Human Reproduction Update, Vol.9, No.5 pp. 429–449, 2003 DOI: 10.1093/humupd/dmg035

Patient predictors for outcome of gonadotrophin ovulation induction in women with normogonadotrophic anovulatory infertility: a meta-analysis

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A systematic review was conducted to determine whether initial screening characteristics of women with normogonadotrophic anovulatory infertility predict clinically significant outcomes of ovulation induction with gonadotrophins, and to obtain pooled estimates of their predictive value through meta-analysis. Only those studies in which pre-treatment screening characteristics (such as body mass index, serum LH and androgens, insulin sensitivity and ultrasound appearance of ovaries) were related to outcome parameters (such as total amount of FSH administered, cancellation, ovulation, pregnancy and miscarriage), were included in this analysis. Thirteen studies fulfilled the inclusion criteria. A positive association was seen in all studies between the level of obesity (definition applied as assessed by individual studies) and total amount of FSH administered [weighted mean difference (WMD) of 771 IU (95% confidence interval (CI): 700–842)]. Pooled odds ratios (OR) of 1.86 (95% CI: 1.13–3.06) and 0.44 (95% CI: 0.31–0.61) were found between obesity with cancellation and ovulation respectively. Pooled analysis did not show a significant association between obesity and pregnancy rate. The pooled OR for obese versus non-obese women and miscarriage rate was significant [3.05 (95% CI: 1.45–6.44)]. Association measures between insulin resistance (definition applied as assessed by individual studies) and total amount of FSH administered produced a WMD of 351 (95% CI: 73–630) IU. A pooled OR of 0.29 (95% CI: 0.10–0.80) was found for insulin resistance with pregnancy rate. The pooled OR for insulin resistance (hyperinsuliaemia versus normoinsuliaemia) and miscarriage rate was not significant. A pooled OR of 1.04 (95% CI: 1.01–1.07) was found for LH (IU/l) with pregnancy rate. The pooled OR for LH and miscarriage rate was not significant. Finally, pooled analysis did not find a significant association between testosterone and pregnancy rate. In conclusion, the best available evidence, though limited, suggests that the most clinically useful predictors of gonadotrophin ovulation induction outcome in normogonadotrophic women are obesity and insulin resistance.

Key words: anovulatory infertility/meta-analysis/obesity/outcome predictors/ovulation induction

Introduction

Chronic anovulation presents with amenorrhoea or oligomenorrhoea and can be classified on the basis of serum FSH and estradiol (E_2) levels. Hypogonadotrophic anovulation, low levels of gonadotrophins and negligible estrogen activity, is also referred to as (World Health Organization (WHO) group 1. Hypergonadotrophic anovulation is characterized by elevated gonadotrophin levels and low E_2 (WHO group 3) (Lunenfeld and Insler, 1974; ESHRE Capri Workshop Group, 1995; Rowe *et al*., 2000). Normogonadotrophic anovulation (FSH and E_2 levels within the normal range) (WHO group 2) represents the most common form of ovarian dysfunction and is a frequent cause of infertility (Laven *et al*., 2002; Rowe *et al*., 2000).

Clomiphene citrate has been used worldwide as the medication of first choice for the treatment of these women, because it is safe, convenient, cheap, and reasonably effective. The risk of developing ovarian hyperstimulation syndrome (OHSS) and multiple gestation is limited (2–3%) (Imani *et al*., 1999). However, a significant proportion (23%) of women remain anovulatory

following clomiphene citrate (Imani *et al*., 1998). A cumulative pregnancy rate of 73% is reported in ovulatory clomiphene citrate-treated women (Imani *et al*., 1999).

Induction of ovulation using exogenous gonadotrophins is generally indicated in patients with normogonadotrophic anovulatory infertility who have failed to ovulate or to conceive during previous clomiphene citrate treatment (Schwartz and Jewelewicz, 1981; Lunenfeld *et al*., 1985; Insler, 1988; Kelly and Jewelewicz, 1990; Franks and Gilling-Smith, 1994; Fauser and Van Heusden, 1997). Since the early 1960s, many anovulatory patients have been treated with hMG and hCG to induce ovulation. This treatment modality has been proven to be effective, but the risks of OHSS (Stephenson, 1991; Navot *et al*., 1992) and multiple pregnancies are considerably increased (Schenker *et al*., 1981; Fauser and Van Heusden, 1997).

Recent studies have focused on the prediction of ovulation induction outcome based upon initial screening characteristics of WHO 2 anovulatory infertile women (Imani *et al*., 1998, 1999, 2002a; Mulders *et al*., 2003). It could be demonstrated that some clinical, sonographic and endocrine characteristics are predictive of ovulation and conception during clomiphene citrate treatment (Imani *et al*., 1998, 1999, 2000, 2002a). Outcome parameters of gonadotrophin treatment in these women correlated with woman's age, ovarian response to preceding clomiphene citrate medication, body mass index (BMI), the mean follicle number assessed by ultrasound, serum levels of FSH, testosterone, androstenedione, and initial insulin-like-growth factor-I (IGF-I) (Imani *et al*., 2002b; Mulders *et al*., 2003).

The aim of gonadotrophin ovulation induction in anovulatory infertility is healthy live-birth, preferably from a singleton pregnancy. This is often hard to achieve despite the recent introduction of low-dose incremental or decremental regimens (Fauser and Van Heusden, 1997). An individualized treatment regimen, based on valid outcome predictors, might optimize ovulation induction strategies by improving the balance between success and complications. The existing literature concerning the prediction of outcome is limited and ambiguous. Some studies observe significant associations, whereas others fail to do so. Therefore, a systematic review was undertaken to establish more firmly which screening parameters are predictive of outcome of gonadotrophin induction of ovulation.

Materials and methods

The objectives of this review were to determine whether screening criteria applied to women with normogonadotrophic anovulatory infertility, predict clinically significant outcomes of ovulation induction with gonadotrophins, and to obtain pooled estimates of their predictive value through meta-analysis.

Criteria for considering studies for this review

Studies reporting gonadotrophin ovulation induction in women with normogonadotrophic anovulatory infertility [WHO 2, including polycystic ovary syndrome (PCOS)] were considered for inclusion if they provided specific information on: the regimens and type of gonadotrophin administered, e.g. standard protocol, step-up protocol, step-down protocol, hMG, urinary-derived (u)FSH and recombinant (r)FSH. The following primary outcome measures were sought: monofollicular growth [arbitrarily defined as one follicle >15 mm on the day of hCG (van Santbrink and Fauser, 1997)], total amount of gonadotrophins administered on the day of hCG in international units (IU), cancellation rate (cycle where there is no hCG administered), ovulation rate (as confirmed by an increased serum progesterone level (>20 nmol/l) in the luteal phase), pregnancy rate (per cycle or per patient) (defined as a positive urinary pregnancy test) and miscarriage rate (sonographic assessment of absence of an intrauterine gestational sac with heart beat at 12 weeks amenorrhoea). The following screening characteristics were also sought: age (years), cycle history (oligo- or amenorrhoea), BMI (kg/m^2), response during previous clomiphene citrate treatment [clomiphene resistant anovulation (CRA)/clomiphene citrate failure (CCF)], ovarian volume (ml), total number of follicles (both ovaries) (Pache *et al*., 1992), ovarian stroma echogenicity (Dewailly *et al*., 1994), serum levels of testosterone, androstenedione, LH, LH/FSH, fasting insulin and glucose. Inclusion was limited to studies in which outcome parameters were related to pre-treatment screening characteristics.

Search strategy for the identification of studies

Studies reporting the prediction of outcomes following gonadotrophin induction were initially identified through a handsearch (no specific criteria: papers at hand were considered). The wide variety of key words used in these reports provided the foundation for the final search strategy. It consisted of: (i) a Medline search by means of MESH headings (in the following order): (follicle stimulating hormone [majr] OR menotrophins [majr]) AND 'female genital diseases and pregnancy complications' [Majr] and (ii) a check of the bibliographies of identified studies.

Identification

Through the MESH headings search strategy ((follicle stimulating hormone [majr] OR menotrophins [majr]) AND 'female genital diseases and pregnancy complications' [Majr]), 631 titles were identified (1986 to October 2002). For 474 titles it was clear that population or intervention did not fulfil the selection criteria. To verify whether it was appropriate to exclude such articles based solely on titles, one of us (A.M.) read 10 of the 474 articles. None fulfilled the inclusion justifying this identification strategy. The remaining 157 articles were then read by one author (A.M.). Twenty-three studies fulfilled the selection criteria. All of their bibliographies were checked. This identified one additional study for inclusion.

Twenty-four potentially relevant studies were read by all authors and 13 were included. There were no disagreements between authors regarding the inclusion of studies.

Methods of the review

The following information was extracted from the potentially relevant studies: study characteristics, specified as observational, cohort, cross-over, consecutive or randomized, multicentre or not, method of randomization, number of patients/cycles (randomized, excluded and analysed), duration, timing and location of the study. Patient characteristics were recorded: definition of normogonadotrophic anovulatory infertility (WHO 2 including PCOS) (clinical, biochemical, ultrasonographic markers or combination of the former), definition and duration of infertility, age, investigative work-up, other causes of infertility and previously administered treatment(s), in particular whether previous treatment with clomiphene citrate had been tried and how CRA or CCF was defined. Finally, the outcome measures and their specific definitions were also recorded: total amount of exogenous FSH administered (IU), duration of administration of exogenous FSH (days), the number of cancelled cycles, the

number of cycles with multi- or monofollicular growth, the number of ovulatory cycles, the number of patients pregnant and not pregnant, miscarriage rate, multiple pregnancy rate and OHSS rate. A study had to give either a direct measure of association between predictor and outcome variables or present data that allowed for the calculation of such a measure. Studies reporting relationships between initial screening characteristics and outcome parameters of ovulation induction as measures of association (odds ratios: OR) and studies from which measures of association could be derived from the data given were included. For example, if a study reported the mean and SD of an outcome variable (eg. cancellation rate) for obese and for lean women separately, the OR of cancellation rate for obesity could be calculated assuming a normal distribution of the outcome variable in both groups, by the formula: $\ln(OR) = (mean_{obese} - mean_{lean})/$ (pooled variance in $_{obese}$ and $_{lean}$).

Results

Studies excluded

Eleven potentially relevant studies were excluded (Table I). These included application of modified stimulation schemes [Norfolk (1, 3, 5) regimen or administration of 150 IU every other day] (Ginsburg and Hardiman, 1991; Remorgida *et al*., 1991), application of modified controlled ovarian hyperstimulation followed by intrauterine and/or intraperitoneal insemination for PCOS and normo-ovulatory patients (Zullo *et al*., 1996), and comparison of two different stimulation regimens for a different subset of patients (repetitive cycles, not equally distributed) (Shoham *et al*., 1991).

Six studies stated insufficient data to allow analysis: only *P*-levels were noted for significant and non-significant prediction of duration of treatment by screening parameters (Coelingh Bennink *et al*., 1998), insufficient data were provided to calculate OR (respectively age versus conception) (Ginsburg and Hardiman, 1991), no clear statement of the background of LH levels supplied (Hamilton-Fairley *et al*., 1991), only data of LH pre-treatment versus ovulation for a subset of patients (Polson *et al*., 1987), no original data of LH levels (separately for pregnant and non-pregnant women) (Strowitzki *et al*., 1994). Finally, data for different subsets of patients (WHO 1 and 2) were not provided separately (Fluker *et al*., 1994).

In one study (Abdel *et al*., 1990), Pearson's correlation statistics showed a significant positive correlation between the BMI and the dose of gonadotrophins ($r = 0.4666$; $P < 0.001$). This dose correlated negatively with ovarian volume ($r = -0.1958$; $P = 0.01$). Since these correlation coefficients could not be incorporated in the pooled analysis, these data were not included.

One study (Imani *et al*., 2002b) provided significant correlations between the amount of exogenous FSH required for ovarian response [sonographic visualisation of a follicle $\geqslant$10 mm (Pache *et al*., 1990)] and initial clinical, sonographic and endocrine screening characteristics. Four of these parameters (i.e. ovarian response to clomiphene citrate medication (CRA), BMI, initial serum levels of FSH and free IGF-I) were included in the multivariate model to predict the FSH response dose (i.e. the amount of exogenous FSH required for ovarian response). Since this study only reported one specific outcome parameter that was not considered in the review, this study was excluded from the pooled analysis.

Methodological quality of included studies

A total of 13 studies was included in the current review (Table II) (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992, 1993; Dale *et al*., 1993; Farhi *et al*., 1993; Balasch *et al*., 1996; White *et al*., 1996; Fulghesu *et al*., 1997; Dale *et al*., 1998; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000). Some researchers performed several studies concerning outcome of ovulation induction in the same patient group of interest (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992, 1993; Dale *et al*., 1993, 1998; White *et al*., 1996). However, these studies appeared to include a different subset of patients (Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993, 1998; White *et al*., 1996) or the focus (screening characteristic versus outcome parameter) of the studies was different (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992, 1993; White *et al*., 1996).

Description of participants

The definitions of normogonadotrophic anovulatory infertility (WHO 2) and PCOS varied between centres, as detailed in Table II. Patients suffering from WHO 2 anovulatory infertility were included (Farhi *et al*., 1993; Balasch *et al*., 1996; Yarali *et al*., 1999). The most comprehensive definition of PCOS specified as a combination of clinical features (oligoamenorrhoea), biochemical parameters (increased androgen concentrations) and polycystic appearance of ovaries on ultrasound scan (enlarged ovaries with multiple small follicles), was used in a number of studies (McClure *et al*., 1992; Fulghesu *et al*., 1997; Vicino *et al*., 2000). Various combinations of clinical, biochemical and ultrasonic findings were also used: ultrasound and clinical or biochemical (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993, 1998; Strowitzki *et al*., 1998), clinical and ultrasound and/or biochemical (McClure *et al*., 1993), or clinical and ultrasound (White *et al*., 1996). According to these definitions, oligoamenorrhoea is not present in all patients *per se* (McClure *et al*., 1992; Dale *et al*., 1993, 1998; Farhi *et al*., 1993; Balasch *et al*., 1996; Strowitzki *et al*., 1998).

The extent of the infertility work-up was stated in all studies (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992, 1993; Dale *et al*., 1993, 1998; Farhi *et al*., 1993; Balasch *et al*., 1996; White *et al*., 1996; Fulghesu *et al*., 1997; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000). This consisted most commonly of a semen analysis and a hysterosalpingography and/or laparoscopic inspection. Twelve studies included only couples with a normal semen analysis (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992, 1993; Dale *et al*., 1993, 1998; Farhi *et al*., 1993; Balasch *et al*., 1996; Fulghesu *et al*., 1997; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000). In all studies, tubal patency (at least one open tube) was confirmed (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; McClure *et al*.,

Table I. Characteristics of studies regarding gonadotrophin ovulation induction in women with normogonadotrophic anovulatory infertility who were excluded (reasons for exclusion are printed in bold in 'Comments' section) for the current meta-analysis

Study	Methodology	Participants	Interventions	Screening parameters[a]	Outcome parameters[a]	Numbers	Comments
Abdel *et al.* (1990)	Randomized controlled trial	PCOS. All CRA	Electrocautery or gonadotrophins. Step-up regimen: hMG or uFSH; starting dose: 75 IU; first dose ↑ after 1 week: 75 IU; subsequent cycle starting dose: individually adjusted; CG (5000 IU): 1 follicle ⩾18 mm + increased E_2; cancellation criteria: 3 follicles ⩾15 mm; OHSS: not reported.	BMI (kg/m^2); Testosterone (nmol/l); Ovarian volume (ml)	Total amount of FSH administered (ampoule: 75 IU); Conception	59 patients; 233 cycles	Monitoring through transabdominal ultrasound? **Significant Pearson's correlation between BMI and ovarian volume with the dose of gonadotrophins.** Correlation for testosterone with pregnancy is provided for both treatments (n = 88 patients). Correlations for age, BMI and mean ovarian volume with viable/ non-viable pregnancies are provided for both treatments (n = 88 patients).
Coelingh Bennink *et al.* (1998)	Prospective, multicentre, randomized trial	WHO 2. CRA + CCF	Step-up regimen: rFSH s.c. versus uFSH i.m.; starting dose: 75 IU; ovarian response: one follicle ⩾12 mm; first dose ↑ after 14 days: 37.5 IU; subsequent dose ↑ after 1 week: 37.5 IU; subsequent cycle: first dose ↑ after 1 week; maximum dose: 225 IU/day; hCG (10000 IU): one follicle ⩾18 mm or 2–3 ⩾15 mm; cancellation criteria: >3 follicles ⩾15 mm or no response after 42 days, OHSS: reported	Cycle history; Age (years); Duration infertility (years); Type of infertility (p/s); BMI (kg/m^2); LH/FSH	Duration of stimulation (days)	172 patients; 172 cycles	Inclusion criteria: Age: 18–39 (years); BMI: 19–32 (kg/m^2). Definition of CRA: dose? Statistical testing for secondary outcome parameters based solely on first cycle data. **Significant (only P-level noted) and non-significant prediction of duration of treatment by screening parameters (no data provided).**
Fluker *et al.* (1994)	Retrospective observational study	WHO 2: Oligomenorrhoeic; Hyperandrogenic; Luteal phase defect (endo/histol). CRA + CCF. (WHO 1)	Step-up regimen: hMG i.m./i.v.; starting dose: 75–450 IU/day; hCG (10 000 IU): 1–4 follicles ⩾16 mm + E_2 > 3600–4500 pmol/l; luteal support; OHSS: not reported	Age (years)	Cumulative conception rates (conception: gestational sac or histological criteria)	118 patients; 396 cycles	18 year span of the study. Hyperandrogenic subgroup WHO 2: 39 of 49 cycles concomittant corticosteroids. **hMG (i.m.: 385 cycles and i.v.: 83 cycles): mode of administration not clearly for WHO 1 and 2 separately.** Luteal support. **Prediction of rates based upon data of both patient groups (WHO 1+2).**
Ginsberg *et al.* (1991)	Cohort study	WHO 2. All failed to respond to clomiphene citrate	Norfolk (1, 3, 5) regimen: modified step-up, hMG; hCG (5000 IU): 1 follicle ⩾18 mm; OHSS: not reported	Age (years)	Conception rate	93 patients	12 year span of the study. Definition of failure to respond to clomiphene citrate not clearly stated. **Norfolk regimen: cumulative conceptionmodified step-up. Insufficient data provided to calculate OR (age with conception rate).**

Table I *Continued*

Study	Methodology	Participants	Interventions	Screening parameters[a]	Outcome parameters[a]	Numbers	Comments
Hamilton-Fairley *et al.* (1991)	Observational study	WHO 2: oligoamenorrhoea + TVS-PCO[b] + (↑ LH, ↑ testosterone and/or both). All CRA	Step-up regimen: hMG i.m. or uFSH i.m.; starting dose: 75 IU; ovarian response: 1 follicle ⩾12 mm; first cycle: first dose ↑ after 14 days: 37.5 IU; further dose ↑ after 7 days: 37.5 IU; subsequent cycle: starting dose: 52.5–75 IU/day; first dose ↑ after 1 week; maximum dose: 225 IU/day; hCG (5000 IU): 1 follicle ⩾18 mm; cancellation criteria: >3 follicles ⩾15 mm; OHSS: reported	LH (IU/l)	Ovulation (progesterone ⩾30 nmol/l); Pregnancy (serum hCG >25 IU/l and presence of an intrauterine gestational sac); Early pregnancy loss (failure of fetus to develop >8 weeks gestation)	100 patients; 401 cycles	Exclusion criteria: BMI > 28. **Data LH (CD?). Data LH per pt/cy?**
Imani *et al.* (2002)	Prospective observational study	WHO 2. CRA + CCF	First cycle: Step-up regimen: uFSH i.m. versus rFSH s.c.; starting dose: 75 IU; ovarian response: 1 follicle ⩾10 mm; first dose ↑ after 7 days: no ovarian response: 37.5 IU, subsequent dose ↑ after 1 week: 37.5 IU; hCG (5000 IU): 1–2 follicles ⩾18 mm; cancellation criteria: ⩾3 follicles ⩾16 mm	Cycle duration; CRA/CCF; BMI (kg/m^2); FSH (IU/l); FAI (100×testosterone/SHBG); Insulin (mU/l); Free IGF-I (ng/ml); IGFBP-1 (ng/ml); Leptin (ng/ml); Ovarian volume (ml)	FSH response dose (ovarian response equal to sonographic visualization of a follicle ⩾10 mm)	90 patients; 90 cycles	Significant correlation between response during clomiphene citrate treatment (CRA), BMI, FSH and free IGF-I with FSH response dose (multivariate model provided). **Correlations for one specific outcome parameter (i.e. FSH response dose) are provided; no further data on treatment outcome available.**
Polson *et al.* (1987)	Prospective observational study	WHO 2. All CRA	Step-up regimen: uFSH s.c., infusion pump: pulse every 90 min: 5 IU; starting dose: 75 IU daily; first dose ↑ after 2 weeks: 37.5 IU; subsequent dose ↑ after 1 week: 37.5 IU; maximum dose: 225 IU/day; hCG (3000 IU): 1 follicle ⩾16 mm; subsequent cycle: starting dose: 75 IU daily, first dose ↑ after 1 week: 37.5 IU, luteal support; OHSS: not reported	LH (IU/l); FSH (IU/l)	Ovulation (TVE and > progesterone)	10 patients; 33 cycles	All patients previously underwent a variety of treatments (i.e. bromocriptine (9 patients), tamoxifen (1), hMG (5), ovarian wedge resection (2), GnRH (2), clomiphene citrate (10). Dose CRA not stated. **No pre-treatment LH data on cycle level for the total group. Data of LH pre-treatment with ovulation are only provided for ovulatory cycles (12 out of 33).**

Table I *Continued*

Study	Methodology	Participants	Interventions	Screening parameters[a]	Outcome parameters[a]	Numbers	Comments
Remorgida *et al.* (1991)	Prospective crossover study	WHO 2. CRA + CCF	GnRH agonist plus gonadotrophins (A) versus gonadotrophins alone (B). (A) GnRH + uFSH: GnRH: starts CD 2, FSH: CD 5 + 7 + 9: dose 75 IU; FSH stop in case of follicular selection: 1 follicle >12 mm and E_2 >150 pg/ml; hCG (5000 IU): ⩾1 follicle ⩾18 mm and E_2 >250 pg/ml. (B) uFSH: FSH: CD 3 + 5 + 7: dose 150 IU; CD 8: individualized therapy: dose adjustment: 0–4 ampoules per day; hCG (5000 IU): ⩾1 follicle ⩾18 mm and E_2 >250 pg/ml; cancellation criteria: >3 pre-ovulatory follicles and/or E_2 > 2000 pg/ml. OHSS: not reported, luteal support	Cycle history; Age (years); BMI (kg/m^2); Testosterone (ngl/ml); LH/FSH; SHBG (nmol/l)	Duration of stimulation (days); Total amount of FSH administered (ampoule: 75 IU)	4 patients; 4 cycles	Previous treatment: GOI: all patients hyper-responded; GnRH: all patients underwent ⩾3 cycles and no ovulation was observed. **Modified ovarian stimulation regimen.**
Shoham *et al.* (1991)	Observational study	PCOS and WHO 2. All CRA	Step-up regimen: hpFSH i.m. Low dose: Starting dose: 75 IU; first dose ↑ after 1 week: 37.5 IU; subsequent cycle: starting dose: 37.5 IU in case of hyper-response first cycle. Conventional: starting dose: 75 IU; first dose ↑ after 1 week: 75 IU. Cancellation criteria: >3 follicles ⩾16 mm. OHSS: not reported	Cycle history; Duration of infertility (years); Age (years); BMI (kg/m^2); Testosterone (nmol/l); LH (IU/l); LH/FSH	Duration of stimulation (days); Total amount of FSH administered (ampoule: 75 IU)	8 patients; 24 cycles	Inclusion: 7 PCOS patients and 1 WHO 2 patient. Dose CRA not stated. Variable previous treatment history for all patients. **Comparison of two different stimulation regimens: 2 patients: low-dose protocol only**; **6 patients: both low-dose and conventional protocol.**
Strowitzky *et al.* (1994)	Prospective observational study	PCOS: TVS-PCO + ⩾2 criteria. CRA + CCF	Step-up regimen: uFSH i.m.; starting dose: 75 IU, first dose ↑ after 10–12 days: 37.5 IU; no further dose ↑; hCG (10 000 IU): 1 follicle ⩾16 mm; cancellation criteria: >3 major follicles or no response, OHSS: reported	LH (IU/l)	Pregnancy (hCG measurement)	20 patie nts; 27 cycles	Included: 1 patient with a regular cycle; 6 couples with andrological factors requiring homologous insemination in 4. Previous treatment: Definition of CRA: dose? Maximum of 30 clomiphene citrate cycles; Severe OHSS for 7 patients during conventional GOI. **No significant differences between pregnant and non-pregnant women concerning LH levels (no data provided).**

Table I *Continued*

Study	Methodology	Participants	Interventions	Screening parameters[a]	Outcome parameters[a]	Numbers	Comments
Zullo *et al.* (1996)	Retrospective observational study	PCOS: TVS-PCO + ⩾1 criteria and normo-ovulatory	Modified COH followed by IUI and/or IPI. COH: uFSH, starting dose: 75 IU; first dose ↑ after 7 days: 75 IU, subsequent dose ↑ after 3 days: 37.5 IU; hCG (10 000 IU): 1–4 follicles ⩾18 mm + >E_2[c], OHSS: reported	Waist/hip ratio	Duration of stimulation (days); Total amount of FSH administered (ampoule:75 IU); No. of follicles >18 mm (day hCG); Ovulation (TVE and > progesterone); Pregnancy	60 patients (PCOS and normo-ovulatory); 53 cycles (PCOS only)	Previous treatment: not reported. **Modified COH followed by IUI/IPI.** Numbers: 111 cycles: 53 PCOS cycles?

[a]Screening parameters and outcome parameters outlined: only those parameters which are discussed as (possibly) related.
[b]Presence of polycystic ovaries based on published criteria (Adams *et al.*, 1985, 1986).
[c]Serum oestradiol levels of between 200 and 1500 pg/ml per follicle >15 mm.
PCOS = polycystic ovary syndrome; BMI = body mass index; CRA = clomiphene-resistant anovulation; OHSS = ovarian hyperstimulation syndrome; WHO = World Health Organization; CCF = clomiphene citrate failure; IGF = insulin-like growth factor; SHBG = sex hormone-binding globulin; COH = controlled ovarian hyperstimulation; IUI = intrauterine insemination; IPI = intraperitoneal insemination; TVS-PCO = transvaginal sonography polycystic ovaries; FAI = free androgen index defined as 100 × T/SHBG; GOI = gonadotrophin ovulation induction; p/s = primary/secondary; endo/histo = endocrine histologic criteria; pt/cy = patient/cycle.

1992, 1993; Farhi *et al*., 1993; Balasch *et al*., 1996; White *et al*., 1996; Fulghesu *et al*., 1997; Strowitzki *et al*., 1998; Vicino *et al*., 2000). In one study, donor sperm (one patient) were used because of co-existing male factor infertility (Hamilton-Fairley *et al*., 1992).

Except for one study (White *et al*., 1996), the patients of interest either had remained anovulatory after clomiphene citrate treatment, or had failed to conceive despite ovulating during clomiphene citrate treatment. A wide variation in the definition of clomiphene citrate-resistant anovulation and failure was used. In two studies, ovarian wedge resection or ovarian electrocauterization had been performed before gonadotrophin induction of ovulation (Dale *et al.*, 1993, 1998).

In three studies, patients with increased BMI levels were excluded from treatment: BMI >28 kg/m^2 (Hamilton-Fairley *et al*., 1992; White *et al*., 1996) and BMI >30 kg/m^2 (Sagle *et al*., 1991).

Description of interventions

The step-up regimen was applied according to the following protocol: a starting dose of 75 IU per day and a first dose increase of 75 IU per day after 5–7 days (Farhi *et al*., 1993). Various alternatives of this protocol were reported (McClure *et al*., 1992, 1993; Fulghesu *et al*., 1997; Vicino *et al*., 2000). Others used the step-up regimen according to the following protocol: starting dose of 50–75 IU per day, a first dose increase of 37.5 IU per day after 14 days and a subsequent dose increase of 37.5 IU per day (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993, 1998; Balasch *et al*., 1996; White *et al*., 1996; Yarali *et al*., 1999). Strowitzky *et al.* utilized a variation of this regimen. In some studies the starting dose was adjusted in the subsequent (>1) cycle performed (McClure *et al*., 1992; Balasch *et al*., 1996; White *et al*., 1996; Yarali *et al*., 1999; Vicino *et al*., 2000).

The following preparations of gonadotrophins were used: hMG (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992; Farhi *et al*., 1993; White *et al*., 1996), uFSH (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992; Dale *et al*., 1993, 1998; Farhi *et al*., 1993; Balasch *et al*., 1996; White *et al*., 1996; Fulghesu *et al*., 1997; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000) and rFSH (Strowitzki *et al*., 1998; Yarali *et al*., 1999). Only one study compared gonadotrophin-only treatment (uFSH/hMG) with a combined regimen (hMG and the concomitant administration of a GnRH agonist) (Farhi *et al*., 1993). Besides gonadotrophin induction of ovulation, electrocautery was also performed in one study (Vicino *et al*., 2000).

Description of outcome measures

In six studies the number of cycles with monofolllicular development was not reported (McClure *et al*., 1992, 1993; Farhi *et al*., 1993; White *et al*., 1996; Fulghesu *et al*., 1997; Vicino *et al*., 2000). The definition of monofollicular growth varied from one follicle >15 mm (Dale *et al*., 1998) and one follicle >17 mm (Balasch *et al*., 1996) in diameter on the day of hCG. In five studies the definition used was not clearly stated

Table II. Characteristics of studies regarding gonadotrophin ovulation induction in women with normogonadotrophic anovulatory infertility whom were included in the current meta-analysis

Study	Methodology	Participants	Interventions	Screening parameters[a]	Outcome parameters[a]	Numbers	Comments
Balasch *et al.* (1996)	Prospective multicentre study	WHO 2. CRA + CCF	Step-up protocol: uFSH im or hpFSH s.c.; starting dose: 75 IU; ovarian response: 1 follicle ⩾11 mm; first dose ↑ after 14 days: 37.5 IU; subsequent dose ↑ after 1 week: 37.5 IU; subsequent cycle starting dose: 37.5–112.5 IU; maximum dose: 225 IU/day; hCG (10 000 IU): 1 follicle ⩾17 mm; cancellation criteria: ⩾4 follicles >14 mm or no response (maximum daily dose: 3 ampoules); luteal support, OHSS: Golan (1989)	LH (IU/l); LH/FSH	Pregnancy (intrauterine gestational sac)	234 patients; 534 cycles	Luteal support. No significant correlations for LH and LH/FSH with viable pregnancy/spontaneous abortion: (no data provided).
Dale *et al.* (1993)	Retrospective observational study	PCOS: TVS-PCO[b] + ⩾2 criteria. CRA + CCF	Step-up regimen: pFSH i.m.; starting dose: 75 IU; ovarian response: 1 follicle ⩾10 mm; first dose ↑ after 2 weeks: 37.5 IU; hCG (9000 IU): 1 follicle ⩾18 mm; cancellation criteria: ⩾4 follicles >16 mm; OHSS: 2 stages, moderate/severe	BMI (kg/m^2); Insulin resistance (CIGMA test)	Total amount of FSH administered (IU); Cancellation; Pregnancy (gestational sac or histological criteria)	50 patients; 66 cycles	Included: 8 patients with a regular cycle; 15 patients previously underwent ovarian wedge resection or electrocautery.
Dale *et al.* (1998)	Prospective observational study	PCOS: TVS-PCO[b] + ⩾3 criteria. CRA + CCF	Step-up regimen: uFSH i.m.; starting dose: 75 IU, first dose ↑ after 14 days: 37.5 IU; subsequent dose ↑ after 1 week: 37.5 IU; hCG (5000 IU): leading follicle ⩾18 mm + ⩽3 follicles ⩾15 mm; cancellation criteria: ⩾4 follicles ⩾15 mm; OHSS: 2 stages moderate/severe	BMI (kg/m^2)	Total amount of FSH administered (IU); Cancellation	42 patients; 70 cycles	19 patients previously underwent ovarian wedge resection or electrocautery. Significant and non-significant correlations for BMI versus outcome (i.e. obese versus non-obese patients).
Farhi *et al.* (1993)	Retrospective observational study	Anovulatory infertility + PCO-TVS[b]. CRA + CCF	Step-up regimen: uFSH i.m. versus hMG i.m. versus hMG i.m. + GnRH; starting dose: 75 IU; first dose ↑ after 5 days: 75 IU; hCG (10 000 IU): 1 follicle ⩾16 mm + ↑ E_2; cancellation criteria: >3 follicles >17 mm or E_2 >2000 pg/ml; OHSS: reported	Cycle history; Age (years); BMI (kg/m^2); Testosterone (ng/ml); LH (IU/l)	Pregnancy	89 patients; 195 cycles	5 year span of the study. Included: 13 patients with a regular cycle.
Fulghesu *et al.* (1997)	Prospective observational study. Consecutive series	PCOS. CCF (+ CRA?)	Step-up regimen: uFSH i.m.; starting dose: 150, first dose ↑ after 7 days: 75 IU if E_2 = insufficient; subsequent dose ↑ after 5 days, maximum dose: 225 IU/day; hCG (5000 IU): 1 follicle ⩾18 mm; OHSS: Golan (1989)	BMI (kg/m^2); Hyperinsulinism (OGTT)	Total amount of FSH administered (IU)	34 patients; 52 cycles	Definition CRA not clearly stated. Inclusion 8 patients: 1 open tube. Significant correlation between obesity with increase ovarian volume ? (no data provided).

Table II *Continued*

Study	Methodology	Participants	Interventions	Screening parameters[a]	Outcome parameters[a]	Numbers	Comments
Hamilton-Fairley *et al.* (1992)	Retrospective observational study	WHO 2: olam + TVS-PCO[b] + (↑ LH, ↑ testosterone and/or both). All CRA	Step-up regimen: hMG i.m. or uFSH i.m.; starting dose: 75 IU; ovarian response: 1 follicle ⩾12 mm; first cycle: first dose ↑ after 14 days: 37.5 IU; further dose ↑ after 7 days: 37.5 IU; subsequent cycle: starting dose: first dose ↑ after 1 week; maximum dose: 225 IU/day; hCG (5000 IU): 1 follicle ⩾18 mm; cancellation criteria: > 3 follicles ⩾16 mm, OHSS: not reported	BMI (kg/m^2)	Total amount of FSH administered (IU); (Uni)ovulatory cycle (progesterone ⩾30 nmol/l); Pregnancy (serum hCG >25 IU/l and presence of an intrauterine gestational sac); Early pregnancy loss (failure of fetus to develop >8 weeks gestation)	100 patients; 405 cycles	Exclusion: BMI >28
McClure *et al.* (1992)	Observational study	PCOS. CRA + CCF	Step-up regimen: hMG i.m.; starting dose: 75 IU (maximum 150 IU); first dose ↑ after 5–7 days: 37.5 IU; subsequent cycle: starting dose: 37.5–225 IU/day; hCG (3000 IU): 1 follicle ⩾16 mm; cancellation criteria: >3 follicles >14 mm + >E_2; luteal support (failing CL 9 days); OHSS: not reported	BMI (kg/m^2)	Total amount of FSH administered (IU)	71 patients; 224 cycles	Luteal support (failing corpus luteum 9 days) *N*: ? Significant correlation between BMI with total amount of FSH administered (IU); (no data provided: only *P*-value). No significant correlation between BMI and pregnancy outcome (no data provided: only *P*-value).
McClure *et al.* (1993)	Retrospective observational study	PCOS. All CRA	Step-up regimen: hpFSH i.m.; starting dose: 75 IU (37.5–225), first dose ↑ after 5–7 days; maximum dose: 225 IU/day; hCG (3000 IU): 1 follicle ⩾16 mm; cancellation criteria: >3 follicles >14 mm + >E_2, luteal support; OHSS: not reported	Age (years); BMI (kg/m^2); LH (IU/l)	Miscarriage (pregnancies ending < 20 weeks)	44 patients; 75 cycles	Definition CRA not clearly stated (dose: ?). Luteal support.
Sagle *et al.* (1991)	Prospective randomized controlled trial	WHO 2: oligo-amenorrhoea + TVS-PCO + (↑ LH, ↑ testosterone and/or both). All CRA	Step-up regimen: hMG i.m. or uFSH i.m.; starting dose: 75 IU; ovarian response: 1 follicle >12 mm; first dose ↑ after 2 weeks: 37.5 IU; subsequent dose ↑ after 1 week: 37.5 IU; subsequent cycle: starting dose: 75 IU; hCG (5000 IU): 1 follicle ⩾18 mm; cancellation criteria: >3 follicles ⩾15 mm; OHSS: not reported	LH (IU/l)	Ovulation (midluteal progesterone >30 nmol/l)	30 patients; 74 cycles	Exclusion criteria: BMI >28

Table II *Continued*

Study	Methodology	Participants	Interventions	Screening parameters[a]	Outcome parameters[a]	Numbers	Comments
Strowitzki *et al.* (1998)	Retrospective study	PCOS: TVS-PCO + ⩾2. Clomiphene citrate treatment unsuccessful.	Step-up regimen: rFSH s.c. or uFSH i.m. or hpFSH i.m.; starting dose: 75 IU; first dose ↑ after 10–12 days: 37.5 IU; no further dose ↑; hCG (10 000 IU): ⩾1 follicle ⩾16 mm; cancellation criteria: >3 follicles >14 mm or no response; OHSS: reported	Obesity: BMI (kg/m^2)	Total amount of FSH administered (IU); Cancellation; Ovulation (TVS); Pregnancy (hCG); Miscarriage	68 patients; 116 cycles	Definition clomiphene citrate response not clearly stated. Inclusion: 1 regular cycle. Definition obesity? No correlations obesity with outcome (insufficient data provided: no BMI levels of obese versus lean groups)
Vicino *et al.* (2000)	Randomized controlled trial	PCOS. All CRA	Electrocautery or gonadotrophins. Step-up regimen: hpFSH i.m.; starting dose: 75 IU; first dose ↑ after 7 days: 37.5 IU; subsequent dose ↑ after 2 days: 37.5 IU; subsequent cycle: starting dose individually adjusted; maximum dose: 225 IU/day; hCG (5000 IU): maximum of 2 follicles ⩾16 mm; cancellation criteria: >2 follicles ⩾16 mm or >6 follicles ⩾12–16 mm or no response	BMI (kg/m^2); Testosterone (ng/ml); Androstenedione (ng/ml); LH (IU/l)	Total amount of FSH administered (IU); Cancellation; Ovulation (TVS and progesterone >10 ng/ml); Pregnancy (intrauterine gestational sac and fetal heartbeat)	21 patients; 107 cycles	Correlations BMI with duration of stimulation and amount of follicles significant as well
White *et al.* (1996)	Observational study	WHO 2: oligomenorrhoea + TVS-PCO[b] + androgen excess	Step-up regimen: hMG or uFSH i.m.; starting dose: 75 IU; ovarian response: 1 follicle >10 mm; first dose ↑ after 14 days: 37.5 IU; subsequent dose ↑ after 1 week: 37.5 IU; subsequent cycle: starting dose subthreshold level: 37.5–75 IU; dose ↑: 25–37.5 IU, maximum dose: 225 IU/day; hCG (5000 IU): 1 follicle ⩾18 mm + endometrial thickness ⩾8 mm; cancellation criteria: >3 follicles ⩾15 mm; OHSS: mild/moderate	BMI (kg/m^2); Testosterone (ng/ml); LH (IU/l)	Ovulation (↑ progesterone); Pregnancy; Miscarriage (abortion + ectopic pregnancy)	91 patients; 429 cycles	Definition PCOS: oligomenorrhoea + TVE-PCO + (>90% androgen excess: based upon ↑ LH, ↑ testosterone or ↑ Ferriman–Gallwey score). Exclusion: BMI >28. Previous clomiphene citrate treatment? Additional factors involved: 9, unilateral tubal disease; 22, subnormal sperm; 2, both. Possible association BMI with cumulative pregnancy rate: insufficient data.
Yarali *et al.* (1999)	Prospective randomized trial	WHO 2. CRA and CCF	Step-up regimen: uFSH i.m. or rFSH s.c.; starting dose: 75 IU; first dose ↑ after 14 days: 37.5 IU; subsequent dose ↑ after 1 week: 37.5 IU; subsequent cycle: starting dose subtreshold level: 37.5–75 IU; dose ↑: 18.7–37.5 IU; maximum dose: 225 IU/day; hCG (10 000 IU): 1 follicle ⩾17 mm; cancellation criteria: >4 follicles ⩾15 mm or no response after 35 days; OHSS: not reported	BMI (kg/m^2)	Ovulation (↑ progesterone)	51 patients; 96 cycles	Logistic regression for prediction of ovulation in first cycle and duration of treatment: insufficient data: only some *P*-values provided

[a]Screening parameters and outcome parameters outlined: only those parameters which are discussed as related
[b]Presence of polycystic ovaries based on previously published criteria (Adams *et al.*, 1985, 1986).
For abbreviations see Table I.

(Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993; Strowitzki *et al*., 1998; Yarali *et al*., 1999). Only seven studies reported the number of cycles with monofollicular growth (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993, 1998; Balasch *et al*., 1996; Strowitzki *et al*., 1998; Yarali *et al*., 1999).

The total amount of gonadotrophins administered per cycle (Sagle *et al*., 1991; McClure *et al*., 1992, 1993; Dale *et al*., 1993; Farhi *et al*., 1993; White *et al*., 1996; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000) or the mean total quantity of gonadotrophins to induce ovulation or achieve follicular maturation (Hamilton-Fairley *et al*., 1992; Balasch *et al*., 1996; Fulghesu *et al*., 1997; Dale *et al*., 1998) was provided for all studies in ampoules or IU. For one study (McClure *et al*., 1992) the total amount of gonodotrophins administered was deduced from a figure illustration. A conversion to IU was made for those studies reporting the total dose in ampoules (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Farhi *et al*., 1993; White *et al*., 1996; Strowitzki *et al*., 1998; Vicino *et al*., 2000).

Criteria for cycle cancellation were based on the number of follicles developed and/or serum E_2 levels. In five studies, cycles were cancelled in case of multifollicular growth ($\geqslant$4 follicles $\geqslant$15 mm) (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993, 1998; White *et al*., 1996; Yarali *et al*., 1999). In four studies, cycles were cancelled because of multifollicular growth or absence of response (Balasch *et al*., 1996; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000). Finally, three studies cancelled treatment cycles based on multifollicular growth and/or increased serum E_2 levels (McClure *et al*., 1992, 1993; Farhi *et al*., 1993). One study did not provide information on criteria for cycle cancellation (Fulghesu *et al*., 1997). Only nine studies reported the number of cancelled cycles (Sagle *et al*., 1991; McClure *et al*., 1992; Dale *et al*., 1993, 1998; Balasch *et al*., 1996; White *et al*., 1996; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000).

Criteria for ovulation were based on the assessment of serum progesterone levels (Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993; White *et al*., 1996; Dale *et al*., 1998; Yarali *et al*., 1999), or ultrasound (Strowitzki *et al*., 1998) or both (Sagle *et al*., 1991; Fulghesu *et al*., 1997; Vicino *et al*., 2000). Four studies did not provide information concerning confirmation of ovulation (McClure *et al*., 1992, 1993; Farhi *et al*., 1993; Balasch *et al*., 1996). A total of 11 studies reported the number of ovulatory cycles (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992; Dale *et al*., 1993; Farhi *et al*., 1993; Balasch *et al*., 1996; White *et al*., 1996; Fulghesu *et al*., 1997; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000).

Explicit details of the definition of pregnancy were given by using serum hCG (Sagle *et al*., 1991; Strowitzki *et al*., 1998; Yarali *et al*., 1999), ultrasound (Balasch *et al*., 1996; Vicino *et al*., 2000), serum hCG and ultrasound (Hamilton-Fairley *et al*., 1992, 1993) or ultrasound and/or histological verification (Dale *et al*., 1993, 1998). Two studies specifically stated the presence of a clinical pregnancy (Sagle *et al*., 1991; Yarali *et al*., 1999). Finally, one study only provided data on the definition of a clinical pregnancy (i.e. intrauterine gestational sac and fetal heart beat) (Vicino *et al*., 2000). In four studies the definition of pregnancy was not stated (McClure *et al*., 1992; Farhi *et al*., 1993; White *et al*., 1996; Fulghesu *et al*., 1997). Pregnancy rate (per cycle and per patient) was provided for all studies except one (McClure *et al*., 1993).

The definition of miscarriage, spontaneous abortion or ongoing pregnancy rate was not clearly stated in seven studies (Farhi *et al*., 1993; Balasch *et al*., 1996; White *et al*., 1996; Fulghesu *et al*., 1997; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000). In two studies the definition of early pregnancy loss was stated (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992). In four studies the definition of miscarriage was based on the division in first and second trimester abortions (McClure *et al*., 1992, 1993; Dale *et al*., 1993, 1998). Data on miscarriage rates were stated in all studies except one (Vicino *et al*., 2000).

Description of screening characteristics related to treatment outcome

Except for one (Sagle *et al*., 1991), all studies stated data of age (means $\pm$ SD) for patients. In only four studies were exact data of cycle history (i.e. oligomenorrhoea or amenorrhoea) for all patients mentioned (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Farhi *et al*., 1993; Balasch *et al*., 1996).

Details of BMI levels for patients were given in nine studies (Dale *et al*., 1993, 1998; Farhi *et al*., 1993; McClure *et al*., 1993; Balasch *et al*., 1996; White *et al*., 1996; Fulghesu *et al*., 1997; Yarali *et al*., 1999; Vicino *et al*., 2000). Some studies divided patients into non-obese (lean) and obese [BMI >25 kg/m^2 (Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993, 1998; White *et al*., 1996; Fulghesu *et al*., 1997), BMI >27 (Vicino *et al*., 2000), or probably BMI >30 (Yarali *et al*., 1999)]. One study (Strowitzki *et al*., 1998) described patients as lean or obese without any further information. The fraction of obese (BMI >25) and non-obese patients was calculated where only continuous data of BMI were provided (McClure *et al*., 1992; Farhi *et al*., 1993; White *et al*., 1996), assuming a normal distribution.

In nine studies, CRA was defined as anovulation during $\geqslant$3 consecutive cycles with an increasing dose up to $\geqslant$150 mg/day for a period of 5 days (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993, 1998; Farhi *et al*., 1993; Balasch *et al*., 1996; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000). One study decreased the threshold for CRA to 100 mg/day (Fulghesu *et al*., 1997). In one study the dose for CRA was not clearly stated (McClure *et al*., 1992). CCF was defined as failure to conceive after $\geqslant$6 ovulatory clomiphene citrate cycles (McClure *et al*., 1992; Farhi *et al*., 1993; Fulghesu *et al*., 1997; Strowitzki *et al*., 1998; Yarali *et al*., 1999). One study decreased the number of cycles for CCF to 3 (Balasch *et al*., 1996). In two other studies the number of ovulatory cycles to fulfil the criteria for CCF were not stated (Dale *et al*., 1993, 1998). In two studies (McClure *et al*., 1993; Strowitzki *et al*., 1998), patients were said to be (un)responsive or resistant to clomiphene citrate, but the dose as well as the duration of

Table III. Possible clinical and endocrine features involved in the total amount of gonadotrophins administered (IU) during gonadotrophin induction of ovulation in normogonadotrophic anovulatory infertility (see also Figure 1)

Study	No. of (cycles)	Mean IU (SD)	Mean difference in IU (95% CI)			
			Obesity[a]	Testosterone	LH	Insulin resistance[b]
Balasch *et al.* (1996)	534	1185 (900)	–	–	–	–
Dale *et al.* (1993)	66	1702 (925)	759 (346–1172)	–	–	741 (290–1192)
Dale *et al.* (1998)	70	1611 (949)	449 (46–852)	–	–	–
Farhi *et al.* (1993)	195	1979 (1027)	–	–	–	–
Fulghesu *et al.* (1997)	52	1462 (638)	263 (-59–585)	–	–	113 (–241–466)
Hamilton-Fairley *et al.* (1992)	405	1360 (719)	1013 (848–1177)	–	–	–
McClure *et al.* (1992)[c,d]	181	1483 (640)	892 (706–1079)	–	–	–
McClure *et al.* (1993)	–	–	–	–	–	–
Sagle *et al.* (1991)	75	1269 (475)	–	–	–	–
Strowitzki *et al.* (1998)	116	1110 (567)	33 (–173–238)	–	–	–
Vicino *et al.* (2000)	107	1444 (578)	908 (801–1014)	–	–	–
White *et al.* (1996)	429	1140 (785)	–	–	–	–
Yarali *et al.* (1999)	96	1145 (762)	–	–	–	–
Pooled estimates	2326	1358	–	–	–	–
WMD (95% CI)			771 (700–842)	–	–	351 (73–630)
Random effects model			629 (317–931)	–	–	–
Test for heterogeneity			$P < 0.001$	–	–	–

[a]Obesity versus total amount of gonadotrophins administered expressed as: weighted mean difference (WMD) in IU: WMD based on obese versus non-obese patients (applied threshold varied from study to study: range 25–30 kg/m^2).
[b]Insulin resistance versus total amount of gonadotrophins administered expressed as: WMD in IU: WMD based on hyperinsulinaemic versus normoinsulinaemic patients (applied definition varied between studies).
[c]Total dose in IU deducted from figure: data not stated in results/table (McClure *et al*., 1992).
[d]Only ovulatory cycles included for the present analysis (i.e. total amount of gonadotrophins administered) (McClure *et al*., 1992).

clomiphene citrate treatment were not stated. In only six studies were the exact number of patients suffering from CRA and CCF mentioned (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992, 1993; Dale *et al*., 1993; Vicino *et al*., 2000).

The definition of polycystic ovaries was based on the Adams criteria (i.e. increased number of follicles and either an increased ovarian volume or increased stromal area or both) (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Farhi *et al*., 1993; White *et al*., 1996; Dale *et al*., 1998; Strowitzki *et al*., 1998; Vicino *et al*., 2000), or based on the presence of an increased number of follicles and/or ovarian stroma (McClure *et al*., 1992, 1993). Others did not report (clear) information on the definition of polycystic ovaries (Dale *et al*., 1993; Balasch *et al*., 1996; Fulghesu *et al*., 1997; Yarali *et al*., 1999). In seven studies the number of patients with polycystic ovaries was stated (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993, 1998; Farhi *et al*., 1993; White *et al*., 1996; Strowitzki *et al*., 1998).

Details of baseline testosterone levels were provided in nmol/l (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993, 1998; Fulghesu *et al*., 1997) or converted to SI units when expressed as ng/ml (Farhi *et al*., 1993; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000). Data regarding androstenedione levels were provided in nmol/l (Dale *et al*., 1993, 1998; Fulghesu *et al*., 1997; Vicino *et al*., 2000) or converted to SI units (Vicino *et al*., 2000).

Details concerning baseline LH levels for patients or subgroups of patients were provided in IU/l in eight studies (Sagle *et al*., 1991; Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993, 1998; Farhi *et al*., 1993; Fulghesu *et al*., 1997; Strowitzki *et al*., 1998; Vicino *et al*., 2000) or converted when expressed as mIU/ml (Vicino *et al*., 2000). Baseline LH/FSH ratios were provided by eight studies (Sagle *et al*., 1991; Farhi *et al*., 1993; Balasch *et al*., 1996; Fulghesu *et al*., 1997; Dale *et al*., 1998; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000).

Dale *et al*. (1998) assessed insulin resistance and glucose tolerance by means of a continuous infusion of glucose with CIGMA (continuous infusion of glucose with model assessment) model assessment test. Fulghesu *et al*. (1997) classified patients as hyperinsulinaemic or normoinsulinaemic based on the insulinaemic response to glucose load (OGTT). Both studies (Fulghesu *et al*., 1997; Dale *et al*., 1998) provided data of fasting glucose (nmol/l) and insulin levels (mIU/l). Conversion to IU units was performed where necessary.

Pooling of data

Data from studies reporting relationships between initial screening characteristics and outcome parameters of ovulation induction as measures of association (OR) were pooled if at least two studies reported an association of similar screening parameter and outcome characteristic. The measures of association were pooled using the inverse of the variance as weight. Heterogeneity was tested for using the Q statistic as defined by DerSimonean and Laird, which has a χ^2 distribution with df = (number of pooled studies – 1) (DerSimonian and Laird, 1986). Random effects estimates were calculated using the likelihood method described by Hardy and Thompson

Table IV. Possible clinical and endocrine features involved in the observed cancellation rate during gonadotrophin induction of ovulation in normogonadotrophic anovulatory infertility (see also Figure 2)

Study	No. of (cycles)	No. of cancelled (%)	Obesity[a] OR (95% CI)	Testosterone OR (95% CI)	LH OR (95%CI)	Insulin resistance[b] OR (95%CI)
Balasch *et al.* (1996)	534	93 (17)	–	–	–	–
Dale *et al.* (1993)	66	11 (17)	0.69 (0.18–2.61)	–	–	21.10 (2.51–176.62)
Dale *et al.* (1998)	70	11 (16)	0.82 (0.23–2.89)	–	–	–
Farhi *et al.* (1993)	195	–	–	–	–	–
Fulghesu *et al.* (1997)	52	–	–	–	–	–
Hamilton-Fairley *et al.* (1992)	405	–	–	–	–	–
McClure *et al.* (1992)	224	14 (6)	–	–	–	–
McClure *et al.* (1993)	–	–	–	–	–	–
Sagle *et al.* (1991)	75	3 (4)	–	–	–	–
Strowitzki *et al.* (1998)	116	30 (26)	1.89 (0.81–4.41)	–	–	–
Vicino *et al.* (2000)	107	39 (36)	3.84 (1.68–8.80)	–	–	–
White *et al.* (1996)	429	76 (18)	–	–	–	–
Yarali *et al.* (1999)	96	11 (16)	–	–	–	–
Pooled estimates	2369	288 (17)	–	–	–	–
Fixed effects OR (95% CI)			1.86 (1.13–3.06)	–	–	–
Test for heterogeneity			$P = 0.2$	–	–	–

[a]Odds ratio (OR) and 95% confidence interval (CI) based on obese versus non-obese patients (applied threshold varied from study to study: range 25–30 kg/m^2).
[b]OR based on hyperinsulinaemic versus normoinsulinaemic patients (applied definition varied between studies).

Table V. Possible clinical and endocrine features involved in the observed ovulation rate during gonadotrophin induction of ovulation in normogonadotrophic anovulatory infertility (see also Figure 3)

Study	No. of cycles	No. of ovulatory cycles (%)	Obesity[a] OR (95% CI)	Testosterone OR (95% CI)	LH OR (95% CI)	Insulin resistance[b] OR (95% CI)
Balasch *et al.* (1996)	534	419 (79)	–	–	–	–
Dale *et al.* (1993)	66	49 (74)	–	–	–	–
Dale *et al.* (1998)	70	–	–	–	–	–
Farhi *et al.* (1993)	195	146 (75)	–	–	–	–
Fulghesu *et al.* (1997)	52	44 (85)	–	–	–	0.87 (0.18–4.09)
Hamilton–Fairley *et al.* (1992)	405	292 (72)	0.39 (0.24–0.63)	–	–	–
McClure *et al.* (1992)	224	181 (81)	–	–	–	–
McClure *et al.* (1993)	–	–	–	–	–	–
Sagle *et al.* (1991)	75	61 (81)	–	–	1.12 (1.02–1.24)[c]	–
Strowitzki *et al.* (1998)	116	86 (74)	0.53 (0.23–1.23)	–	–	–
Vicino *et al.* (2000)	107	68 (64)	0.26 (0.11–0.60)	–	–	–
White *et al.* (1996)	429	305 (71.1)	–	0.68 (0.44 –1.05)[d]	1.02 (0.65–1.59)[d]	–
Yarali *et al.* (1999)	51	39 (76.5)	0.78 (0.36–1.71)[e]	–	–	–
Pooled estimates	2324	1690 (75)	–	–	–	–
Fixed effects OR (95% CI)			0.44 (0.31– 0.61)	–	[f]	–
Test for heterogeneity			$P = 0.4$	–	–	–

[a]Odds ratio (OR) and 95% confidence interval (CI) based on obese versus non-obese patients (applied threshold varied from study to study: range 25–30 kg/m^2).
[b]OR based on hyperinsulinaemic versus normoinsulinaemic patients (applied definition varied between studies).
[c]Indirect calculation of OR: based on continuous data (deducted from figure) (Sagle *et al.*, 1991).
[d]OR calculated based on subdivision of testosterone and LH serum levels (respectively testosterone >2.6 nmol/l or <2.7 nmol/l and LH >11.0 IU/l or <11.1 IU/l) (White *et al.*, 1996).
[e]Only first cycle data included in the present analysis (Yarali *et al.*, 1999).
[f]Pooled OR not calculated because continuous (Sagle *et al.*, 1991) and categorical (White *et al.*, 1996) data were provided by either studies.

(1998), when at least three studies were available. Association measures were extracted from studies for the following outcome parameters: total amount of FSH administered (Table III), cancellation rate (Table IV), ovulation rate (Table V), pregnancy rate (Table VI and Table VII) and miscarriage rate (Table VIII).

Results of pooling

A total number of seven studies reported an association (all positive) between obesity and total amount of gonadotrophins administered (IU) (Figure 1) (Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992; Dale *et al*., 1993, 1998; Fulghesu *et al*.,

Table VI. Possible clinical and endocrine features involved in the observed pregnancy rate per cycle during gonadotrophin induction of ovulation in normogonadotrophic anovulatory infertility

Study	No. of cycles	No. of pregnancies (%)	Obesity[a] OR (95% CI)	Testosterone OR (95% CI)	LH OR (95% CI)	Insulin resistance[b] OR (95% CI)
Balasch *et al.* (1996)	534	93 (17)	–	–	–	–
Dale *et al.* (1993)	66	12 (18)	1.35 (0.38–4.72)	–	–	0.14 (0.03–0.69)
Dale *et al.* (1998)	70	16 (23)	–	–	–	–
Farhi *et al.* (1993)	195	35 (18)	–	–	–	–
Fulghesu *et al.* (1997)	52	11 (21)	–	–	–	0.48 (0.13–1.85)
Hamilton-Fairley *et al.* (1992)	405	45 (11)	1.7 (0.87–3.30)	–	–	–
McClure *et al.* (1992)	224	45 (20)	–	–	–	–
McClure *et al.* (1993)	–	–	–	–	–	–
Sagle *et al.* (1991)	75	10 (13)	–	–	–	–
Strowitzki *et al.* (1998)	116	21 (18)	0.60 (0.23–1.59)	–	–	–
Vicino *et al.* (2000)	107	8 (8)	0.45 (0.09–2.35)[c]	–	–	–
White *et al.* (1996)	429	49 (11)	–	0.93 (0.51–1.69)[d]	1.61 (0.88–2.94)[d]	–
Yarali *et al.* (1999)	96	21 (22)	–	–	–	–
Pooled estimates	2369	366 (15)	–	–	–	–
Fixed effects OR (95% CI)			1.13 (0.70–1.84)	–	–	0.29 (0.10–0.80)
Test for heterogeneity			$P = 0.4$	–	–	–

[a]Odds ratio (OR) and 95% confidence interval (CI) based on obese versus non-obese patients (applied threshold varied from study to study: range 25–30 kg/m^2).
[b]OR based on hyperinsulinaemic versus normoinsulinaemic patients (applied definition varied between studies).
[c]Vicino *et al.* (2000) provides continuous data of BMI for pregnant versus non-pregnant women: assume BMI is normally distributed among pregnant versus non-pregnant women: calculate the fraction obese versus non-obese (2×2 table constructed): indirect calculation of OR (based on number of cycles): 0.45.
[d]OR calculated based on subdivision of testosterone and LH serum levels (respectively testosterone >2.6 nmol/l or <2.7 nmol/l and LH >11.0 IU/l or <11.1 IU/l) (White *et al.*, 1996).

Table VII. Possible clinical and endocrine features involved in the observed pregnancy rate per patient during gonadotrophin induction of ovulation in resistant normogonadotrophic anovulatory infertility (see also Figure 4)

Study	No. of patients	Mean no. of cycles per patient	No. of pregnancies (%)	Obesity[a] OR (95% CI)	Testosterone OR (95% CI)	LH OR (95% CI)	Insulin resistance[b] OR (95% CI)
Balasch *et al.* (1996)	234	2.3	93 (40)	–	–	1.07 (1.06–1.16)	–
Dale *et al.* (1993)	50	1.3	12 (24)	–	–	–	0.10 (0.02–0.56)
Dale *et al.* (1998)	42	1.7	16 (38)	–	–	–	–
Farhi *et al.* (1993)	89	2.2	35 (39)	2.95 (1.09–7.96)[c]	0.90 (0.73–1.12)	1.00 (0.96–1.04)	–
Fulghesu *et al.* (1997)	34	1.5	11 (32)	–	–	–	0.44 (0.10–1.92)
Hamilton-Fairley *et al.* (1992)	100	4.1	45 (45)	2.25 (0.89–5.67)	–	–	–
McClure *et al.* (1992)	71	3.2	45 (63)	–	–	–	–
McClure *et al.* (1993)	–	–	–	–	–	–	–
Sagle *et al.* (1991)	30	2.5	10 (33)	–	–	–	–
Strowitzki *et al.* (1998)	68	1.7	21 (31)	0.59 (0.21–1.69)	–	–	–
Vicino *et al.* (2000)	21	5.1	8 (38)	0.39 (0.06–2.70)	0.95 (0.70–1.29)	0.73 (0.35–1.53)	–
White *et al.* (1996)	91	4.7	49 (54)	0.79 (0.35–1.80)[c]	1.0 (0.73–1.37)	1.01 (0.96–1.08)	–
Yarali *et al.* (1999)	51	1.9	21 (41)	–	–	–	–
Pooled estimates	881	2.7	366	–	–	–	–
Fixed effects OR (95% CI)				1.22 (0.77–1.93)[d]	0.94 (0.80 –1.09)[e]	1.04 (1.01 –1.07)[f]	0.24 (0.08–0.71)
Test for heterogeneity				$P = 0.16$	–	–	–

[a]Odds ratio (OR) and 95% confidence interval (CI) based on obese versus non-obese patients (applied threshold varied from study to study: range 25–30 kg/m^2).
[b]OR based on hyperinsulinaemic versus normoinsulinaemic patients (applied definition varied between studies).
[c]Farhi *et al.* (1993) and White *et al.* (1996) both provide continuous data of BMI for pregnant versus non-pregnant women: assume BMI is normally distributed among pregnant versus non-pregnant patients: calculate the fraction obese and non-obese patients (2×2 table constructed): indirect calculation of OR (based on number of patients): 2.95 and 0.79 respectively.
[d]Second best analysis performed (per patient), because not all studies provided data per cycle: analysis based on obese versus non-obese patients (applied threshold varied from study to study: range 25–30 kg/m^2): obesity versus pregnancy rate expressed as: OR.
[e]For testosterone levels expressed as SI units (nmol/l) pooled analysis was performed (Farhi *et al.*, 1993; White *et al.*, 1996; Vicino *et al.*, 2000).
[f]For LH levels expressed as SI units (IU/l) pooled analysis was performed (Farhi *et al.*, 1993; Balasch *et al.*, 1996; White *et al.*, 1996; Vicino *et al.*, 2000).

Table VIII. Possible clinical and endocrine features involved in the observed miscarriage rate during gonadotrophin induction of ovulation in normogonadotrophic anovulatory infertility (see also Figure 5)

Study	No. of pregnancies	Mean no. of miscarriages (%)	Obesity[a] OR (95% CI)	Testosterone OR (95% CI)	LH OR (95% CI)	Insulin resistance[b] OR (95% CI)
Balasch *et al.* (1996)	93	10 (11)	–	–	–	–
Dale *et al.* (1993)	12	4 (33)	–	–	–	∞
Dale *et al.* (1998)	16	7 (44)	–	–	–	–
Farhi *et al.* (1993)	35	13 (37)	–	–	–	–
Fulghesu *et al.* (1997)	11	2 (18)	–	–	–	1.25 (0.06–26.9)
Hamilton–Fairley *et al.* (1992)	45	17 (38)	4.13 (1.11–15.32)	–	–	–
McClure *et al.* (1992)	45	12 (27)	–	–	–	–
McClure *et al.* (1993)	50	14 (28)	1.44 (0.35–5.84)[c]	–	1.004 (0.93–1.09)	–
Sagle *et al.* (1991)	10	4 (40)	–	–	–	–
Strowitzki *et al.* (1998)	21	3 (14)	4.0 (0.30–53.47)	–	–	–
Vicino *et al.* (2000)	–	–	–	–	–	–
White *et al.* (1996)	49	13 (27)[d]	4.12 (1.08–15.71)[c]	0.86 (0.54–1.37)	1.03 (0.93–1.14)	–
Yarali *et al.* (1999)	21	4 (19)	–	–	–	–
Pooled estimates	408	288 (17)	–	–	–	–
Fixed effects OR (95% CI)			3.05 (1.45–6.44)	–	1.013 (0.95–1.08)[e]	1.8 (0.3–10.3)
Test for heterogeneity			$P = 0.17$	–	–	–

[a]Odds ratio (OR) and 95% confidence interval (CI) based on obese versus non-obese patients (applied threshold varied from study to study: range 25–30 kg/m^2).
[b]OR based on hyperinsulinaemic versus normoinsulinaemic patients (applied definition varied between studies).
[c]McClure *et al.* (1993) and White *et al.* (1996) both provide continuous data of BMI for pregnant versus non-pregnant women: assume BMI is normally distributed among pregnant versus non-pregnant patients: calculate the fraction obese and non-obese patients (2×2 table constructed): indirect calculation of OR (based on number of patients): 1.44 and 4.12 respectively.
[d]Miscarriage: ectopic pregnancy included (White *et al.*, 1996).
[e]For LH levels expressed as SI units (IU/l) pooled analysis was performed (McClure *et al.*, 1993; White *et al.*, 1996).

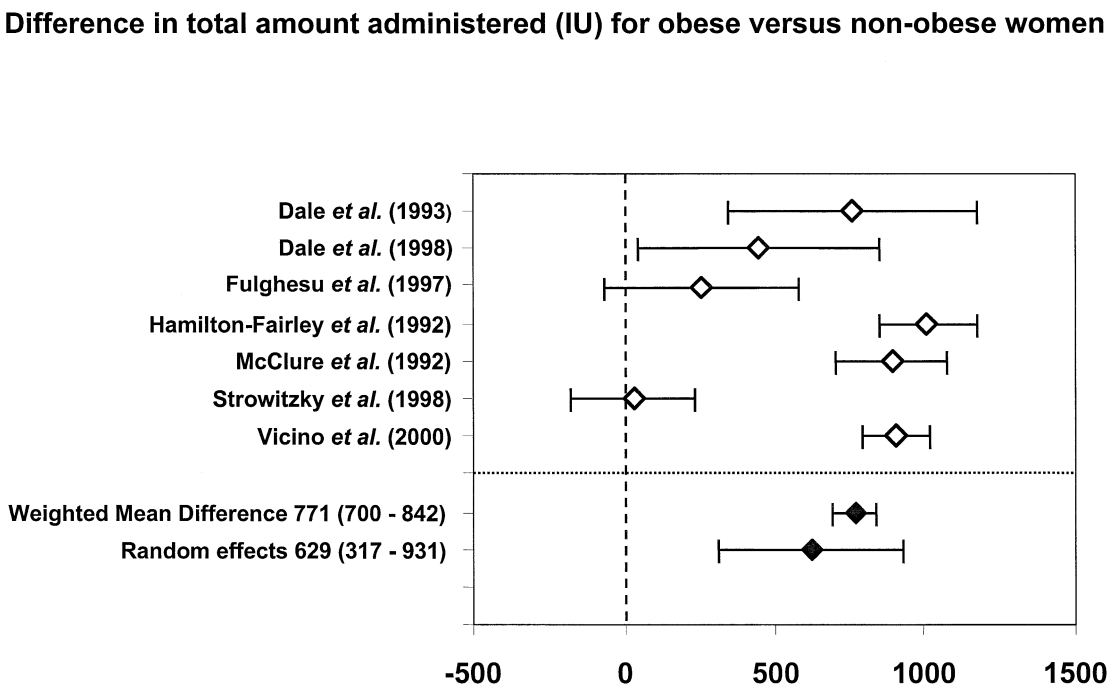

Figure 1. Association measures between obesity and total amount of gonadotrophins administered (IU) for ovulation induction in normogonadotrophic anovulatory infertility (median and 95% confidence interval). The weighted mean difference (WMD) was generated using inverse variance weighting. Heterogeneity was tested for and random effects estimates were calculated using the likelihood method as described by Hardy and Thompson (1998).

1997; Strowitzki *et al.*, 1998; Vicino *et al.*, 2000). The weighted mean difference (WMD) (obese versus non-obese) for total dose used was 771 (95% CI: 700–842) IU. Significant heterogeneity was detected between studies ($P < 0.001$). The random effects estimate of the difference between obese and non-obese patients was 629 (95% CI: 317–931) IU. Two studies reporting on insulin resistance versus total amount of FSH administered (Fulghesu *et al.*, 1997; Dale *et al.*, 1998)

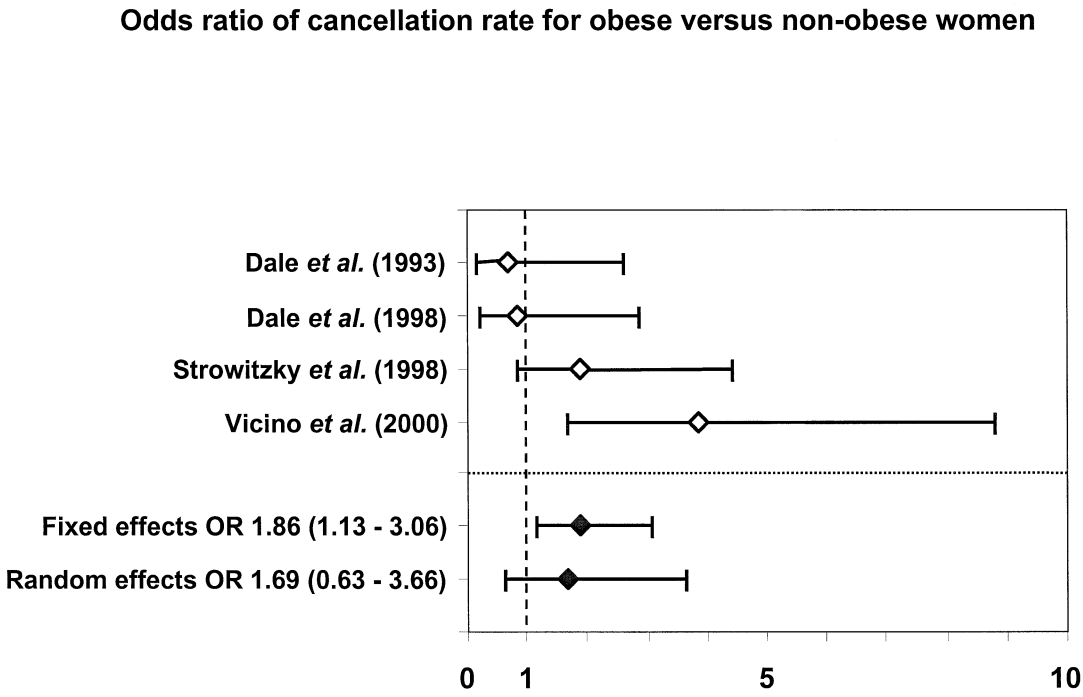

Figure 2. Four studies reported an association between obesity and cancellation rate. The pooled odds ratio and 95% confidence interval (obese versus non-obese) was calculated by inverse variance weighting.

produced a WMD (hyperinsulinaemic versus normoinsulinaemic) of 351 (95% CI: 73–630) IU.

Four studies reported an association between obesity and cancellation rate (Dale *et al*., 1993, 1998; Strowitzki *et al*., 1998; Vicino *et al*., 2000) (Figure 2). The pooled OR (obese versus non-obese) was 1.86 (95% CI: 1.13–3.06). Despite conflicting directions of association, the test for heterogeneity was not significant ($P = 0.2$).

Four studies (Hamilton-Fairley *et al*., 1992; Strowitzki *et al*., 1998; Yarali *et al*., 1999; Vicino *et al*., 2000) reported an association between obesity and ovulation rate, with a pooled OR (obese versus non-obese) of 0.44 (95% CI: 0.31–0.61) (Figure 3). The test for heterogeneity was not significant ($P = 0.4$). Two studies (Sagle *et al*., 1991; White *et al*., 1996) reported an association between LH and ovulation rate. Pooling of the results was not possible because one study reported LH as a continuous variable (Sagle *et al*., 1991) and the other provided data of LH in two categories (White *et al*., 1996). Association measures for respectively testosterone (White *et al*., 1996) and insulin resistance (Fulghesu *et al*., 1997) with ovulation were calculated from the data provided.

Pregnancy was analysed per cycle and per patient. Four studies reported an association (three positive and one negative) between obesity and pregnancy rate per cycle, pooled OR (obese versus non-obese) 1.13 (95% CI: 0.70–1.84) (Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993; Strowitzki *et al*., 1998; Vicino *et al*., 2000). The test for heterogeneity was not significant ($P = 0.4$). Five studies reported an association (two positive and three negative) between obesity and pregnancy rate per patient (Hamilton-Fairley *et al*., 1992; Farhi *et al*., 1993; White *et al*., 1996; Strowitzki *et al*., 1998; Vicino *et al*., 2000). The pooled OR (obese versus non-obese) was 1.22 (95% CI: 0.77–1.93). The test for heterogeneity was not significant ($P = 0.16$). Three studies (Farhi *et al*., 1993; White *et al*., 1996; Vicino *et al*., 2000) reported an association between testosterone and pregnancy rate per patient. The pooled OR (per nmol/l) was 0.94 (95% CI: 0.80–1.09). Four studies (Farhi *et al*., 1993; Balasch *et al*., 1996; White *et al*., 1996; Vicino *et al*., 2000) reported an association between LH and pregnancy rate per patient (Figure 4). The pooled OR (per IU/l) was 1.04 (95% CI: 1.01–1.07). The test for heterogeneity was not possible in the latter two cases. Association measures between insulin resistance and pregnancy rate per cycle as well as per patient (Fulghesu *et al*., 1997; Dale *et al*., 1998) were calculated. Both studies (Fulghesu *et al*., 1997; Dale *et al*., 1998) reported a negative association between insulin resistance and pregnancy rate, with pooled OR (hyperinsulinaemic versus normoinsulinaemic) of 0.29 (95% CI: 0.10–0.80) and 0.24 (95% CI: 0.08–0.74).

Four studies reported an association between obesity and miscarriage rate (Figure 5) (Hamilton-Fairley *et al*., 1992; McClure *et al*., 1993; White *et al*., 1996; Strowitzki *et al*., 1998). The pooled OR (obese versus non-obese) was 3.05 (95% CI: 1.45–6.44). The test for heterogeneity was not significant (P = 0.17). Two studies (McClure *et al*., 1993; White *et al*., 1996) reported an association between LH and miscarriage rate. The pooled OR (per IUl/l) was 1.013 (95% CI: 0.95–1.08). Two studies (Fulghesu *et al*., 1997; Dale *et al*., 1998) reported an

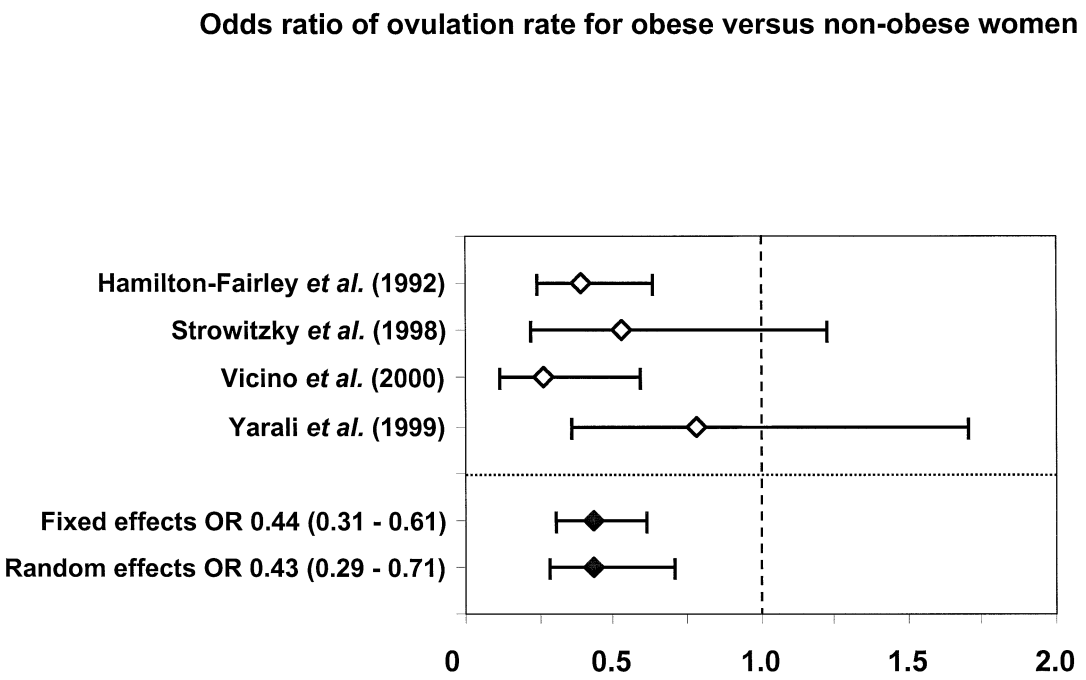

Figure 3. Four studies reported an association between obesity and ovulation rate, with a pooled odds ratio and 95% confidence interval (obese versus non-obese) generated calculated by inverse variance weighting. Note: the range of the *x*-axis is different from Figure 2.

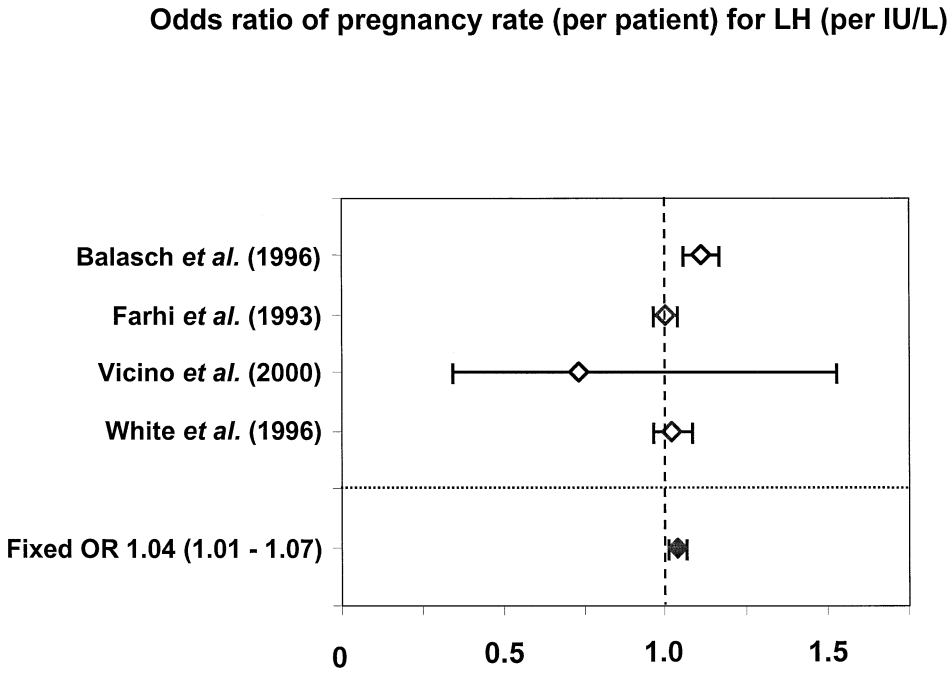

Figure 4. Association measures between LH (per IU/l) and pregnancy rate per patient was provided by a total number of four studies. The pooled odds ratio and 95% CI (obese versus non-obese) was calculated by inverse variance weighting.

association between insulin resistance and miscarriage rate. The pooled OR (hyperinsulinaemic versus normoinsulinaemic) was 1.75 (95% CI: 0.30–10.3). An association of age (McClure *et al*., 1993) versus testosterone (White *et al*., 1996) and miscarriage rate was calculated from the data provided.

None of the studies provided a measure of association between CRA/CCF or the presence of polycystic ovaries and treatment outcome.

In summary, significant associations were found for the total amount of FSH administered, cancellation rate, ovulation rate

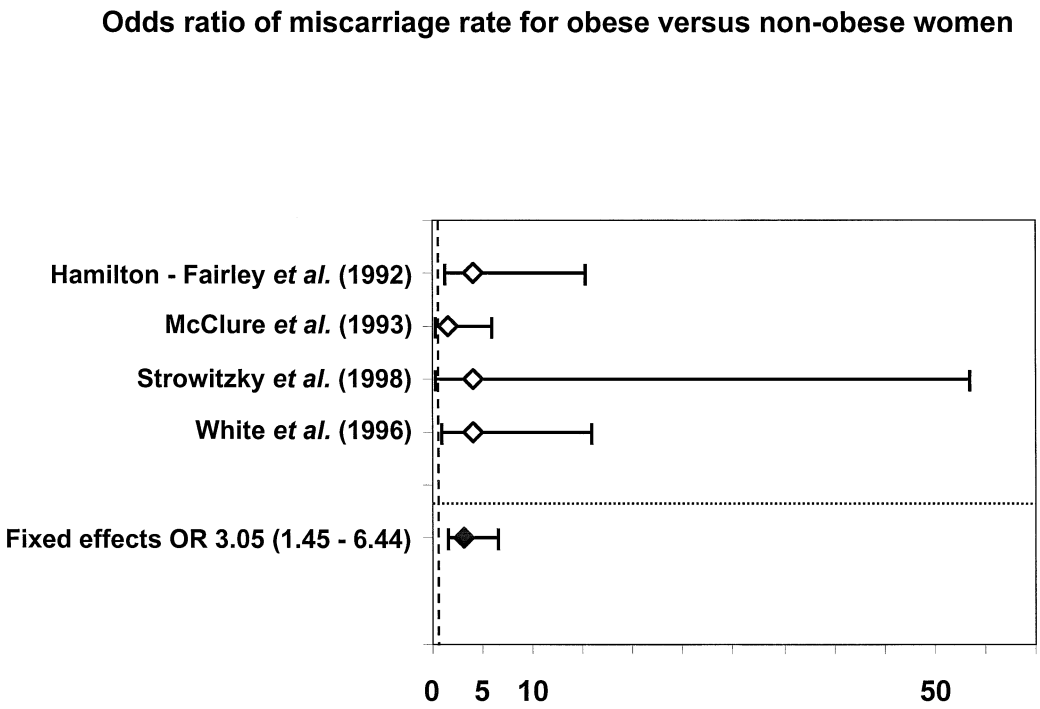

Figure 5. Four studies reported an association between obesity and miscarriage rate. The pooled odds ratio and 95% CI (obese versus non-obese) was calculated by inverse variance weighting. Note: the range of the *x*-axis is different from Figure 2.

and miscarriage rates with BMI. Furthermore, significant associations were found for the total amount of FSH and pregnancy rate with insulin resistance.

Discussion

This systematic review and meta-analysis demonstrates how few studies have provided measures of association between screening characteristics in women with normogonadotrophic anovulatory infertility and gonadotrophin ovulation induction treatment outcome. The studies included used various criteria for patient inclusion and intervention and are prone to bias. The best available evidence suggests that obesity and insulin resistance are both associated with adverse treatment outcomes, including increased FSH requirements, increased cancellation and miscarriage rates and most importantly decreased ovulation and pregnancy rates.

Obesity frequently coincides with normogonadotrophic anovulation and represents an important clinical feature associated with PCOS (Laven *et al*., 2002). Differences in pharmacokinetic characteristics of gonadotrophin preparations (Mannaerts *et al*., 1993) as well as the amount of exogenous gonadotrophins required to achieve follicular maturation (Hamilton-Fairley *et al*., 1992; McClure *et al*., 1992; Dale *et al*., 1993; Vicino *et al*., 2000; Imani *et al*., 2002b) related to body weight, have been reported. Obesity is associated with reduced circulating levels of sex hormone-binding globulin (SHBG), mildly elevated androgen levels (Poretsky *et al*., 1999) and hyperinsuliaemia (Norman *et al*., 2002). Insulin resistance [associated with PCOS as well (Dunaif, 1999)] is also related to the total amount of gonadotrophins administered, as previously reported (Homburg *et al*., 1996).

So far, the impact of obesity on the cycle cancellation rates in women with anovulatory infertility has not been convincingly established. However, the impact of obesity on ovulation rates was previously mentioned by several authors (Hamilton-Fairley *et al*., 1992; Yarali *et al*., 1999; Vicino *et al*., 2000). The present meta-analysis explicitly shows that obese women are less likely to ovulate following gonadotrophin ovulation induction and therefore suggests that ovarian dysfunction in these women is more severe. However, differences in absorption and distribution of exogenous FSH may also be involved (Mannaerts *et al*., 1993). Weight reduction may normalize insulin resistance and androgen metabolism (Kiddy *et al*., 1992; Holte *et al*., 1995) and may significantly improve menstrual abnormalities, ovulation, and fertility rates (Norman *et al*., 2002).

Obesity does not seem to be associated with decreased pregnancy rates, as previously reported (Hamilton-Fairley *et al*., 1992; Dale *et al*., 1993; White *et al*., 1996; Strowitzki *et al*., 1998; Vicino *et al*., 2000). It should be noted that some of these conclusions were drawn based on studies of a selected group of non-obese women (i.e. BMI <27 kg/m^2). The current analysis, however, shows an increased incidence of spontaneous miscarriage with increasing BMI in women with PCOS. This finding has been reported before (Hamilton-Fairley *et al*., 1992). The present analysis, though, shows that all other studies are in line with this observation. This result again stresses the importance of weight reduction. Likewise, it has been described that the incidence of spontaneous miscarriage increases with decreasing insulin sensitivity (Dale *et al*., 1998). However, the small number of miscarriages precludes definitive conclusions in this regard. Along these lines, it has been suggested that insulin-sensitizing agents also reduce miscarriage rates (Glueck *et al*., 2001).

Hyperandrogenism is considered to be a key feature in PCOS and constitutes a hallmark for the diagnosis (Dunaif *et al*., 1992). Intraovarian inhibitors of FSH action (such as the IGF system) (Schipper *et al*., 1997; van Dessel *et al*., 1999) might possibly promote follicle maturation arrest and concomitantly ovarian hyperandrogenism (Giudice, 1999). Hyperandrogenism has proven to be a powerful predictor for the response to ovulation induction, emphasizing its significance for ovarian dysfunction in these women (Imani *et al.*, 1998, 1999, 2000, 2002a,b; Mulders *et al*., 2003). The impact of these biologically plausible factors involved in ovarian dysfunction in normogonadotrophic anovulation, such as serum androgens and free IGF-I, unfortunately could not be scrutinized in the current analysis, because of lack of data.

Elevated LH levels are frequently encountered in PCOS, but this is not a mandatory diagnostic of PCOS (Laven *et al*., 2002). Although it was previously reported that elevated serum LH concentrations were associated with increased miscarriage rates on the basis of retrospective studies (Howles *et al*., 1986; Balen *et al*., 1993; Watson *et al*., 1993), prospective data do not support the concept that elevated LH is implicated in ovarian dysfunction and ovulation induction outcome (Imani *et al*., 2002a). The present analysis, however, shows a small but significant association of elevated serum LH with increased pregnancy rates.

Upon pelvic ultrasound, ovaries of women with normogonadotrophic anovulation might be enlarged (Puzigaca *et al*., 1991; Pache *et al*., 1992), contain an increased number of follicles (Obhrai *et al*., 1990; Jonard *et al*., 2003), and exhibit an increased density of ovarian stroma (Dewailly, 1997). It has been shown that the value of these sonographic parameters as a screening test to predict endocrine abnormalities characteristic of PCOS is limited (van Santbrink *et al*., 1997). In addition, sonographic parameters are predictive of patients remaining anovulatory following clomiphene citrate (Imani *et al*., 1998). Others recently described a correlation between initial ovarian volume or mean follicle number and subsequent response applying gonadotrophin induction of ovulation (van der Meer *et al*., 1998; Lass *et al*., 2002; Mulders *et al*., 2003). These findings could not be reconfirmed in the current analysis since none of the included studies reported sufficient data to perform the analysis.

The association of advanced age with poorer treatment outcome following clomiphene citrate- or FSH-induced cycles, as previously reported (McClure *et al*., 1993; Imani *et al*., 2002a; Mulders *et al*., 2003), could not be confirmed by the present meta-analysis because of lack of data.

In summary, the current results are perhaps somewhat disappointing. However, this should not be too surprising as most studies did not intend to predict treatment outcome by patient characteristics. The possibility that some conclusions from this analysis may be affected by the repetitive inclusion of data cannot be completely discarded. However, we believe that such effects, if they exist, are minor. In addition, pooling of the original data files rather than the published data might also have resulted in slightly different outcomes. Principally, the association between initial clinical screening parameters (reflecting the extent of ovarian dysfunction in normogonadotrophic anovulatory infertility) and treatment outcome deserves further attention. In addition, more individualized ovulation induction treatment algorithms may subsequently be developed. For the future, there is a need to standardize the definitions of ovulation induction treatment outcome in women with normogonadotrophic anovulatory infertility (including PCOS). Live-birth from a singleton pregnancy following gonadotrophin induction of ovulation could then be more effectively achieved by treatment strategies individually tailored on the basis of initial screening characteristics.

Acknowledgements

This study was supported by CVZ/NWO 'Doelmatigheidsonderzoek' project 99201 and by the 'Stichting Voortplantingsgeneeskunde Rotterdam'.

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