*, 2008; Olivennes *et al.*, 2009).

Authors' roles

M.D.S., S.M.V.-V., M.J.E., F.J.B. and B.C.J.M.F. involved in study design, analysis, manuscript drafting and critical discussion; E.G.H. involved analysis, manuscript drafting and critical discussion; N.S.M. participated in study design, manuscript drafting and critical discussion.

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