

University of Groningen

Individualized versus standard FSH dosing in women starting IVF/ICSI

Oudshoorn, Simone C.; Van Tilborg, Theodora C.; Eijkemans, Marinus J. C.; Oosterhuis, G. Jur E.; Friederich, Jaap; van Hooff, Marcel H. A.; van Santbrink, Evert J. P.; Brinkhuis, Egbert A.; Smeenk, Jesper M. J.; Kwee, Janet

Published in:
Human Reproduction

DOI:
[10.1093/humrep/dex319](https://doi.org/10.1093/humrep/dex319)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Oudshoorn, S. C., Van Tilborg, T. C., Eijkemans, M. J. C., Oosterhuis, G. J. E., Friederich, J., van Hooff, M. H. A., ... OPTIMIST study group (2017). Individualized versus standard FSH dosing in women starting IVF/ICSI: An RCT. Part 2: The predicted hyper responder. *Human Reproduction*, 32(12), 2506-2514. DOI: 10.1093/humrep/dex319

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 2: The predicted hyper responder

Simone C. Oudshoorn^{1,*}, Theodora C. van Tilborg¹,
Marinus J.C. Eijkemans², G. Jur E. Oosterhuis³, Jaap Friederich⁴,
Marcel H.A. van Hooff⁵, Evert J.P. van Santbrink⁶, Egbert
A. Brinkhuis⁷, Jesper M.J. Smeenk⁸, Janet Kwee⁹, Corry H. de
Koning¹⁰, Henk Groen¹¹, Cornelis B. Lambalk¹², Ben Willem
J. Mol^{13,14}, Frank J. M. Broekmans¹, and Helen L. Torrance¹, on behalf
of the OPTIMIST study group[†]

¹Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, Utrecht University, PO Box 85500, 3508 GA Utrecht, The Netherlands ²Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, PO Box 85500, 3508 GA Utrecht, The Netherlands ³Department of Obstetrics and Gynaecology, St. Antonius Hospital, PO box 2500, 3430 EM Nieuwegein, The Netherlands ⁴Department of Obstetrics, Gynaecology and Reproductive Medicine, Noordwest Ziekenhuisgroep, PO Box 750, 1780 AT Den Helder, The Netherlands ⁵Department of Gynaecology, St. Franciscus Gasthuis, PO Box 10900, 3004 BA Rotterdam, The Netherlands ⁶Fertility Clinic Reinier de Graaf group, Diaconessenhuis Voorburg, PO Box 998, 2275 CX, Voorburg, The Netherlands ⁷Department of Obstetrics and Gynaecology, Meander Medical Centre, PO Box 1502, 3800 BM Amersfoort, The Netherlands ⁸Centre for Reproductive Medicine, Elisabeth-TweeSteden Hospital, PO Box 90151, 5000 LC Tilburg, The Netherlands ⁹Department of Obstetrics and Gynaecology, Onze Lieve Vrouwe Gasthuis West, PO Box 9243, 1006 AE Amsterdam, The Netherlands ¹⁰Department of Obstetrics and Gynaecology, Tergooi Hospital, PO Box 1201 DA Blaricum, The Netherlands ¹¹Department of Epidemiology, University of Groningen, University Medical Centre Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands ¹²Centre for Reproductive Medicine, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands ¹³The Robinson Research Institute, School of Paediatrics and Reproductive Health, University of Adelaide, SA 5006 Adelaide, Australia ¹⁴The South Australian Health and Medical Research Unit, PO Box 11060, SA 5001 Adelaide, Australia

*Correspondence address. Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, Utrecht, The Netherlands. E-mail: s.c.oudshoorn-4@umcutrecht.nl

Submitted on January 27, 2017; resubmitted on September 19, 2017; accepted on October 12, 2017

STUDY QUESTION: Does a reduced FSH dose in women with a predicted hyper response, apparent from a high antral follicle count (AFC), who are scheduled for IVF/ICSI lead to a different outcome with respect to cumulative live birth rate and safety?

SUMMARY ANSWER: Although in women with a predicted hyper response (AFC > 15) undergoing IVF/ICSI a reduced FSH dose (100 IU per day) results in similar cumulative live birth rates and a lower occurrence of any grade of ovarian hyperstimulation syndrome (OHSS) as compared to a standard dose (150 IU/day), a higher first cycle cancellation rate and similar severe OHSS rate were observed.

WHAT IS KNOWN ALREADY: Excessive ovarian response to controlled ovarian stimulation (COS) for IVF/ICSI may result in increased rates of cycle cancellation, the occurrence of OHSS and suboptimal live birth rates. In women scheduled for IVF/ICSI, an ovarian reserve test

[†]OPTIMIST study group: Theodora C. van Tilborg, Simone C. Oudshoorn, Marinus J.C. Eijkemans, Monique H. Mochtar, Carolien A.M. Koks, Ron J.T. van Golde, Harold R. Verhoeve, Annemiek W. Nap, Gabrielle J. Scheffer, A. Petra Manger, Annemieke Hoek, Bendictus C. Schoot, G. Jur E. Oosterhuis, Walter K.H. Kuchenbecker, Kathrin Fleischer, Jan Peter de Bruin, Alexander V. Sluijmer, Jaap Friederich, Arie Verhoeff, Marcel H.A. van Hooff, Evert J.P. van Santbrink, Egbert A. Brinkhuis, Jesper M.J. Smeenk, Janet Kwee, Corry H. de Koning, Henk Groen, Madelon van Wely, Cornelis B. Lambalk, Joop S.E. Laven, Ben Willem J. Mol, Frank J.M. Broekmans, Helen L. Torrance.

(ORT) can be used to predict response to COS. No consensus has been reached on whether ORT-based FSH dosing improves effectiveness and safety in women with a predicted hyper response.

STUDY DESIGN SIZE, DURATION: Between May 2011 and May 2014, we performed an open-label, multicentre RCT in women with regular menstrual cycles and an AFC > 15. Women with polycystic ovary syndrome (Rotterdam criteria) were excluded. The primary outcome was ongoing pregnancy achieved within 18 months after randomization and resulting in a live birth. Secondary outcomes included the occurrence of OHSS and cost-effectiveness. Since this RCT was embedded in a cohort study assessing over 1500 women, we expected to randomize 300 predicted hyper responders.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women with an AFC > 15 were randomized to an FSH dose of 100 IU or 150 IU/day. In both groups, dose adjustment was allowed in subsequent cycles (maximum 25 IU in the reduced and 50 IU in the standard group) based on pre-specified criteria. Both effectiveness and cost-effectiveness were evaluated from an intention-to-treat perspective.

MAIN RESULTS AND THE ROLE OF CHANCE: We randomized 255 women to a daily FSH dose of 100 IU and 266 women to a daily FSH dose of 150 IU. The cumulative live birth rate was 66.3% (169/255) in the reduced versus 69.5% (185/266) in the standard group (relative risk (RR) 0.95 [95%CI, 0.85–1.07], $P = 0.423$). The occurrence of any grade of OHSS was lower after a lower FSH dose (5.2% versus 11.8%, RR 0.44 [95%CI, 0.28–0.71], $P = 0.001$), but the occurrence of severe OHSS did not differ (1.3% versus 1.1%, RR 1.25 [95%CI, 0.38–4.07], $P = 0.728$). As dose reduction was not less expensive (€4.622 versus €4.714, delta costs/woman €92 [95%CI, –479–325]), there was no dominant strategy in the economic analysis.

LIMITATIONS, REASONS FOR CAUTION: Despite our training programme, the AFC might have suffered from inter-observer variation. Although strict cancellation criteria were provided, selective cancelling in the reduced dose group (for poor response in particular) cannot be excluded as observers were not blinded for the FSH dose and small dose adjustments were allowed in subsequent cycles. However, as first cycle live birth rates did not differ from the cumulative results, the open design probably did not mask a potential benefit for the reduced dosing group. As this RCT was embedded in a larger cohort study, the power in this study was unavoidably lower than it should be. Participants had a relatively low BMI from an international perspective, which may limit generalization of the findings.

WIDER IMPLICATIONS OF THE FINDINGS: In women with a predicted hyper response scheduled for IVF/ICSI, a reduced FSH dose does not affect live birth rates. A lower FSH dose did reduce the incidence of mild and moderate OHSS, but had no impact on severe OHSS. Future research into ORT-based dosing in women with a predicted hyper response should compare various safety management strategies and should be powered on a clinically relevant safety outcome while assessing non-inferiority towards live birth rates.

STUDY FUNDING/COMPETING INTEREST(S): This trial was funded by The Netherlands Organization for Health Research and Development (ZonMw, Project Number 171102020).

SCO, TCvT and HLT received an unrestricted research grant from Merck Serono (the Netherlands). CBL receives grants from Merck, Ferring and Guerbet. BWJM is supported by a NHMRC Practitioner Fellowship (GNT1082548) and reports consultancy for OvsEva, Merck and Guerbet. FJMB receives monetary compensation as a member of the external advisory board for Ferring pharmaceuticals BV and Merck Serono for consultancy work for Gedeon Richter (Belgium) and Roche Diagnostics (Switzerland) and for a research cooperation with Ansh Labs (USA). All other authors have nothing to declare.

TRIAL REGISTRATION NUMBER: Registered at the ICMJE-recognized Dutch Trial Registry (www.trialregister.nl). Registration number: NTR2657.

TRIAL REGISTRATION DATE: 20 December 2010.

DATE OF FIRST PATIENT'S ENROLMENT: 12 May 2011.

Key words: Antral follicle count / FSH / individualized / RCT / hyper ovarian response / live birth / cost-effectiveness / IVF / ICSI / ovarian reserve

Introduction

The optimization of ovarian response to controlled ovarian stimulation (COS) for IVF continues to be an important topic of debate and research in the field of reproductive medicine. Over the last decade a shift has been taking place from 'the more oocytes, the better' towards an optimal range of number of retrieved oocytes at ovum pick-up (OPU) to maximize the chances of conceiving (van der Gaast *et al.*, 2006; Sunkara *et al.*, 2011), while controlling costs and side effects (Chen *et al.*, 2015). The most severe complication of an excessive response to COS is the ovarian hyperstimulation syndrome (OHSS). Cycles are often cancelled

before OPU or a freeze-all approach is chosen when a woman turns out to have a high risk of developing OHSS during stimulation (Humaidan *et al.*, 2016). OHSS is not only associated with an increased risk of thromboembolism (Hignett *et al.*, 1995) but also women are withheld a chance of conceiving in the cancelled cycle. In an attempt to avoid a hyper response, the clinician often adjusts the FSH dose pragmatically based on known response predictors, which usually include a woman's age combined with one or more ovarian reserve tests (ORTs). Anti-Müllerian hormone (AMH) and the antral follicle count (AFC) have been shown to be the most accurate ORTs in the prediction of ovarian response to COS (Broekmans *et al.*, 2006; Broer *et al.*, 2009).

However, it remains unclear whether lowering the FSH dose in women with a predicted hyper response influences treatment outcome in terms of live birth rates and safety, as recently reviewed by [van Tilborg et al. \(2016\)](#). Therefore, the aim of the present RCT was to assess whether a reduced gonadotrophin dose in women scheduled for IVF/ICSI with a predicted hyper response based on a high AFC influences cumulative live birth rates and safety.

Materials and Methods

Study design and population

This open-label, multicentre RCT in predicted hyper responders was embedded in a Dutch prospective, multicentre cohort study in women scheduled for a first IVF/ICSI cycle (the OPTIMIST study). The study protocol was published previously ([van Tilborg et al., 2012](#)) and details can also be found in [van Tilborg et al. \(2017a,b\)](#).

Most importantly, inclusion criteria included a regular indication for IVF/ICSI, female age <44 years, and a regular cycle (average cycle length of 25–35 days). Women with polycystic ovary syndrome (PCOS) ([Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group](#)) were excluded. After written informed consent was obtained, all participating women underwent a transvaginal ultrasound (TVS) for measurement of their AFC.

Study procedures

The AFC was performed in the early follicular phase (cycle Day 1–3) of the stimulation cycle ([Broekmans et al., 2010](#)). If the total AFC of both ovaries was >15 follicles, women were classified as a predicted hyper responder and randomized to receive a reduced dose of 100 IU of FSH or a standard dose of 150 IU of FSH daily. No consensus exists for precise AFC cut-off levels for predicting a hyper response, however, a cut-off between 14 and 16 antral follicles seems to provide the best balance between sensitivity and false positive rate ([Broer et al., 2011](#); [La Marca and Sunkara, 2014](#)).

Further details of the COS and IVF/ICSI procedures have been published previously ([van Tilborg et al., 2012](#)) and are written in [van Tilborg et al. \(2017b\)](#). All participating women were followed for 18 months after randomization and all treatment cycles (fresh and cryo/thaw) within that period were reported.

Dose adjustments during stimulation were not allowed. Between treatment cycle dose adjustments were allowed in both study arms following strict, pre-determined criteria. In the reduced dose group the FSH dose could be adjusted with a step of 25 IU in case of a poor or hyper response. Poor response was defined as the cancellation of a stimulation cycle if <2 follicles >12 mm in diameter or <3 follicles >17 mm were observed on TVS, or if <5 oocytes were retrieved. Hyper response was defined as cancellation of a stimulation cycle because >20 follicles >12 mm in diameter were growing and estradiol levels exceeded 11 700 pmol/l (= 3187,08 ng/l), if >30 follicles >12 mm were growing or if >15 oocytes were retrieved. For the standard dose group a dose adjustment between cycles was allowed with a maximum of 50 IU FSH, following the criteria mentioned above.

Outcome measures

The primary outcome was the cumulative live birth rate of which the ongoing status had to be achieved within 18 months of randomization. Pregnancies could be achieved by fresh or cryo/thawed embryo transfers. Spontaneous pregnancies and pregnancies from IUI after cancellation of IVF/ICSI cycles were also considered. Secondary outcome measures consisted of: other pregnancy stages (definitions given in [van Tilborg et al., 2017b](#)), number of treatment cycles, number of dose adjustments and

amount of dose adjustment between the first and second treatment cycle, cycle cancellation rate, number of retrieved oocytes, the occurrence of a poor or hyper response (for definitions see above), occurrence of OHSS (mild, moderate or severe) and number of frozen embryo transfers. These outcomes measures were assessed and reported for all treatment cycles within 18 months of follow-up and for the first treatment cycle only, as dose adjustments were allowed in subsequent cycles and the first treatment cycle results therefore reflect the two strategies most plainly.

Definitions of OHSS classification

OHSS was divided into three categories. Mild OHSS was defined as abdominal bloating or mild abdominal pain, with ovarian size usually <8 cm. Moderate OHSS was defined as moderate abdominal pain, nausea with or without vomiting or ultrasound evidence of ascites, and ovarian size usually 8–12 cm, while severe OHSS was defined as clinical ascites (occasionally hydrothorax), oliguria, haemoconcentration with haematocrit >45% or hypoproteinaemia, and ovarian size usually >12 cm (adapted from [Golan and Weissman, 2009](#) and [Navot and Bergh, 1993](#) in the Dutch guideline 'Ovarieel Hyperstimulatiesyndroom' by the Dutch society of Obstetrics and Gynaecology).

Sample size calculation

This RCT was embedded in a larger cohort study the design of which was published previously ([van Tilborg et al., 2012](#)). The total sample size of the cohort study was 1500, of which we expected 300 women to be predicted hyper responders.

Statistical analyses

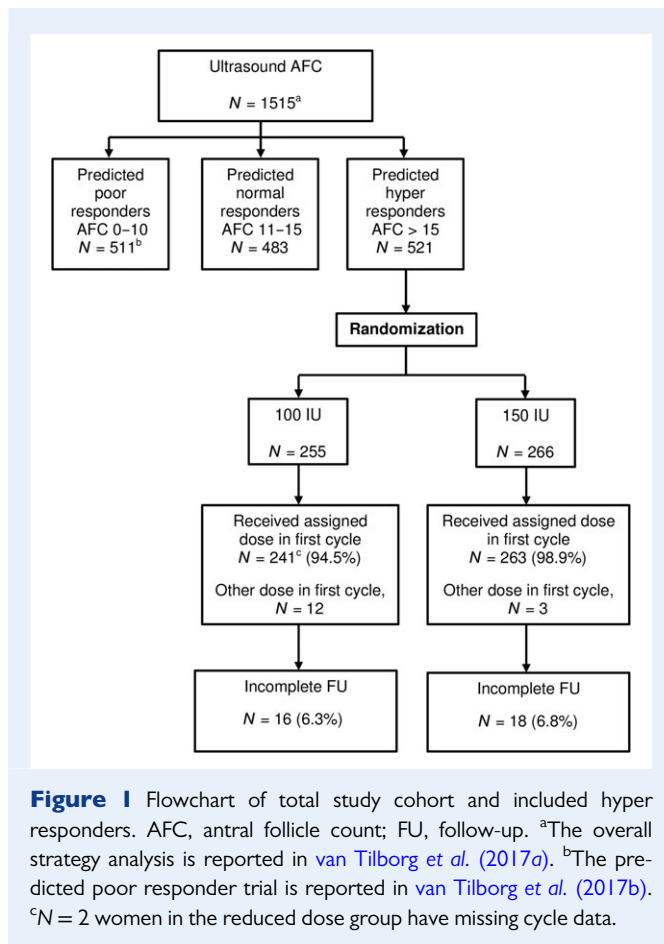
Statistical analysis was performed using SPSS Statistics for Windows (version 21.0: IBM Corp, Armonk, NY, USA) and R (version 3.1.3, R Foundation for Statistical Computing, Vienna, Austria). Further details on the statistical and cost-effectiveness analyses can be found in [van Tilborg et al. \(2017a,b\)](#). In addition, as it has been suggested that using a GnRH-antagonist in predicted hyper responders can prevent the occurrence of OHSS ([Tarlitzis and Kolibianakis, 2007](#)), a pre-specified sensitivity analysis of first treatment cycles was performed in women using GnRH agonists only. The subgroup of women using antagonists was too small to also perform this sensitivity analysis for antagonist co-treatment only.

Results

Between 12 May 2011 and 5 May 2014, we included 1515 women in the OPTIMIST cohort of whom 521/1515 (34.4%) had an AFC > 15 and were classified as a predicted hyper responder. Of these women, 255 were randomized to receive the reduced dose of 100 IU and 266 were randomized to receive the standard dose of 150 IU of FSH daily (Fig. 1). Expecting a clinically relevant gain in pregnancy rate from 35–42% in the reduced dose group as compared to the standard dose group, the group size provided a power of 37% to detect this difference (two-sided alpha, 0.05). Baseline characteristics of the women are listed in Table 1.

Loss to follow-up was minimal in both groups (16/255 (6.3%) in the reduced dose group versus 18/266 (6.8%) in the standard dose group, $P = 0.820$). Mean duration of follow-up for women with incomplete follow-up was 213 days (SD 177) for the reduced and 269 days (SD 135) for the standard group ($P = 0.304$).

Table 2 and Fig. 2 depict cumulative pregnancy results. There was no statistically significant difference in our primary outcome, cumulative live birth rate, in the reduced (169/255, 66.3%) versus the standard group



(185/266, 69.5%), RR 0.953 [0.85–1.07], $P = 0.423$), nor in the time to achieving this pregnancy (mean 185.4 days (SD 129.4) versus 191.4 days (SD 129.8), $P = 0.664$).

Data for all treatment cycles performed within 18 months after randomization are listed in Table III. Women in both groups underwent a similar number of fresh treatment cycles. After completion of the first cycle, the dose was increased in 77/135 (57.3%) of the women in the lower dose group as compared to 19/136 (14.0%) in the standard group ($P < 0.001$) in cycle 2. Conversely, the dose was reduced in 6/135 (4.4%) in the lower dose group versus 53/136 (39.0%) in the standard group ($P < 0.001$). A lower number of oocytes was obtained at OPU in the reduced dose as compared to the standard dose group (9.0 versus 11.9, $P < 0.001$). When combining cancellation rate and oocyte yield, a poor response was more often seen in the reduced dose group than in the standard group (133/459 (29.0%) versus 68/474 (14.3%), $P < 0.001$). In contrast, a hyper response occurred more often in the standard dose group as compared to the reduced dose group (144/474 (30.4%) versus 48/459 (10.5%), $P < 0.001$). Mild and moderate OHSS occurred less often in the reduced dose group as compared to the standard group (mild 18/456 (3.9%) versus 40/474 (8.4%), $P = 0.008$, RR 0.47 [0.27–0.81] and moderate 0/456 versus 11/474 (2.3%), $P = 0.001$, respectively). The incidence of severe OHSS was low and did not differ between groups (6/456 (1.3%) in the reduced dose versus 5/474 (1.1%) in standard dose group, $P = 0.712$, RR 1.25 [0.38–4.07]).

Table 1 Baseline characteristics of predicted hyper responders in a study comparing a reduced versus a standard FSH dose for IVF/ICSI.

Baseline characteristics	100 IU (n = 255)	150 IU (n = 266)
Age (years)	32.0 (4.3)	31.6 (4.5)
Duration of infertility (years)	2.7 (1.7)	2.5 (1.4)
Smoking	38/246 (15.4%)	45/256 (17.6%)
BMI - kg/m ²	23.8 (3.6)	23.9 (3.8)
Primary infertility	166/254 (65.4%)	167 (62.8%)
Cause of infertility ^a		
Unexplained	74 (29.4%)	81 (30.5%)
Male factor	153 (60.0%)	162 (60.9%)
Endometriosis	20 (7.8%)	6 (2.3%)
Tubal factor	27 (10.6%)	24 (9.0%)
AFC (median, IQR)	20.0 (7.0)	21.0 (8.0)
AMH (ng/ml) (median, IQR)	3.26 (1.98)	3.00 (1.89)
GnRH co-treatment ^b		
GnRH-agonist	187 (73.9%)	196 (73.7%)
GnRH-antagonist	66 (26.1%)	70 (26.3%)

Data are presented as mean (SD) or number (%) unless otherwise specified. AFC, antral follicle count; IQR, interquartile range. AMH, anti-Müllerian hormone.

^aMore than one cause of infertility can be present in a given couple.

^bTwo women in the reduced group have missing cycle data.

First cycle

Almost all included women received the assigned dose in the first treatment cycle (241/255 (94.5%) in the reduced dose and 263/266 (98.9%) in the standard dose group). In the reduced dose group, first cycles were more often cancelled because of insufficient follicle growth (53/253 (20.9%) versus 9/266 (3.4%), $P < 0.001$) and less often because of excessive response (5/253 (2.0%) versus 21/266 (7.9%), $P = 0.002$). Other results for the first cycle were comparable to those of all treatment cycles (Table IV).

Sensitivity analyses

The per protocol analysis for all treatment cycles showed similar results to the intention-to-treat analysis (Supplementary Table SI). The sensitivity analysis in women treated with a GnRH-agonist did not change the first cycle results (Supplementary Table SII).

Health economic evaluation

No significant difference in cost-effectiveness was found in the reduced versus the standard FSH dose group (Supplementary Table SIII and Supplementary Fig. S1).

Discussion

This study shows that in women undergoing IVF/ICSI with a predicted hyper response (defined as AFC > 15, but without PCOS), a first cycle FSH dose reduction of 50 IU does not influence live birth rates or the incidence of severe OHSS as compared to a standard FSH dose (150 IU), despite a clearly reduced number of retrieved

Table II Pregnancy data per woman.

Pregnancy data per woman ^a	100 IU (n = 255)	150 IU (n = 266)	RR [95% CI]	P-value
Ongoing pregnancy within 18 months of FU resulting in live birth	169 (66.3%)	185 (69.5%)	0.953 [0.85–1.07]	0.423
First cycle	91 (36.0%)	104 (39.1%)		
Second cycle	39 (15.3%)	45 (16.9%)		
Third cycle	24 (9.4%)	18 (6.8%)		
Fourth cycle	4 (1.6%)	6 (2.3%)		
Fifth cycle	0			
Biochemical pregnancy	190 (74.5%)	215 (80.8%)	0.922 [0.84–1.01]	0.083
Clinical pregnancy	180 (70.6%)	207 (77.8%)	0.907 [0.82–1.00]	0.059
Miscarriage	18 (7.1%)	32 (12.0%)	0.587 [0.34–1.02]	0.054
Ongoing pregnancy	173 (67.8%) ^e	189 (71.1%) ^f	0.955 [0.85–1.07]	0.426
Multiple pregnancy ^b	5 (3.0%)	12 (6.5%)	0.434 [0.16–1.21]	0.101
Conception mode (% of live birth)				0.748
Spontaneous	9 (5.3%)	8 (4.3%)		
IVF/ICSI fresh ^c	118 (69.8%)	123 (66.8%)		
IVF/ICSI cryo	40 (23.7%)	50 (27.2%)		
Other ^d	2 (1.2%)	4 (1.6%)		
Time to ongoing pregnancy leading to live birth (days)	185.4 (129.4)	191.4 (129.8)		0.664

Data are presented as mean (SD) or number (%) unless otherwise specified.

FU, follow-up; RR, relative risk. P-value calculated by using a Chi-square test.

^aShown with a maximum of one event per woman.

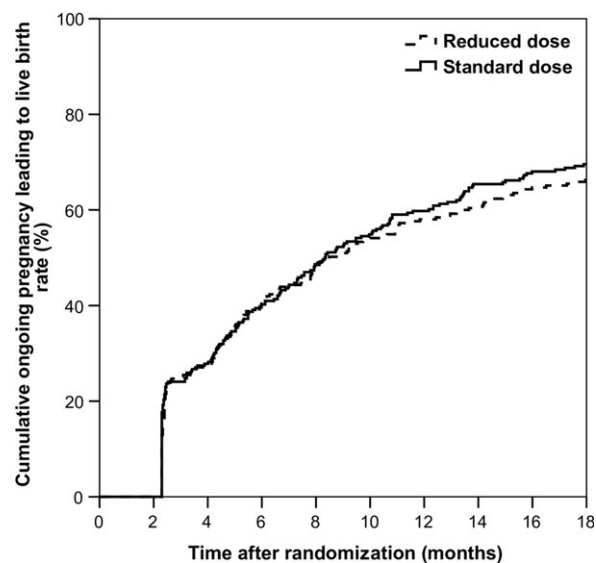
^bPercentage based on the number of multiple pregnancies.

^cIncluding live births from escape IUI treatments.

^dAfter treatment in another centre without cycle data.

^e2 × Loss to FU, 1 × Foetal demise, 1 × Immature birth.

^f2 × Foetal demise, 1 × Loss to FU, 1 × Termination of pregnancy for trisomy 21.

**Figure 2** Cumulative live birth incidence curve. Log rank = 0.504.

Number at risk	0	2 (%)	4 (%)	6 (%)	8 (%)	10 (%)	12 (%)	14 (%)	16 (%)	18 (%)
Reduced, N (%)	255	255 (100)	184 (72.2)	152 (59.6)	131 (51.4)	118 (46.3)	107 (42.0)	101 (39.6)	90 (35.3)	86 (33.7)
Standard, N (%)	266	266 (100)	192 (72.2)	159 (59.8)	137 (51.5)	120 (45.1)	107 (40.2)	92 (34.6)	85 (32.0)	81 (30.5)

Table III Cumulative treatment results.

Results 18 months follow-up	100 IU (n = 253 ^a)	150 IU (n = 266)	P-value
Number of fresh cycles per woman	1.8 (0.9)	1.8 (0.9)	0.722
Total number of fresh cycles	461	476	0.761 ^b
First cycle	253 (54.9%)	266 (55.9%)	
Second cycle	136 (29.5%)	136 (28.6%)	
Dose increase between first and second cycle	77/135 (57.3%)	19/136 (14.0%)	<0.001
Amount of increase (IU/L) Median (IQR)	25.0 (25)	50.0 (0)	<0.001
Dose reduction between first and second cycle	6/135 (4.4%)	53/136 (39.0%)	<0.001
Amount of reduction (IU/L) Median (IQR)	25.0 (12.5)	50.0 (14.6)	0.002
Third cycle	56 (12.1%)	58 (12.2%)	
Fourth cycle	14 (3.0%)	16 (3.4%)	
Fifth cycle	2 (0.4%)	0	
Cycle cancellation	82/461 (17.8%)	65/475 (13.7%)	0.104 ^b
Cancellation reason			
Insufficient growth	72/461 (15.6%)	25/475 (5.3%)	
Excessive response	6/461 (1.3%)	32/475 (6.7%)	
Other	4/461 (0.9%)	8/475 (1.7%)	
Number of oocytes ^c	9.0 (4.9)	11.9 (6.0)	<0.001 ^b
Poor response	133/459 (29.0%)	68/474 (14.3%)	<0.001 ^b
Hyper response	48/459 (10.5%)	144/474 (30.4%)	<0.001 ^b
Number of embryo transfers	349/461 (75.7%)	376/475 (79.2%)	0.219 ^b
Number of OHSS events	24/456 (5.2%)	56/474 (11.8%)	0.001 ^b
Classification OHSS			
Mild	18/456 (3.9%)	40/474 (8.4%)	0.008 ^b
Moderate	0/456	11/474 (2.3%)	0.001 ^d
Severe	6/456 (1.3%)	5/474 (1.1%)	0.712 ^b
Number of cryo embryo transfers per woman	0.9 (1.4)	1.0 (1.4)	0.314

Data are presented as mean (SD) or number (%) unless otherwise specified. OHSS, ovarian hyper stimulation syndrome.

^aTwo women have missing cycle data.

^bP-value calculated by using a generalized estimating equation (GEE) model.

^cBased on the women who had an ovum pick-up.

^dCould not be tested with GEE for no events in the reduced dose group. No clustering took place (all moderate OHSS events occurred in different women), so Chi-square was used.

oocytes. As reduced dosing was only slightly and non-significantly less expensive, there was no dominant strategy in the economic analysis.

A recent systematic review by van Tilborg *et al.* concluded that there was a lack of evidence favouring individualized dosing over standard treatment for the IVF population as a whole (van Tilborg *et al.*, 2016). Since the studies on which this review was based did not compare live birth rates or cost-effectiveness and did not provide sufficient data on predicted hyper responders only, it is difficult to directly compare these results to the current RCT. The review by van Tilborg *et al.* (2016) stated that there might be a benefit of individualized dosing with respect to safety in predicted hyper responders. This is based on two studies assessing safety as a secondary outcome. Popovic-Todorovic *et al.* (2003) reported that individualized FSH dosing based on an algorithm leads to a lower number of retrieved oocytes in women predicted to be hyper responders (12.7 versus 15.3 in the standard group, $P < 0.001$). However, the occurrence of OHSS was low, did not differ between groups (0% in the individualized versus

2.3% in the standard group) and was not assessed for predicted hyper responders alone. The second RCT by Olivennes *et al.* (2015) stated a safety benefit for individualized dosing. This was based on the observation that both the cancellation rate for excessive response and the rate of OHSS were lower in the individualized strategy. However, no statistical test was performed for this combined outcome measure, while the outcome measures separately did not differ significantly between groups (calculated only in the review, not in original article, van Tilborg *et al.*, 2016).

A very recent RCT studying individualized dosing using a gradual dosing system based on AMH and body weight also showed no difference in single cycle ongoing pregnancy rates (Nyboe Andersen *et al.*, 2017). In contrast to our results, no difference in the occurrence of any grade of OHSS was observed. The authors suggest that OHSS was averted by cancellation of stimulation or using an agonist trigger instead of hCG and a statistically significant difference in this combined outcome measure (prevention and occurrence of all OHSS) was observed (5.6% in the individualized group versus 8.0% in the standard

Table IV Treatment results for the first cycle.

	100 IU (N = 253 ^a)	150 IU (N = 266)	P-value
Cycle cancellation	61 (24.1%)	33 (12.4%)	0.001
Cancellation reason			<0.001
Insufficient growth	53 (20.9%)	9 (3.4%)	<0.001
Excessive response	5 (2.0%)	21 (7.9%)	0.002
Other	3 (1.2%)	3 (1.1%)	0.95
Number of oocytes ^b	8.8 (5.0)	13.2 (6.1)	<0.001
Poor response	91 (34.0%)	20 (7.5%)	<0.001
Hyper response	28 (11.6%)	102 (38.3%)	<0.001
Number of embryo transfers	175 (69.2%)	212 (79.7%)	0.006
Number of OHSS events	12 (4.7%)	39 (14.7%)	<0.001
Classification OHSS			<0.001
Mild	8 (3.2%)	29 (10.9%)	0.001
Moderate	0	7 (2.6%)	0.009
Severe	4 (1.6%)	3 (1.1%)	0.66
Number of cryo embryo transfers per woman	0.5 (1.1)	0.7 (1.2)	0.079
Live birth (fresh only) ^c	65 (25.7%)	67 (25.2%)	0.90
Live birth (fresh and cryo) ^c	91 (36.0%)	104 (39.1%)	0.46

Data are presented as mean (SD) or number (%) unless otherwise specified. OHSS, ovarian hyper stimulation syndrome.

^aTwo women missing cycle data.

^bBased on women who had an ovum pick-up.

^cIncluding pregnancies obtained after escape IUI in cancelled cycles.

group, $P = 0.037$). A similar conclusion may be drawn from our first cycle data, however as this combined outcome (cycle cancellation and occurrence of OHSS) was not predefined, we did not perform a statistical test on our data.

AFC and AMH have been shown to be the most accurate ORTs in the prediction of ovarian response to stimulation, but do not add relevant information when applied simultaneously, or in combination with female age (Broer, et al., 2013a, Broer et al., 2013b). Therefore, we consider that using the AFC alone is, in principle, sufficient for ORT-based dosing. A fixed dose strategy was used as van Hooff et al. (1993) have demonstrated that dosage alterations during ovarian stimulation in actual poor responders do not affect the cycle outcome in terms of pregnancy or response. Unfortunately, there are no other studies available demonstrating the relevance of dose adjustments during stimulation.

A first strength of this trial is that it is a RCT embedded in a large, multicentre cohort study using the easily applicable AFC as an ORT. Because this was a multicentre study it is pragmatic, which increases generalizability and results in better knowledge of and implementation of study outcomes in participating centres (Litjens et al., 2013). Another strength is that we chose live birth rate as our primary outcome, the most important outcome for the patient, which is in contrast to most other studies that do not look beyond ovarian response or pregnancy rates (Wilkinson et al., 2016). In addition, we not only reported first cycle results, but also cumulative results, which is a better reflection of clinical practice, as most women undergo multiple treatment cycles after failure of previous ones (Scholten et al., 2016). For this study, it was especially important to report both first cycle and cumulative treatment cycle data as dose adjustments were allowed between cycles. The first

cycle therefore most clearly reflects the effects of the two treatment strategies. As no differences in live birth rate and safety were found between first and cumulative cycle data, our interpretation of the results remains the same. Finally, a health economic evaluation was performed, which provides essential information on costs of the two treatment strategies before implementation can be considered.

Several limitations must be mentioned. The limitations for the OPTIMIST study as a whole have been addressed in the overall strategy paper and the paper including predicted poor responders (van Tilborg et al., 2017a,b). In addition to those limitations, for the current paper we first need to point out that the sample size calculation of the OPTIMIST study was based on 80% power to detect a difference in live birth rates in the expected poor responders only (van Tilborg et al., 2012, 2017b). The number of women included in the current RCT provided a power of only 37% to detect the pre-specified clinically relevant difference in live birth rate of 7%. A small difference of 3.2% in live birth rate was observed, which is not considered to be clinically relevant. Moreover, a sample size of over 3000 women in both study arms would have been needed to prove that this small difference is statistically significant. As the difference observed was in the advantage of the standard dose group, we can still conclude that a reduced FSH dose in predicted hyper responders does not improve live birth rates.

Second, we need to point out that the BMI of the women included was relatively low (23.8 kg/m² in the reduced dose group and 23.9 kg/m² in the standard dose group) when viewed from an international perspective. The results may therefore not be generalizable to women with a higher BMI, although the relationship for BMI or body weight and ovarian response may be subject to a considerable degree of variation,

making translation towards dosing a difficult task (Oudshoorn *et al.*, 2017). Further planned OPTIMIST analyses should elucidate if BMI or body weight play a role in FSH dose individualization.

Third, our results indicate that the dose reduction of 50 IU (from 150 IU to 100 IU) might have been too rigorous. In the reduced dose group, 91 of 133 poor responses (68%) occurred in the first cycle and the dose was increased between the first and second cycle in 77 of 135 women (57%). Since a dose-response relation is present when an FSH starting dose <150 IU is given (Sterrenburg *et al.*, 2011), a smaller decrease of the starting dose (e.g. 125 IU/day) will probably reduce the occurrence of a poor response. On the other hand, it might still increase the incidence of a hyper response, which could jeopardize safety. A previous patient preference study has shown that women are willing to trade off pregnancy rate for a decreased risk of OHSS (van den Wijngaard *et al.*, 2014). From this perspective, the standard dose of 150 IU may be slightly too high for predicted hyper responders, as a lower dose did reduce the incidence of mild and moderate OHSS, with no detrimental effect on live birth rates. In all, this could suggest that FSH dose reduction might have to be done using a more gradual dosing system.

Finally, in recent years consensus has been increasing that women with a predicted hyper response should be treated with a GnRH-antagonist for pituitary suppression and, if needed, a GnRH-agonist trigger to increase safety without affecting efficacy. This was not yet common practice at the time the trial was designed and so only one-third of the women in the current trial received a GnRH-antagonist. Moreover, only hCG triggering was allowed. As the percentage of women receiving GnRH-antagonist co-treatment was equal in the dosing groups, this should not have affected the results. It still has to be established whether antagonist with agonist triggering leads to a more optimal balance between efficacy and safety as compared to first line preventive management by FSH dose reduction.

In conclusion, this RCT demonstrates that a first cycle FSH dose reduction in predicted hyper responders based on the AFC does not influence live birth rates. With respect to safety, the current study shows that using a reduced FSH dose of 100 IU/day does not reduce the risk of severe OHSS in predicted hyper responders, although the rate of any grade of OHSS was reduced. The occurrence of severe OHSS alone may not be the most meaningful safety outcome in women undergoing COS. Future studies should therefore also include the effect of prevention measures such as cancellation for hyper response, GnRH-agonist triggering and a freeze-all policy. However, as cycle cancellation occurred twice as often in the first cycle in the reduced dose group, a definite claim advocating FSH dose reduction in predicted hyper responders cannot be made until results from future studies comparing various safety management approaches have become available.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Acknowledgements

We thank the women who participated in this study, the staff of the participating hospitals, and the office members of the Dutch Consortium for their contribution.

Authors' roles

M.J.C.E., H.L.T., F.J.M.B. and B.W.J.M. designed the trial. T.C.v.T., H.L.T., F.J.M.B. and B.W.J.M. coordinated the trial. T.C.v.T., S.C.O., G.J.E.O., J.F., M.A.H.v.H., E.J.P.v.S., E.A.B., J.M.J.S., J.K., C.H.d.K., C.B.L., F.J.M.B. and all other members from the OPTIMIST study group collected data. S.C.O. performed the statistical analyses. H.G. and M.J.C.E. provided input on the statistical analyses. S.C.O., M.J.C.E., H.L.T., F.J.M.B. and B.W.J.M. interpreted the data. S.C.O. drafted the manuscript. All authors revised the report, and approved the final submitted version.

Funding

This trial was funded by The Netherlands Organization for Health Research and Development (ZonMw, Project Number 171102020).

Conflict of interest

S.C.O., T.C.v.T. and H.L.T. received an unrestricted research grant from Merck Serono (the Netherlands). C.B.L. receives grants from Merck, Ferring and Guerbet. B.W.J.M. is supported by a NHMRC Practitioner Fellowship (GNT1082548) and reports consultancy for OvsEva, Merck and Guerbet. F.J.M.B. receives monetary compensation as a member of the external advisory board for Ferring pharmaceuticals BV and Merck Serono for consultancy work for Gedeon Richter (Belgium) and Roche Diagnostics (Switzerland) and for a research cooperation with Ansh Labs (USA). All other authors have nothing to declare.

References

- Broekmans FJM, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve an IVF outcome. *Hum Reprod Update* 2006;**12**:685–718.
- Broekmans FJ, de Ziegler D, Howles CM, Gougeon A, Trew G, Olivennes F. The antral follicle count: practical recommendations for better standardization. *Fertil Steril* 2010;**94**:1044–1051.
- Broer SL, Mol BW, Hendriks D, Broekmans FJM. The role of antimüllerian hormone in prediction of outcome after IVF: comparison with the antral follicle count. *Fertil Steril* 2009;**91**:705–714.
- Broer SL, Dölleman M, Opmeer BC, Fauser BC, Mol BW, Broekmans FL. AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis. *Hum Reprod Update* 2011;**17**:46–54.
- Broer SL, van Disseldorp J, Broeze KA, Dölleman M, Opmeer BC, Bossuyt P, Eijkemans MJC, Mol BWJ, Broekmans FJM, Anderson R. *et al.* Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: An individual patient data approach. *Hum Reprod Update* 2013a;**19**:26–36.
- Broer SL, Dölleman M, van Disseldorp J, Broeze KA, Opmeer BC, Bossuyt PMM, Eijkemans MJC, Mol BW, Broekmans FJM. Prediction of an excessive response in in vitro fertilization from patient characteristics and ovarian reserve tests and comparison in subgroups: An individual patient data meta-analysis. *Fertil Steril* 2013b;**100**:420–429.
- Chen YH, Xu XH, Wang Q, Zhang SD, Jiang LL, Zhang CL, Ge ZJ. Optimum oocyte retrieved and transfer strategy in young women with normal ovarian reserve undergoing a long treatment protocol: a retrospective cohort study. *J Assist Reprod Genet.* 2015;**32**:1459–1467.

- Golan A, Weissman A. Symposium: update on prediction and management of OHSS. A modern classification of OHSS. *Reprod Biomed Online* 2009;**19**:28–32.
- Humaidan P, Nelson SM, Devroey P, Coddington CC, Schwartz LB, Gordon K, Frattarelli JL, Tarlatzis BC, Fatemi HM, Lutjen P et al. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. *Hum Reprod* 2016;**31**:1997–2004.
- Hignett M, Spence JE, Claman P. Internal jugular vein thrombosis: a late complication of ovarian hyperstimulation syndrome despite mini-dose heparin prophylaxis. *Hum Reprod* 1995;**10**:3121–3123.
- La Marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. *Hum Reprod Update* 2014;**20**:124–140.
- Litjens RJ, Oude Rengerink K, Danhof NA, Kruitwagen RF, Mol BW. Does recruitment for multicenter clinical trials improve dissemination and timely implementation of their results? A survey study from the Netherlands. *Clin Trials* 2013;**10**:915–923.
- Navot D, Bergh PA. Ovarian hyperstimulation syndrome: a practical approach. In: *Ovarian endocrinopathies. The Proceedings of the 8th Reinier de Graaf Symposium*, Amsterdam, 2–4 September 1993;215–25.
- Nyboe Andersen A, Nelson SM, Fauser BC, Garcia-Velasco JA, Klein BM, Arce JC. ESTHER-I study group. Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicentre, randomize, controlled, assessor-blinded, phase 3 noninferiority trial. *Fertil Steril* 2017;**107**:387–396.
- Olivennes F, Trew G, Borini A, Broekmans F, Arriagada P, Warne DW, Howles CM. Randomized, controlled, open-label, non-inferiority study of the CONSORT algorithm for individualized dosing of follitropin α . *Reprod Biomed Online* 2015;**30**:248–257.
- Oudshoorn SC, van Tilborg TC, Hamdine O, Torrance HL, Eijkemans MJC, Lentjes EGWM, Lambalk CB, Broekmans FJM. Ovarian response to controlled ovarian hyperstimulation: what does serum FSH say?. *Hum Reprod* 2017;**32**:1701–1709.
- Popovic-Todorovic B, Loft A, Bredkjaer HE, Bangsbøll S, Nielsen IK, Andersen AN. A prospective randomized clinical trial comparing an individual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients undergoing IVF/ICSI treatment. *Hum Reprod* 2003;**18**:2275–2282.
- Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;**19**:41.
- Scholten I, Braakhekke M, Limpens J, Hompes PG, van der Veen F, Mol BW, Gianotten J. Reporting multiple cycles in trials on medically assisted reproduction. *Reprod Biomed Online* 2016;**33**:646–651.
- Sterrenburg MD, Veltman-Verhulst SM, Eijkemans MH, Hughes EG, Macklon NS, Broekmans FJ, Fauser BC. 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. *Hum Reprod Update* 2011;**17**:184–196.
- Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. *Hum Reprod* 2011;**26**:1768–1774.
- Tarlatzis BC, Kolibianakis EM. GnRH agonists vs antagonists. *Best Pract Res Clin Obstet Gynaecol* 2007;**21**:57–65.
- van den Wijngaard L, van Wely M, Dancet EAF, van Mello NM, Koks CAM, van der Veen F, Mol BWJ, Mochtar MH. Patients' preferences for gonadotrophin-releasing hormone analogs in in vitro fertilization. *Gynecol Obstet Invest* 2014;**78**:16–21.
- van der Gaast MH, Eijkemans MJ, van der Net JB, de Boer EJ, Burger CW, van Leeuwen FE, Fauser BC, Macklon NS. Optimum number of oocytes for a successful first IVF treatment cycle. *Reprod Biomed Online* 2006;**13**:476–480.
- van Hooff MH, Alberda AT, Huisman GJ, Zeilmaker GH, Leerentveld RA. Doubling the human menopausal gonadotrophin dose in the course of an in-vitro fertilization treatment cycle in low responders: a randomized study. *Hum Reprod* 1993;**8**:369–373.
- van Tilborg TC., Eijkemans MJC, Laven JSE, Koks CA, de Bruin JP, Scheffer GJ, van Golde RJ, Fleischer K, Hoek A, Nap AW et al. The OPTIMIST study: optimisation of cost effectiveness through individualised FSH stimulation dosages for IVF treatment. A randomised controlled trial. *BMC Women's Health* 2012;**12**:article 29.
- van Tilborg TC, Broekmans FJ, Dólleman M, Eijkemans MJ, Mol BW, Laven JS, Torrance HL. Individualised FSH dosing and IVF outcome in agonist downregulated cycles: a systematic review. *Acta Obstet Gynecol Scand* 2016;**95**:1333–1344.
- van Tilborg TC, Torrance HL, Oudshoorn SC, Eijkemans MJC, Koks CAM, Verhoeve HR, Nap AW, Scheffer GJ, Manger AP, Schoot BC et al. Individualised versus standard FSH dosing in women starting IVF/ICSI: a randomized controlled trial. Part I: The predicted poor responder. *Hum Reprod* 2017a;**32**:2485–2495.
- van Tilborg TC, Oudshoorn SC, Eijkemans MJC, Mochtar MH, van Golde RJT, Hoek A, Kuchenbecker WKH, Fleischer K, de Bruin JP, Groen H et al. Individualized FSH dosing based on ovarian reserve testing in women starting IVF/ICSI: a multicentre trial and cost-effectiveness analysis. *Hum Reprod* 2017b;**32**:2496–2505.
- Wilkinson J, Roberts SA, Showell M, Brison DR, Vail A. No common denominator: a review of outcome measure in IVF RCTs. *Hum Reprod* 2016;**31**:2714–2722.