Human Reproduction, pp. 1–10, 2017
doi:10.1093/humrep/dex235

human reproduction

ORIGINAL ARTICLE *Infertility*

Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial

Snorri Einarsson[1,2], Christina Bergh[1,3], Britt Friberg[4], Anja Pinborg[5], Anna Klajnbard[6], Per-Olof Karlström[7], Linda Kluge[3], Ingrid Larsson[8], Anne Loft[9], Anne-Lis Mikkelsen-Englund[10], Kaj Stenlöf[11], Anna Wistrand[12], and Ann Thurin-Kjellberg[1,3,*]

[1]Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, 416 84 Gothenburg, Sweden [2]IVF Klinikin Reykjavik, Álfheimar 74, 104 Reykjavík, Iceland [3]Reproductive Medicine, Sahlgrenska University Hospital, Blå stråket 6, SE-413 45 Gothenburg, Sweden [4]RMC, Skåne's University Hospital, Jan Waldenströmsg.47, SE-214 21 Malmö, Sweden [5]Hvidovre Hospital, Copenhagen University Hospital, Fertilitetsklinikken, Kettegård Allé 30, 2650 Hvidovre, Denmark [6]Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark [7]Karolinska University Hospital, Huddinge, Novumhuset plan 4, SE-141 86 Stockholm, Sweden [8]Department of Gastroenterology and Hepatology, Sahlgrenska University Hospital, Blå stråket 3 SE-413 45, Gothenburg, Sweden [9]Fertility Clinic, Rigshospital, Copenhagen University Hospital, Juliane Maries Vej 8, 2100 København Ø, Denmark [10]Holbaek Hospital, Copenhagen University Hospital, Akacievej 114300 Holbæk, Denmark [11]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, Gothenburg University, 4E-413 46 Gothenburg, Sweden [12]Örebro University Hospital, Fertility clinic, SE-701 85 Örebro, Sweden

*Correspondence address. Sahlgrenska University Hospital, Reproductive Medicine, Blå Stråket 6, SE-413 45 Gothenburg, Sweden. Tel: +46-70-540-1475; E-mail: ann.thurin@vgregion.se

Submitted on March 18, 2017; resubmitted on June 6, 2017; accepted on June 11, 2017

STUDY QUESTION: Does an intensive weight reduction programme prior to IVF increase live birth rates for infertile obese women?

SUMMARY ANSWER: An intensive weight reduction programme resulted in a large weight loss but did not substantially affect live birth rates in obese women scheduled for IVF.

WHAT IS ALREADY KNOWN: Among obese women, fertility and obstetric outcomes are influenced negatively with increased risk of miscarriage and a higher risk of maternal and neonatal complications. A recent large randomized controlled trial found no effect of lifestyle intervention on live birth in infertile obese women.

STUDY DESIGN, SIZE, DURATION: A prospective, multicentre, randomized controlled trial was performed between 2010 and 2016 in the Nordic countries. In total, 962 women were assessed for eligibility and 317 women were randomized. Computerized randomization with concealed allocation was performed in the proportions 1:1 to one of two groups: weight reduction intervention followed by IVF-treatment or IVF-treatment only. One cycle per patient was included.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Nine infertility clinics in Sweden, Denmark and Iceland participated. Women under 38 years of age planning IVF, and having a BMI ≥30 and <35 kg/m^2 were randomized to two groups: an intervention group (160 patients) with weight reduction before IVF, starting with 12 weeks of a low calorie liquid formula diet (LCD) of 880 kcal/day and thereafter weight stabilization for 2–5 weeks, or a control group (157 patients) with IVF only.

MAIN RESULTS AND ROLE OF CHANCE: In the full analysis set (FAS), the live birth rate was 29.6% (45/152) in the weight reduction and IVF group and 27.5% (42/153) in the IVF only group. The difference was not statistically significant (difference 2.2%, 95% CI: 12.9 to −8.6, $P = 0.77$). The mean weight change was −9.44 (6.57) kg in the weight reduction and IVF group as compared to +1.19 (1.95) kg in the IVF only group, being highly significant ($P < 0.0001$). Significantly more live births were achieved through spontaneous pregnancies in the weight reduction and IVF group, 10.5% (16) as compared to the IVF only group 2.6% (4) ($P = 0.009$). Miscarriage rates and gonadotropin dose used for IVF stimulation did not differ between groups. Two subgroup analyses were performed. The first compared women with PCOS in the two randomized groups, and the second compared women in the weight reduction group reaching BMI ≤ 25 kg/m^2 or reaching

a weight loss of at least five BMI units to the IVF only group. No statistical differences in live birth rates between the groups in either subgroup analysis were found.

LIMITATIONS, REASON FOR CAUTION: The study was not powered to detect a small increase in live births due to weight reduction and was not blinded for the patients or physician. Further, the intervention group had a longer time to achieve a spontaneous pregnancy, but were therefore slightly older than the control group at IVF. The study only included women with a BMI lower than 35 kg/m^2.

WIDER IMPLICATIONS OF THE FINDINGS: The study suggests that weight loss for obese women (BMI: 30–34.9 kg/m^2) may not rectify the outcome in IVF cycles, although a significant higher number of spontaneous conceptions occurred in the weight loss group. Also, the study suggests that intensive weight reduction with LCD treatment does not negatively affects the results.

STUDY FUNDING/COMPETING INTEREST(S): The study was funded by Sahlgrenska University Hospital (ALFGBG-70 940), Merck AB, Solna, Sweden (an affiliate of Merck KGaA, Darmstadt, Germany), Impolin AB, Hjalmar Svensson Foundation and Jane and Dan Olsson Foundation. Dr Thurin-Kjellberg reports grants from Merck, non-financial support from Impolin AB, during the conduct of the study, and personal fees from Merck outside the submitted work. Dr Friberg reports personal fees from Ferring, Merck, MSD, Finox and personal fees from Studentlitteratur, outside the submitted work. Dr Englund reports personal fees from Ferring, and non-financial support from Merck, outside the submitted work. Dr Bergh reports and has been reimbursed for: writing a newsletter twice a year (Ferring), lectures (Ferring, MSD, Merck), and Nordic working group meetings (Finox). Dr Karlström reports lectures (Ferring, Finox, Merck, MSD) and Nordic working group meetings (Ferring). Ms Kluge, Dr Einarsson, Dr Pinborg, Dr Klajnbard, Dr Stenlöf, Dr Larsson, Dr Loft and Dr Wistrand have nothing to disclose.

TRIAL REGISTRATION NUMBER: ClinicalTrials.gov number, NCT01566929.

TRIAL REGISTRATION DATE: 23-03-2012.

DATE OF FIRST PATIENT'S ENROLMENT: 05-10-2010.

Key words: weight loss / obesity / infertility / IVF / low calorie diet

Introduction

Obesity is a major global health problem. In the Nordic countries, obesity prevalence varies between 18.0 and 28.8% in the female population (Ng *et al.*, 2014). Fertility and obstetric outcome are negatively affected by obesity in women, with an increased risk of miscarriage (Metwally *et al.*, 2008) and a higher risk of obstetric and neonatal complications (Dokras *et al.*, 2006; Cnattingius *et al.*, 2013; Johansson *et al.*, 2014). For obese women undergoing assisted reproductive techniques such as IVF, the pregnancy and live birth rate is compromised (Maheshwari *et al.*, 2007; Luke *et al.*, 2011; Bellver *et al.*, 2013; Petersen *et al.*, 2013; Provost *et al.*, 2016). Compared to women with a normal BMI, obese women undergoing IVF treatment require higher doses of gonadotropins, illustrating an impaired response to ovarian stimulation, and they also have an increased miscarriage rate (Fedorcsàk *et al.*, 2004; Metwally *et al.*, 2008). A weight loss of 5–10% in obese women has, however, been demonstrated to be effective in normalizing menstruation, ovulation and spontaneous pregnancy rates (Norman *et al.*, 2004). Although it has often been suggested that weight reduction interventions should be considered for obese infertile women (Norman *et al.*, 2004; Maheshwari *et al.*, 2007), very few trials have been published supporting such a strategy. In addition to a few trials, not powered for pregnancy and live birth rates (Tsagareli *et al.*, 2006; Moran *et al.*, 2011; Sim *et al.*, 2014; Becker *et al.*, 2015), a recent large Dutch randomized controlled trial found that lifestyle intervention had no effect on live births in infertile obese women (Mutsaerts *et al.*, 2016).

The aim of this study was to evaluate whether weight reduction in infertile obese women (BMI $\geq$ 30 $<$ 35 kg/m^2) scheduled for IVF improved the outcome assessed as live births, compared with women who received IVF treatment without previous weight loss.

Materials and Methods

We performed a multicentre, multidisciplinary, prospective, randomized controlled trial (RCT) at nine infertility clinics starting between 2010 and 2012 in Sweden and from 2013 in Denmark and Iceland. All participants provided written informed consent. The trial was approved by research ethics committees in Sweden, Denmark and Iceland. Sahlgrenska University Hospital, Gothenburg, Sweden provided the trial database and the computerized randomization programme and acted as the data-coordinating centre for this study. The first and last authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the trial protocol.

Study population

Those eligible for the trial were infertile women between 18 and 38 years of age with indications for IVF and planning to start their first, second or third IVF treatment and with a BMI $\geq$ 30 $<$ 35 kg/m^2. In general, public clinics in the Nordic countries do not treat women if they are over 40 years of age or have a BMI above 35 kg/m^2. Women were excluded from the trial if they had insulin dependent diabetes mellitus and other exclusion factors such as planned oocyte donation, planned pre-implantation genetic diagnosis, husband having azoospermia known at randomization, not having adequate knowledge of the local language, binge eating disorder (defined by Questionnaire of Eating and Weight Patterns-Revised; Yanovski, 1993) or previous participation in the study. Only one cycle per patient was included in the study. In the case of an emergency medical problem which resulted in the freezing of all embryos, the first transfer using cryopreserved embryos was included in the analysis.

Randomization

Randomization was performed with a computerized randomization programme with concealed allocation of patients and in the proportion of 1:1.

Optimal allocation was applied according to Pocock's minimization technique for sequential randomization (Pocock, 1983) taking account of the number of previously performed fresh IVF cycles, age of the woman, parity, polycystic ovarian syndrome (PCOS), fertilization method planned, tubal factor, smoking, BMI and waist circumference. The randomization was performed by the physician or the midwife/nurse at the first visit to the IVF clinic for first cycle patients or at a consultation between IVF cycles for second and third cycle patients. Blinding was not possible for patients or physicians; however, the embryologists and statisticians were unaware as to which group the patients were allocated.

Weight reduction intervention

The aim of the weight reduction was to reach a BMI as close to normal as possible during a time period of approximately 16 weeks. The intervention started with 12 weeks of a strict low calorie liquid formula diet (LCD), with a daily energy intake of 880 kcal (Modifast, Nutrition & Santé, France). During the LCD period, all patients had scheduled visits with a health professional at weeks 0 (baseline), 2, 5, 8 and 12, where weight was recorded. After termination of the 12-week LCD period, the patients were scheduled for individual visits with a dietician for a period of between 2 and 5 weeks, for the re-introduction of solid foods and weight control stabilization. Prior to IVF treatment, the patient met the dietician again for a follow-up visit. Patients unable to complete the LCD treatment received individualized weight loss counselling until the start of IVF treatment. The patients started IVF after the weight intervention period regardless of the weight reduction achieved. During and after IVF treatment, all patients in the weight intervention group were offered complementary dietary counselling by the dietician for one year from randomization.

IVF treatment

All patients in the study were treated with a gonadotropin releasing hormone agonist and individualized doses of follitropin alfa (Gonal-F, Merck, Germany) from 112.5 to 450 IU/day. The cycles were monitored according to local routines in each clinic with serum-estradiol measurements and/or vaginal sonography. Ovulation was induced with choriongonadotropin alfa (Ovitrelle, Merck, Germany) and approximately 36 h later, oocyte retrieval was performed by means of transvaginal puncture. Fertilization was carried out using standard IVF technique or, in the case of male infertility, ICSI according to standard procedures. Embryo transfer (ET) was mostly performed using cleaving stage embryos (Day 2 or 3). Luteal-phase support was given from the day of oocyte retrieval with progesterone by vaginal route until a pregnancy test was performed 14 days after ET. If the patient was pregnant, defined as serum-human chorionic gonadotropin >5 IU/L, a vaginal sonography was performed ~4 weeks after ET, i.e. pregnancy week 7.

Outcomes

The primary outcome was live birth, defined as at least one child born alive regardless of gestational age. Pre-specified secondary outcomes were pregnancy-related measurements such as biochemical pregnancy rate, clinical pregnancy rate, miscarriage rate, live birth rate after spontaneous pregnancy and multiple birth rates. Further secondary outcomes were IVF-related measurements including number of cancelled cycles, total dose of gonadotropins, number of oocytes retrieved and the rate of ovarian hyperstimulation syndrome (OHSS). Embryological measurements included the number of good quality embryos and the number of frozen embryos. Finally, dietary-related measurements included weight change between randomization and the last weight measurement recorded before or at oocyte retrieval and the number of patients showing compliance, defined as reaching normal BMI (<25.0 kg/m^2) or lowering the BMI by at least five units.

Statistical analysis

Our power calculation was based on a previous study (Kahnberg *et al.*, 2009), where the live birth rate was 12.5% (7/56) for obese women (BMI $\geq$ 30 kg/m^2) and 26.3% (81/308) for women with a normal weight (BMI: 20–25 kg/m^2). To find a difference of 13% (12–25%), 152 patients were needed in each group, giving a total of 304 patients (significance 5%, power 80%). To compensate for dropouts, the sample size was increased to 316. No loss of follow up was expected.

The main analysis was performed on the full analysis set (FAS) population and consisted of all randomized women having at least one follow-up variable and having started the IVF treatment (defined as having started stimulation with follitropin alfa) or having achieved a spontaneous pregnancy. Each woman was evaluated in the group to which she was randomized, regardless of what treatment she received or whether or not she completed the weight-loss programme. A complementary analysis was performed on the per protocol (PP) population and consisted of all randomized subjects having completed the study without significant protocol deviation. All spontaneous pregnancies occurring in both groups after randomization were included in both FAS and PP analyses.

Comparison between the two randomized groups was performed unadjusted. Fisher's exact test was used for the primary efficacy variable, live birth, and for all dichotomous variables. The Mann–Whitney *U*-test was used for continuous variables, Mantel–Haenszel chi-square test was used for ordered categorical variables and Pearson's chi-square test was used for all non-ordered categorical variables. The distribution of continuous variables, as well as changes in continuous variables, are given as mean, SD, median, minimum and maximum. Categorical variables are given as number and percentages. Complementary analyses for primary and selected secondary efficacy variables were performed in the FAS, and adjusted for differences in baseline variables. Adjustments were performed by multivariable logistic regression for dichotomous variables and by ANCOVA for continuous variables.

For the primary variable, live birth, and for important secondary variables, risk differences and risk ratios with 95% CI and exact 95% CI for the estimated proportions were calculated. All significance tests were two sided and conducted at the 5% significance level. A futility analysis was performed when approximately half of the planned patients had been included. The steering committee recommended that the study should continue. Two subgroup analyses were performed for the primary efficacy variable and for selected secondary variables; one for PCOS patients (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004) and one for patients completing the diet programme and reaching BMI $\leq$ 25 kg/m^2 or lowering BMI by at least five units.

Results

Patients

Between October 2010 and January 2016, 962 women were assessed for eligibility (Fig. 1). Of these, 645 women did not meet inclusion criteria, declined to participate or were not included for other reasons. Thus 317 women were randomized to one of the two groups. Follow-up on pregnancies was completed in February 2017. Baseline characteristics were similar in the two groups, except that more terminations of pregnancies had occurred in the control group. The median

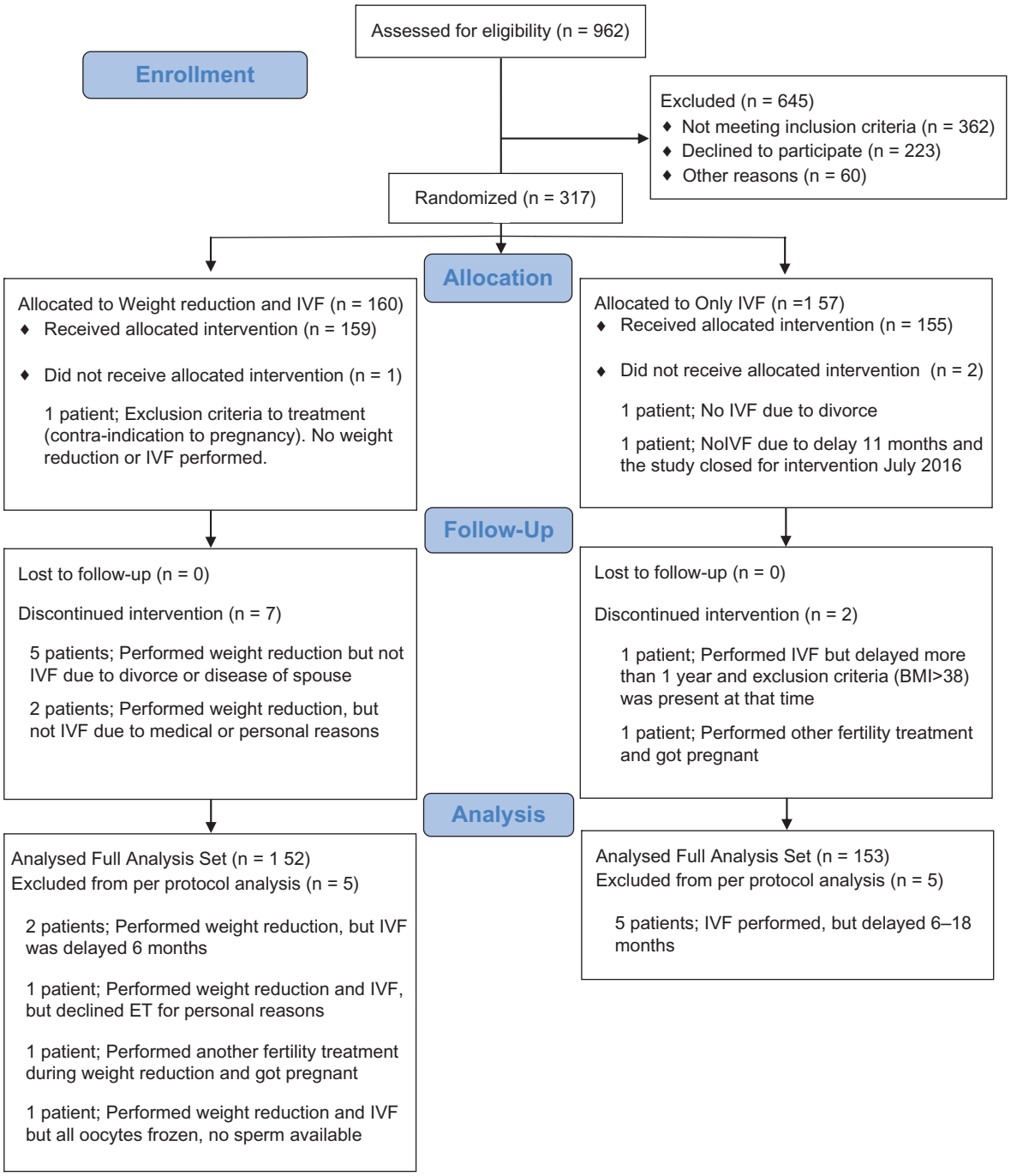

Figure 1 Flow chart of eligibility, randomization and follow-up.

duration of infertility was quite long in both groups, being 3 years (Table I).

In the weight reduction and IVF group, one patient did not receive the allocated intervention and seven patients discontinued the intervention. In the IVF only group, two patients did not receive the allocated intervention and two patients discontinued the intervention. No patients were lost to follow up (Fig. 1).

Live births and secondary outcomes

In the FAS analysis, the live birth rate was 29.6% (45/152) in the weight reduction and IVF group and 27.5% (42/153) in the IVF only group. The difference was not statistically significant (difference 2.2%, 95% CI: 12.9 to –8.6, $P = 0.77$).

Significantly more live births were achieved through spontaneous pregnancies in the weight reduction and IVF group than in

Table I Characteristics of the patients in the full analysis set.

Variable	Weight reduction and IVF group ($n = 152$)	IVF only group ($n = 153$)	*P*-value
Age of the woman at randomization (years)	31.5 (4.3)	31.7 (4.1)	0.70
	31.6 (22.3; 38.0)	31.8 (22.7; 38.0)	
	$n = 152$	$n = 153$	
Duration of infertility (months)	38.7 (24.3)	38.6 (21.4)	0.41
	36.0 (6.0; 168.0)	36.0 (1.0; 180.0)	
	$n = 152$	$n = 153$	
Cause for infertility			
Tubal factor	13 (8.6%)	14 (9.2%)	
Endometriosis	6 (3.9%)	2 (1.3%)	
Polycystic ovary syndrome	35 (23.0%)	28 (18.3%)	
Male factor	49 (32.2%)	47 (30.7%)	
Unexplained infertility	43 (28.3%)	48 (31.4%)	
Other	6 (4.0%)	14 (9.1%)	0.32
Smoking	16 (10.5%)	13 (8.5%)	0.68
Ethnicity			
Caucasian	141 (92.8%)	140 (91.5%)	
Other	11 (7.3%)	8 (5.2%)	0.91
History of previous pregnancies			
Live birth	11 (7.2%)	12 (7.8%)	1.00
Miscarriage	7 (4.6%)	7 (4.6%)	1.00
Termination of pregnancy	12 (7.9%)	31 (20.3%)	0.0029
Ectopic pregnancy	0 (0.0%)	3 (2.0%)	0.25
History of previous treatment with in vitro fertilization			
No treatments	124 (81.6%)	124 (81.0%)	
One treatment	15 (9.9%)	19 (12.4%)	
Two treatments	13 (8.6%)	10 (6.5%)	0.83

For categorical variables *n* (%) is presented.
For continuous variables mean (SD)/median (min; max)/*n* = is presented.
For comparison between groups Fisher´s Exact test (lowest 1-sided *P*-value multiplied by 2) was used for dichotomous variables and chi square test was used for non-ordered categorical variables and the Mann–Whitney *U* test was used for continuous variables.

the IVF only group, 10.5% (16) as compared to 2.6% (4) (difference 7.9, 95% CI: 14.1–1.8, $P = 0.009$) (Table II). No difference between the groups occurred concerning treatments with IVF or ICSI. The PP analysis showed similar results and with no significant difference in live birth rates and more spontaneous pregnancies resulting in live births in the weight reduction group (Supplementary Table S1).

Weight reduction intervention

The mean weight change from randomization to last recorded weight during intervention, often the weight at oocyte retrieval, was −9.44 (±6.57) kg in the weight reduction and IVF group, as compared to +1.19 (±1.95) kg in the IVF only group (Fig. 2). These results were highly significant ($P < 0.0001$). At the last recorded assessment before or at oocyte retrieval, the weight and BMI differed significantly between the two groups (weight 83.3 and 92.2 kg; BMI: 29.8 and 33.4 kg/m^2) ($P < 0.0001$) (Table III).

Subgroup analyses

Two subgroup analyses were performed. The first compared women with PCOS in the two randomized groups and the live birth rate was 11/40 (27.5%) for the weight reduction group and 9/41 (22.0%) for the IVF-only group ($P = 0.75$). The second subgroup analysis compared women in the weight reduction group reaching BMI $\leq$ 25 kg/m^2, or achieving a weight loss of five BMI units, to the IVF-only group and the live birth rate was 7/38 (18.4%) in the weight reduction group and 42/153 (27.5%) for the IVF-only group ($P = 0.35$). The comparisons showed no statistical differences in live birth rates between groups (Supplementary Tables SII and SIII).

Adverse events

A total of fourteen severe adverse events that demanded hospitalization, including ten events related to the IVF treatment, occurred in the study. There were three cases of severe OHSS, three cases of ovarian or endometrial infections, two cases of miscarriage and two cases of

Table II Outcomes according to treatment group in the full analysis set.

Variable	Weight reduction and IVF group (*n* = 152)	IVF only group (*n* = 153)	*P*-value
Spontaneous pregnancy leading to live birth¤	16 (10.5%)	4 (2.6%)	0.0089
No. of patients starting follitropin alfa stimulation	136 (89.5%)	149 (97.4%)	<0.005
Cancelled cycle**	3 (2.2%)	9 (6.0%)	0.19
Total dose of follitropin alfa (IU)	2122 (855)	2184 (1034)	0.89
	1886 (925; 5550)	1850 (859; 6000)	
	n = 136	*n* = 149	
Follitropin alfa (IU) required per oocyte retrieved	434.9 (629.5)	411.2 (444.7)	0.91
	265.4 (44.9; 5550.0)	262.1 (41.0; 2850.0)	
	n = 133	*n* = 139	
No. of oocytes retrieved per patient	8.56 (5.28)	9.00 (5.85)	0.63
	7.00 (1.00; 25.00)	8.00 (0.00; 32.00)	
	n = 133	*n* = 140	
Moderate or severe ovarian hyperstimulation syndrome	5 (3.8%)	7 (5.0%)	0.74
No. of oocytes fertilized***	4.35 (3.78)	4.76 (3.63)	0.24
	4.00 (0.00; 21.00)	4.00 (0.00; 17.00)	
	n = 133	*n* = 139	
Rate of fertilization=	0.51 (0.30)	0.54 (0.27)	0.40
	0.53 (0.000; 1.000)	0.57 (0.000; 1.000)	
	n = 133	*n* = 139	
No. of good quality embryos* Day 2	2.43 (2.57)	2.64 (2.59)	0.51
	2.00 (0.00; 14.00)	2.00 (0.00; 12.00)	
	n = 131	*n* = 137	
No. of frozen embryos	1.32 (1.66)	1.64 (2.56)	0.84
	1.00 (0.00; 8.00)	1.00 (0.00; 15.00)	
	n = 127	*n* = 133	
No. of transferred embryos			
0	24 (18.6%)	16 (11.6%)	
1	94 (72.9%)	110 (79.7%)	
2	11 (8.5%)	12 (8.7%)	0.22
Embryo transfer performed	105 (77.2%)	122 (81.9%)	0.46
No. of good quality embryos* transferred			
0	17 (16.2%)	20 (16.4%)	
1	82 (78.1%)	96 (78.7%)	
2	6 (5.7%)	6 (4.9%)	0.87
Day of embryo transfer			
2	95 (90.5%)	109 (89.3%)	
3	8 (7.6%)	8 (6.6%)	
5	2 (1.9%)	5 (4.1%)	0.47
Clinical pregnancy##	53 (34.9%)	47 (30.7%)	0.52
Ectopic pregnancy###	1/66 (1.5%)	1/56 (1.8%)	
Biochemical pregnancy####	12/66 (18.2%)	8/56 (14.3%)	
Miscarriage gestational weeks 6–12	8/66 (12.1%)	4/56 (7.1%)	
Miscarriage gestational weeks 13–22	0 (0.0%)	1/56 (1.8%)	
Live birth (including spontaneous pregnancies)	45 (29.6%)	42 (27.5%)	0.77

Continued

Table II *Continued*

Variable	Weight reduction and IVF group (n = 152)	IVF only group (n = 153)	P-value
Singleton births	45 (100.0%)	41 (97.6%)	
Twin births	0 (0.0%)	1 (2.4%)	1.00

For categorical variables n (%) is presented.
For continuous variables mean (SD)/median (min; max)/n = is presented.
For comparison between groups Fisher's Exact test (lowest 1-sided P-value multiplied by 2) was used for dichotomous variables and the Mantel–Haenszel chi square test was used for ordered categorical variables and chi square test was used for non-ordered categorical variables and the Mann–Whitney U-test was used for continuous variables.
Calculation of CI for continuous variables is based on the assumption of normality. When variances are not equal ($P < 0.05$) the SD is based on Satterthwaite's approximation, otherwise the SD is based on the pooled SDs.
*Day 2; 4–5 blastomeres, <20% fragmentation and no multinucleated blastomeres
**After starting the stimulation with follitrophin alfa.
***Defined as when two pronuclei were visible Day 1 after fertilization.
=No. of two pronuclei/no. of oocytes retrieved.
¤Pregnancy occurring without assisted reproduction technique treatment.
##Amniotic sac, with or without fetus, observed at sonography in gestational week 7.
###Pregnancy located outside the uterine cavity.
####Human chorion gonadotrophin in serum >5 IE/L but no amniotic sac visible at sonography gestational week 7.

ectopic pregnancy. In addition, two cases of surgery and two cases of infection unrelated to the treatment occurred.

Discussion

This large randomized, multicentre study showed that a weight reduction intervention with LCD and diet re-introduction, lasting 16 weeks in total, resulted in a substantial weight loss. Nevertheless, it did not improve live birth rates in moderately obese women scheduled for IVF, compared to women scheduled for IVF without previous weight reduction.

However, the frequency of live births after spontaneous pregnancy was higher in the weight reduction group. Some of the explanation for this finding would naturally be that the women in the weight reduction group had longer time to achieve a spontaneous pregnancy, but it might also be because of the weight reduction in itself, as has been shown previously (Norman *et al.*, 2004). For the patients and for the society reimbursing the patients, spontaneous pregnancy was a very important occurrence since fewer patients needed to undergo IVF in this group.

It has been described previously (Panidis *et al.*, 2008; Legros *et al.*, 2015) that especially infertile women with PCOS would benefit from weight reduction, but our subgroup analysis did not confirm this, showing no statistical difference between the groups.

Encouragingly, no detrimental effect of LCD on IVF outcome was noticed, as had been proposed (Tsagareli *et al.*, 2006). Rather unexpectedly, our results indicates that weight loss for moderately obese women (BMI: 30–35 kg/m^2) might not rectify the outcome in IVF cycles, although poorer results after IVF in this group, and especially for women with higher BMI, has been shown in many large observational studies. (Maheshwari *et al.*, 2007; Luke *et al.*, 2011; Bellver *et al.*, 2013; Petersen *et al.*, 2013; Provost *et al.*, 2016). Of late, articles have been published arguing that is unethical not to offer IVF to obese women, since the results are better than for many other groups that are currently being treated (Legro, 2016; Tremellen *et al.*, 2017). The live birth rates in the IVF only group, i.e. in women not losing weight, were much higher than

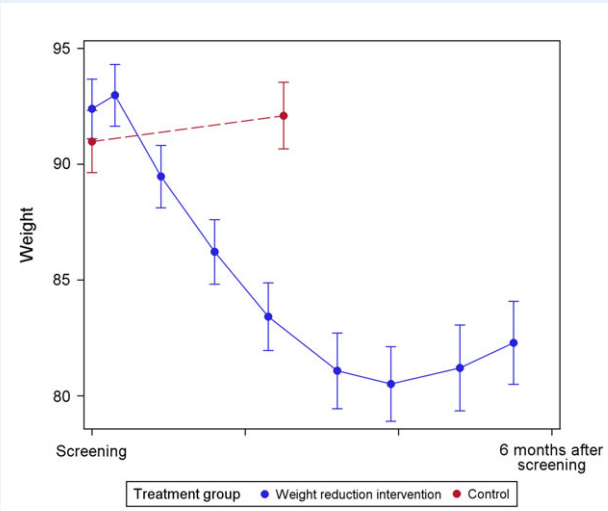

Figure 2 Graph of weight change for the two study groups from randomization to oocyte retrieval.

expected and in line with current national data from the Swedish national quality registry for assisted reproduction (Q-IVF).

Our study does not confirm the results of an Australian RCT (Sim *et al.*, 2014), that started after ours with fewer participants, and was not powered for life birth results. It showed that after an intensive 12-week lifestyle intervention, the patients had an average of 6.6 kg weight loss and a significantly higher live birth rate than the control group (44 vs 14%), and required fewer treatment cycles (two vs four). On the other hand, our results are in accordance with a large Dutch RCT (Mutsaerts *et al.*, 2016), recently published, where no improvement in live birth rates was noticed after an intensive lifestyle intervention in obese women. In that study more than 600 obese women were randomized to 6 months of lifestyle intervention before 18 months of infertility treatment or to immediate infertility treatment for 24 months. The average weight loss in the intervention group was 4.4 kg, The

Table III BMI and weight changes during time between randomization and the last recorded measurement up to oocyte retrieval for the full analysis set population.

Variable	Weight reduction and IVF ($n = 152$)	IVF only ($n = 153$)	*P*-value
BMI (kg/m^2) at randomization	33.1 (1.3)	33.0 (1.5)	0.77
	33.4 (29.9; 35.1)	33.3 (30.0; 35.1)	
Change in BMI from randomization to last BMI recorded up to oocyte retrieval	−3.25 (2.42)	0.449 (0.724)	<0.0001
	−3.63 (−7.91; 2.91)	0.312 (−1.121; 4.060)	
Weight at randomization (kg)	92.4 (8.0)	91.0 (8.4)	0.25
	91.6 (74.3; 111.0)	91.4 (68.0; 114.7)	
Change in weight (kg) from randomization to last recorded weight up to oocyte retrieval	−9.10 (6.83)	1.19 (1.95)	<0.0001
	−10.15 (−23.30; 7.90)	0.90 (−3.30; 9.60)	
Change in weight (%) from randomization to last weight recorded up to oocyte retrieval			
≤4.9% weight change, *n* (%) (including weight gain)	40 (26.3%)	153 (100.0%)	
5.0–9.9% weight change, *n* (%)	29 (19.1%)	0 (0.0%)	
≥10.0% weight change, *n* (%)	83 (54.6%)	0 (0.0%)	<0.0001

For categorical variables *n* (%) is presented.
For continuous variables mean (SD)/median (min; max)/*n* = is presented.
For comparison between groups the Mantel–Haenszel chi square test was used for ordered categorical variables and the Mann–Whitney *U*-test was used for continuous variables.

primary outcome was term vaginal birth rate within 24 months, which was significantly higher in the immediate treatment group (35.2 vs 27.1%). Nor did our study confirm, as previously described (Fedorcsàk *et al.*, 2004), that lower doses of gonadotropins are required in women with lower BMI, nor did it confirm that the miscarriage rate in this group is lower compared to the miscarriage rate in obese women. It has been discussed that the only effective treatment of obesity is bariatric surgery (Carlsson *et al.*, 2012). However, in the Nordic countries, as well as in international guidelines, the eligibility criteria for bariatric surgery is considerably higher (BMI ≥ 40 kg/m^2) than for the patients in our study, who were obese with a BMI of ≥ 30 < 35 kg/m^2. We thus chose a LCD for weight reduction since this is a well-documented, safe and effective method (Mustajoki and Pekkarinen, 2001; Parretti et al., 2016), giving substantial weight loss within a reasonable time frame for patients planning IVF. The higher frequency of prior termination of pregnancy noticed in the baseline characteristics for the IVF only group can be regarded as a random finding. Randomization was only balanced for parity, not for all outcomes of pregnancy. However, previous pregnancies, including terminations, have been found to be a positive predictor of clinical pregnancy (Templeton *et al.*, 1996). Adjustment for this imbalance in baseline did not alter the results.

The lack of a positive effect of weight reduction prior to IVF on subsequent live births might be surprising in view of earlier observational studies (Maheshwari *et al.*, 2007; Luke *et al.*, 2011; Petersen *et al.*, 2013; Provost *et al.*, 2016), showing a clear association between BMI and success after IVF. Although only a few of our patients reached a BMI ≤ 25 kg/m^2, a substantial weight loss was achieved in the weight reduction and IVF group for most patients. Despite no significantly improved effects being detected in live birth rates in the weight reduction group, the weight reduction per se ought to be beneficial in the longer term (Gregg *et al.*, 2016) and might also be a positive factor when assessing cumulative live birth rates. Furthermore, it is indeed important to bear in mind the increased obstetric risks for mother and child that follow with obesity (Dokras *et al.*, 2006; Luke *et al.*, 2011; Cnattingius *et al.*, 2013; Johansson *et al.*, 2014), and weight reduction before pregnancy obviously must lower these risks.

The strength of this study is that it was randomized and included many centres, allowing for generalizability and a substantial weight reduction was achieved by most patients.

A limitation was that the intervention group had a longer time to achieve a spontaneous pregnancy, ~4 extra months prior to IVF. This was impossible to avoid, since the IVF-only group could not be motivated to wait for their IVF treatment for such a long period of time. On the other hand, this resulted in the intervention group being older than the control group at the time of the IVF. This is important to consider, since age is the most prominent predictor of success after IVF. Also, the study was for obvious reasons not blinded for the patients or physician. A further limitation is that despite being quite large, the study was not powered to detect small differences in the number of live births between groups. Concerning the power calculation behind this study, one could argue that even a smaller difference in live birth rate would be valuable for the patient. However, we believe that a rather large difference in LBR is required to motivate young women to participate in this rather demanding trial, a statement well supported by the randomization process indicating a high decline rate. Further, the study only included women with a BMI lower than 35 kg/m^2 from participation, due to the Nordic IVF regulations. Another limitation to the study is that the time from the weight reduction up to the IVF treatment might have been too short, although a stabilizing diet re-introduction phase of 2–5 weeks was added, to correct for negative effects of obesity and adipose tissue both on the endometrium and oocytes (Bellver *et al.*, 2013; Comninos *et al.*, 2014; Leary *et al.*, 2015; Cardozo *et al.*, 2016).

In conclusion, this randomized trial showed that an intensive weight reduction programme resulted in a large weight loss, but did not substantially affect live birth rates in obese women scheduled for IVF. The study suggests that weight loss for obese women (BMI: 30–34.9 kg/m^2)

may not rectify the outcome in IVF cycles, although a significant higher number of spontaneous conceptions occurred. Also, it suggests that an intensive weight reduction with LCD treatment does not negatively affects the results.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Acknowledgements

We thank statisticians Nils-Gunnar Pehrsson and Mattias Molin for valuable statistical support and Niklas Svensson, who provided IT assistance. We also thank all co-workers at the following participating clinics, both IVF and obesity units. Sweden: Sahlgrenska University Hospital, Gothenburg; Karolinska University Hospital, Stockholm; Skåne University Hospital, Malmö; Örebro University Hospital, Örebro. Denmark: Rigshospitalet, Copenhagen University Hospital, Copenhagen; Hvidovre Hospital, Copenhagen University Hospital, Copenhagen; Herlev Hospital, Copenhagen University Hospital, Copenhagen; Holbaek Hospital, Copenhagen University Hospital, Copenhagen and Department of Nutrition, Exercise and Sports of Copenhagen University, Copenhagen. Iceland: IVF klinikin, Reykjavik.

Authors' roles

S.E., C.B. and A.T.K. participated in the design of the study, enrolment of patients, analysis and interpretation of data, writing of the article and approval of the final version. B.F., A.P., A.K., P.K., L.K., A.L., A.M.E. and A.W. participated in enrolment of patients, final interpretation of data, revision of the article and approval of the final version. I.L. and K.S. participated in the design of the study, analysis and interpretation of data, revision of the article and approval of the final version.

Funding

Sahlgrenska University Hospital (ALFGBG-70 940), Merck AB Solna, Sweden (an affiliate of Merck KGaA, Darmstadt, Germany), Impolin AB, Hjalmar Svensson Foundation and Jane and Dan Olsson Foundation for science. The funders had no role in the design of the study, statistical analysis or interpretation of the results, or in writing the article or the decision to submit it for publication.

Conflict of interest

Dr Thurin-Kjellberg reports grants from Merck, non-financial support from Impolin AB, during the conduct of the study, and personal fees from Merck outside the submitted work. Dr Friberg reports personal fees from Ferring, Merck, MSD, Finox and personal fees from Studentlitteratur, outside the submitted work. Dr Englund reports personal fees from Ferring, and non-financial support from Merck, outside the submitted work. Dr Bergh reports and has been reimbursed for writing a newsletter twice a year (Ferring), lectures (Ferring, MSD, Merck), and Nordic working group meetings (Finox). Dr Karlström reports lectures (Ferring, Finox, Merck, MSD) and Nordic working group meetings (Ferring). Ms Kluge, Dr Einarsson, Dr Pinborg, Dr Klajnbard, Dr Stenlöf, Dr Larsson, Dr Loft and Dr Wistrand have nothing to disclose.

References

Becker GF, Passos EP, Moulin CC. Short-term effects of a hypocaloric diet with low glycemic index and low glycemic load on body adiposity, metabolic variables, ghrelin, leptin, and pregnancy rate in overweight and obese infertile women: a randomized controlled trial. *Am J Clin Nutr* 2015;**102**:1365–1372.

Bellver J, Pellicer A, Garcia-Velasco JA, Ballesteros A, Remohi J, Meseguer M. Obesity reduces uterine receptivity: clinical experience from 9,587 first cycles of ovum donation with normal weight donors. *Fertil Steril* 2013;**100**:1050–1058.

Cardozo ER, Karmon AE, Gold J, Petrozza JC, Styer AK. Reproductive outcomes in oocyte donation cycles are associated with donor BMI. *Hum Reprod* 2016;**31**:385–392.

Carlsson LM, Peltonen M, Ahlin S, Anveden Å, Bouchard C, Carlsson B, Jacobson P, Lönroth H, Maglio C, Näslund I *et al*. Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. *N Engl J Med* 2012;**367**:695–704.

Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikström AK, Granath F. Maternal obesity and risk of preterm delivery. *J Am Med Assoc* 2013;**309**:2362–2370.

Comninos AN, Jayasena CN, Dhillo WS. The relationship between gut and adipose hormones, and reproduction. *Hum Reprod Update* 2014;**20**:153–174.

Dokras A, Baredziak L, Blaine J, Syrop C, Van Voorhis BJ, Sparks A. Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. *Obstet Gynecol* 2006;**108**:61–69.

Fedorcsàk P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, Omland AK, Abyholm T, Tanbo T. Impact of overweight and underweight on assisted reproduction treatment. *Hum Reprod* 2004;**19**:2523–2528.

Johansson S, Villamor E, Altman M, Bonamy AK, Granath F, Cnattingius S. Maternal overweight and obesity in early pregnancy and risk of infant mortality: a population based cohort study in Sweden. *Br Med J* 2014;**349**:g6572.

Kahnberg A, Enskog A, Brannstrom M, Lundin K, Bergh C. Prediction of ovarian hyperstimulation syndrome in women undergoing in vitro fertilization. *Acta Obstet Gynecol Scand* 2009;**88**:1373–1381.

Leary C, Leese HJ, Sturmey RG. Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. *Hum Reprod* 2015;**30**:122–132.

Legro RS, Dodson WC, Kris-Etherton PM, Kunselman AR, Stetter CM, Williams NI, Gnatuk CL, Estes SJ, Fleming J, Allison KC *et al*. Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. *Clin Endocrinol Metab* 2015;**100**:4048–4058.

Legro RS. Mr. Fertility Authority, tear down that weight wall! *Hum Reprod* 2016;**32**:2662–2664.

The Look AHEAD Research Group, Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, Coday M, Curtis JM, Egan C, Evans M *et al*. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2016;**4**:913–921.

Luke B, Brown MB, Sterna JE, Missmer SA, Fujimote VY, Leach RA, SART writing group. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. *Hum Reprod* 2011;**26**:245–252.

Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology—systematic review. *Hum Reprod Update* 2007;**13**:433–444.

Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril* 2008;**90**:714–726.

Moran L, Tsagareli V, Norman R, Noakes M. Diet and IVF pilot study: short-term weight loss improves pregnancy rates in overweight/obese women undertaking IVF. *Aust N Z J Obstet Gynaecol* 2011;**51**:455–459.

Mustajoki P, Pekkarinen T. Very low energy diet in treatment of obesity. *Obes Rev* 2001;**2**:61–72.

Mutsaerts MA, van Oers AM, Groen H, Burggraaff JM, Kuchenbecker WK, Perquin DA, Koks CA, van Golde R, Kaaijk EM, Schierbeek JM *et al*. Randomized trial of a lifestyle program in obese infertile women. *N Engl J Med* 2016;**374**:1942–1953.

Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF *et al*. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014;**384**:766–781.

Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. *Hum Reprod Update* 2004;**10**:267–280.

Panidis D, Farmakiotis D, Rousso D, Kourtis A, Katsikis I, Krassas G. Obesity, weight loss and the polycystic ovary syndrome: effect of treatment with diet and orlistat for 24 weeks on insulin resistance and androgen levels. *Fertil Steril* 2008;**89**:899–906.

Parretti HM, Jebb SA, Johns DJ, Lewis AL, Christian-Brown AM, Aveyard P. Clinical effectiveness of very low-energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev* 2016;**17**:225–234.

Petersen GL, Schmidt L, Pinborg A, Kamper-Jorgensen M. The influence of female and male body mass index on live births after assisted reproductive technology treatment: a nationwide register-based cohort study. *Fertil Steril* 2013;**99**:1654–1662.

Pocock SJ. *Clinical Trials: A Practical Approach*. Chichester, England: John Wiley, 1983.

Provost MP, Acharya KS, Acharya CR, Yeh JS, Steward RG, Eaton JL, Goldfarb JM, Muasher SJ. Pregnancy outcomes decline with increasing body mass index: analysis of 239,127 fresh autologous in vitro fertilization cycles from the 2008–2010 Society for Assisted Reproductive Technology Registry. *Fertil Steril* 2016;**105**:663–669.

Q-IVF Available at: http://www.qivf.se (18 June 2017, date last accessed).

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**:41–47.

Sim KA, Dezarnaulds GM, Denyer GS, Skilton MR, Caterson ID. Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. *Clin Obes* 2014;**4**:61–68.

Templeton A, Morris J, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. *Lancet* 1996;**348**:1402–1406.

Tremellen K, Wilkinson D, Savulescu J. Should obese women's access to assisted fertility treatment be limited? A scientific and ethical analysis. *Aust N Z J Obstet Gynaecol* 2017:1–6.

Tsagareli V, Noakes M, Norman RJ. Effect of a very-low-calorie diet on in vitro fertilization outcomes. *Fertil Steril* 2006;**86**:227–229.

Yanovski SZ. Binge eating disorder: current knowledge and future directions. *Obes Res* 1993;**1**:306–324.