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Effect of overweight and obesity on assisted reproductive technology—a systematic review

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Obesity is known to be associated with sub-optimal reproductive performance but its direct effect on the outcome of assisted reproduction techniques (ART) is less clear. This present study aimed to perform a systematic review of the available evidence to assess the effects of obesity on the outcome of ART. A number of observational studies were identified. Interpretation of the results was compromised by variations in the methods used to define overweight and obese populations and inconsistencies in the choice and definition of outcome measures. Compared with women with a BMI of 25 kg/m^2 or less, women with a BMI ≥25 kg/m^2 have a lower chance of pregnancy following IVF [odds ratio (OR) 0.71, 95% CI: 0.62, 0.81], require higher dose of gonadotrophins (weighed mean differences 210.08, 95% CI: 149.12, 271.05) and have an increased miscarriage rate (OR 1.33, 95% CI: 1.06, 1.68). There is insufficient evidence on the effect of BMI on live birth, cycle cancellation, oocyte recovery and ovarian hyperstimulation syndrome. Further studies with clear entry criteria and uniform reporting of outcomes are needed to investigate the true impact of weight on the outcome of ART.

Keywords: obesity; overweight; ART; systematic review; observational studies

Introduction

The proportion of obese women (BMI ≥30) in the UK has increased from 16.4% in 1993 to 23.8% in 2004 (http://www.ic.nhs.uk/pubs/hlthsvyeng2004upd). In the 25–44 years age group, ~30% women are overweight (BMI 25–30) and 20% are obese. Along with the other conditions like diabetes, hypertension, cardiovascular diseases, pancreatitis and musculoskeletal diseases, obese women are more likely to experience reproductive problems (Clark *et al*., 1998). Overweight women are known to be at a higher risk of menstrual dysfunction and anovulation, possibly due to altered secretion of pulsatile GnRH, resulting in altered sex hormone binding globulin (SHBG), ovarian and adrenal androgens and Luteinizing hormone (LH). Weight loss in these women is associated with the return of spontaneous ovulation and a reduced likelihood of requiring induction of ovulation (Clark *et al*., 1995).

In women undergoing assisted reproduction techniques (ART), obesity has been associated with the need for higher doses of gonadotrophins, increased cycle cancellation rates and fewer oocytes retrieved (Fedorcsak *et al*., 2004). Lower rates of embryo transfer, pregnancy and live birth have also been reported, as have higher miscarriage rates (Wang *et al*., 2000; Fedorcsak *et al*., 2004). However, other studies have been unable to find any negative impact of obesity on ART outcome (Lashen *et al*., 1999; Dechaud *et al*., 2006).

A recent survey of assisted reproduction clinics in UK demonstrates a wide variation in their approach towards obese infertile women (Zachariah *et al*., 2006). This is especially relevant at the present time when criteria for access to IVF in some health care settings include strict upper limits for BMI. Existing studies on the affect of obesity on ART population show variable results. The aim of this study is to perform a systematic review of the literature in order to determine whether increased BMI has an adverse effect on the outcome of ART, and if so, to assess the size of this effect.

Materials and Methods

Search strategy

Medline (1966–2006), Embase (1966–2006) and the Cochrane Database of Systematic Reviews were searched using the key words 'overweight', or 'obesity' or 'body mass index', 'BMI' and 'follicle stimulating hormone' or 'gonadotrophin'. 'mp', 'oocytes' or 'oocyte quality', 'embryo transfer' or 'fertilization *in vitro*' or 'oocytes' or 'embryo' or 'embryo quality' or 'pregnancy rate' 'pregnancy' or 'sperm injections', 'intracytoplasmic' 'embryo.mp', 'fertilization

in vitro' or 'mp IVF', ', abortion', 'spontaneous', 'early pregnancy loss', 'mp live birth', 'pregnancy', 'infertility' and 'waist hip ratio'. Relevant journals in the specialty (Human Reproduction and Fertility and Sterility) were searched electronically and all cross references were hand searched. Contact with authors was attempted wherever appropriate. Guidelines for meta-analysis and systematic reviews of observational studies (MOOSE guidelines) were followed (Stroup *et al*., 2000).

Inclusion criterion

Only published studies were included. Due to the nature of the question, randomized controlled trials were not anticipated. All observational studies on the effect of obesity/overweight on IVF and ICSI were included.

Exclusion criterion

Studies were excluded if they investigated the effect of obesity/overweight in natural cycle conceptions/intrauterine insemination/ovulation induction. Where studies reported a combination of effects (i.e. smoking, advanced reproductive age, and raised FSH), only those which reported on the independent effect of BMI were included (as BMI is the most commonly used measure of obesity). Studies which exclusively investigated selected populations[e.g. only women with polycystic ovary syndrome (PCOS) or oocyte recipients] were excluded, as were studies which reported alternative parameters (i.e. waist hip ratio, WHR or body weight) for obesity, without providing any data on BMI.

Independent searches were conducted by two researchers (A.M. and L.S.) and all identified studies were reviewed separately by them. Any disagreement was resolved after discussion with S.B. Data were extracted according to a pre-designed proforma.

Outcome measures

The primary outcome measure was live birth rate per woman. Secondary outcome measures included total dose of gonadotrophins, cancellation rates, number of oocytes retrieved, number of embryos obtained, pregnancy rate, miscarriage rate and ovarian hyperstimulation syndrome (OHSS) rate.

Results

Identification

A total of 1843 studies were identified. Of them only 37 studied the effect of obesity on an ART population. All were in English except for two papers, one of which was in German (Munz *et al*., 2005) and the other in Czech (Krizanovska *et al*., 2002). These were translated in full by the University of Aberdeen translation service. Of these studies, only 21 fulfilled the inclusion criterion (Supplementary Fig.1). Details of included studies are provided in Table 1 and excluded studies are shown in Supplementary Table 1.

Analysis and pooling of data

Of 21 studies fulfilling the inclusion criteria only 11 studies had cut-off values for BMI, to define overweight and obese groups, according to the WHO criteria (Table 2). Cut-off values for BMI, varied in nine studies (Lewis *et al*., 1990; Crosignani *et al*., 1994; Lashen *et al*., 1999; Loveland *et al*., 2001; Unkila-Kallio *et al*., 2001; Urbancsek *et al*., 2002; Nichols *et al*., 2003; Spandorfer et. al, 2004; Ku *et al*., 2006). As a consequence of this, results from these individual studies could not be compared and their data could not be aggregated. We tried to contact the authors of these studies via email and letters. Only one author (Nichols *et al*., 2003) re-analysed their data according to the BMI cut-offs specified in our review and their data were included in the final meta-analysis. Two authors indicated (Lashen *et al*., 1999; Urbancsek *et al*., 2002) that they cannot re-analyse the data. Two emails bounced back (Loveland *et al*., 2001; Ku *et al*., 2006) and we did not receive any reply from the authors of other studies (Lewis *et al*., 1990; Crosignani *et al*., 1994; Unkila-Kallio *et al*., 2001; Spandorfer et. al, 2004; Fig. 1). Frattarelli and Kodama (2004) have not reported the number of women/cycles in any BMI category. We tried to contact the corresponding authors but email bounced back and we did not receive any reply to the written letter.

All the included studies were cohort studies except for two case control studies (Lashen *et al*., 1999; Urbancsek *et al*., 2002). Data from the latter could not be aggregated due to the use of different ranges of BMI to define cases and controls (Table 1). Of the 12 studies included in the final meta-analysis, three (Fedrorcsak et al., 2000; Wang *et al*., 2002; Winter *et al*., 2002) only reported on the miscarriage rates in pregnancies conceived following ART.

For each outcome, data were only pooled if there were at least two studies with similar range of BMI for the comparison groups. A random effect model was used (because of statistical heterogeneity in the outcome data) to calculate combined odds ratios (OR) (95% CI) with the help of Revman 4.2 software. Weighed mean differences (WMD) were calculated for continuous variables. Tests of heterogeneity were performed prior to pooling of data.

Methodological quality of included studies

The recommended classification of overweight and obesity as suggested by National Institute of Health is shown in Table 2. In accordance with the suggested categories, outcomes were compared in the following groups, i.e. BMI $<$ and $\geq$25, and BMI $<$ and $\geq$30. Data on women with BMI $\geq$35 were only available in a single study (Wang *et al*., 2000), which did not report live birth rate. Only one study (Dokras *et al*., 2006) reported outcomes for women with BMI $>$40. Wherever this was reported, women with low BMI (BMI $<$18.5 or $<$20) were excluded from analysis in order to provide an accurate comparison of normal versus increased BMI. However, this information is only provided in some studies (Wang *et al*., 2000; Wittemer *et al*., 2000; Krizanovska *et al*., 2002; Wang *et al*., 2002; Winter *et al*., 2002; Fedorcsak *et al*., 2004; Dechaud *et al*., 2006). Moreover, variable definition for low BMI is used by various authors [BMI $<$18.5 (Fedorcsak *et al*., 2004) and BMI $<$20 (Wittemer *et al*., 2000)].

Some authors have reported outcomes per cycle (Wittemer *et al*., 2000; Nichols *et al*., 2003; Dechaud *et al*., 2006), while others have chosen to report outcomes per woman (Wang *et al*., 2000; Krizanovska *et al*., 2002; Fedorcsak *et al*., 2004; van Swieten *et al*., 2005; Dokras *et al*., 2006). Except for three (Wang *et al*., 2000; Krizanovska *et al*., 2002; Nichols *et al*., 2003), all studies reporting outcomes per woman have only included one cycle per woman. Only Fedorcsak *et al*. (2004) provided data separately for both denominators (cycle and

Table 1: Characteristics of the included studies

Study ID	Methodology	Participants	BMI categories (*n*)	Outcome measures	Comments
Studies actually included in the meta-analysis					
Dechaud *et al*. (2006)	Retrospective study (September 2003–May 2005)	All women undergoing IVF/ICSI Excluded h/o uterine surgery Endometrial pathologies Hydrosalpinges Three or more attempts at failed IVF Women using other than long protocol for stimulation	<20 (264 cycles) 20–25 (394 cycles) 25–30 (83 cycles) ≥30 (48 cycles)	Dose of FSH Oocytes retrieved Implantation rate Clinical pregnancy rate Miscarriages rate	Starting dose of gonadotrophins was adjusted according to BMI at the start of cycle Women with PCOS were included in the data
Darks *et al*. (2006)	Retrospective study (Janua 1995–April 2005)	All women undergoing IVF/ICSI Excluded GIFT, ZIFT Women >38 years old	<25 (683 women/cycle) 25–29.9 (295 women/cycle) 30–39.9 (236 women/cycle) ≥40 (79 women/cycle)	Cancellation rate Total mature oocytes OHSS Implantation rate Clinical pregnancy rate Miscarriage rate Delivery rate	Starting dose of FSH was not adjusted for BMI Data combined for both long and microdose flare up protocol Miscarriage rate was defined as spontaneous pregnancy loss upto 20 weeks of gestation after detection of a gestational sac Delivery rate is defined as delivery after 20 weeks of gestation. Only first IVF cycle is considered.
Fedorcsak *et al*. (2004)	Retrospective study	All women undergoing IVF/ICSI cycle	<18.5 (136 cycles, 76 women) 18.5–24.9 (3457 cycles1839 women) 25–29.9 (963 cycles, 504 women) ≥30 (463 cycles, 241 women)	Dose of FSH No of cancelled cycles No of oocytes collected No of biochemical pregnancies Miscarriages Live birth	Starting dose of FSH was adjusted for BMI Early pregnancy loss was defined as a biochemical pregnancy without subsequent USG sign of viable pregnancy BMI measured with a median of 80 days before the start of treatment
Krizanovska *et al*. (2002)	Retrospective (January 1997–June 1999)	All women undergoing IVF/ICSI	<16 (2 women) 18–20 (30 women) 20–25 (173 women) 25–30 (79 women) ≥30 (25 women)	Average number of oocytes Average fertilized oocytes Average number of embryos Clinical pregnancy Miscarriages OHSS	Only mean of average number of oocytes and embryos give. No data on variation within sample is available. No clear definition of clinical pregnancy.
Munz *et al*. (2005)	Retrospective	All women undergoing IVF/ICSI	<25 (28 patients) >25 (24 patients)	Pregnancy rate OHSS rate Mean number of eggs obtained Mean number of fertilized eggs	Pregnancy is defined as biochemical pregnancy
Nichols *et al*. (2003)	Retrospective study (November 1996–June 2000)	All women undergoing IVF/ICSI cycles	<25 (cylces) 25–29.9 (cycles) ≥30 (30 cycles)	Duration of FSH Number of ampules Oocytes retrieved Implantation rate Clinical pregnancy Spontaneous miscarriage	BMI measured within 4 weeks of initiating the cycle Clinical pregnancy defined as presence of gestational sac at 6–7 weeks
Van Swieten *et al*. (2005)	Observational study	All women undergoing IVF/ICSI. Excluded >40 years old poor Ovarian reserve	<25 (101women) 25–30 (32 women) ≥30 (29 women)	Dose of FSH Cancellation OHSS Oocytes retrieved Fertilization rate Clinical pregnancy rate Miscarriage rate	Only first stimulation cycle was studied BMI was measured immediately before starting down-regulation Provide separate data for cancellation due to OHSS and poor stimulation Report only cancelled cycles for OHSS

Continued

Table 1: *Continued*

Study ID	Methodology	Participants	BMI categories (*n*)	Outcome measures	Comments
Wang *et al*. (2000)	Retrospective data	All women undergoing ART (IVF/ ICSI/GIFT)	<20 (441 women) 20–24.9 (1910 women) 25–29.9 (814 women) 30–34.9 (304 women) ≥35 (117 women)	Probability of achieving at least one clinical pregnancy	Clinical pregnancy defined as embryonic sacs in womb, 4–6 weeks after ET Outcomes reported per woman, some women underwent more than one cycle
Wittemer *et al*. (1999)	Retrospective study (December 1997–April 1998)	All couples referred for IVF/ICSI Excluded PCOS	<20 (77 cycles) 20–25 (178 cycles) ≥25 (70 cycles)	Initiated pregnancies Miscarriages Deliveries	Results reported per cycle Pregnancy data is available for only less than 38 years old women Data is combined for different stimulation protocols (long and short protocols) Data for oocytes collected is available only forstimulation with long protocol but it is not possible to get total dose for each BMI group Different BMI groups are formed for different parameters like number of ampules of gonadotrophins and duration of stimulation, hence it is difficult to extract the data for dose and duration of gonadotrophins
Fedorcsak *et al*. (2000)[a]	Cohort study (August 1996–January 1998)	Women pregnant as a result of IVF or ICSI	<25 (304 pregnancies) ≥25 (79 pregnancies)	Miscarriage	Only first pregnancy for each couple was included Variable regimens for ovulation induction were used Reported separately for miscarriage at <6 weeks, 6–12 weeks and >12 weeks.
Wang *et al*. (2002)[a]	Cohort study (1987–1999)	Women pregnant as a result of IVF or ICSI or GIFT	<18.5 (70 pregnancies) 18.5–24.9 (1508 pregnancies) 25–29.9 (503 pregnancies) 30–34.9 (198 pregnancies) ≥35 (70 pregnancies)	Spontaneous miscarriage	Included PCOS women as well BMI has been measured upto an year before start of treatment Spontaneous miscarriage is defined as pregnancy loss at <20 weeks gestation
Winter *et al*. (2002)[a]	Cohort study (1994–1999)	Women pregnant as a result of IVF or ICSI or GIFT	<18.5 (26 pregnancies) 18.5–24.9 (701 pregnancies) 25–29.9 (243 pregnancies) 30–34.9 (107 pregnancies) ≥35 (46 pregnancies)	Early pregnancy loss	Early pregnancy loss ascertained by either a self reported miscarriage before 6 weeks of gestation or by absence of embryonic sacs or gestational sacs as detected on ultrasound around 6–7 weeks of gestation. Pregnancy loss after this has not been considered in this study.
Studies fulfilled the inclusion criterion but are not included in the meta-analysis					
Crosignani *et al*. (1994)	Retrospective cohort	Women undergoing IVF Excluded PCOS	<20 (38 women) 20–22 (29 women) >22 (43 women)	Number of follicles >10 mm in diameter Number of oocytes retrieved	No mention of pregnancy rate (primary outcome measure).

Frattarelli and Kodama (2004)	Retrospective cohort study (January 2000 to January 2001)	Women undergoing assisted conception Excluded Elevated FSH >42 years of age	≤24 >24	Number of oocytes Dose of FSH Pregnancy rate	It is not documented in the article the number of women/ cycles in each BMI category. We have emailed to the corresponding author, which bounced back.
Ku *et al*. (2006)	Retrospective	All women undergoing IVF/ICSI less than 37 years old	<24 (185 women) ≥24 (38 women)	Dose of gonadotrophins Clinical pregnancy rate Implantation rate	Clinical pregnancy was defined as presence of cardiac activity 3–4 weeks after embryo transfer
Lashen *et al*. (1999)	Case control (January 1995–December 1996)	White caucasian women in their first IVF/ICSI cycle Excluded Basal FSH >12	>27.9 (76) 20–24 (152)	Dose of FSH Number of oocytes Fertilization rate Pregnancy rate Miscarriage rate OHSS	Women with BMI between 24–27.9 missed. Hence cannot be incorporated in pooled data
Lewis *et al*. (1990)	Retrospective (1985–1988)	Women undergoing IVF/ICSI Excluded Irregular cycles Endometriosis Single ovary	<19.1 (34) 19.1–20.7 (114) 20.8–22.2 (72) 22.3–27.6 (112) >27.6 (36)	Number of oocytes recovered Clinical pregnancy rate	CC+HMG used for COH
Loveland *et al*. (2001)	Retrospective (January 1997–March 1999)	All women undergoing IVF/ICSI cycles Excluded Women ≥40 yrs old Women who had blastocyst transfer	≤25 (87 cycles, 70 women) >25 (93 cycles, 69 women)	Dose and duration of FSH Cancellation rate Number of oocytes Implantation rate Clinical pregnancy rate Spontaneos abortion Ongoing pregnancy rate	Used either long or modified microdose flare up protocol Biochemical pregnancies were considered failure to conceive Ongoing pregnancies implies delivered or ongoing pregnancies beyond 20 weeks.
Unkila-Kallio *et al*. (2001)	Prospective	Caucasian women aged 23–41 years with duration of subfertility 2–16 years were included in the study.	≤19.4 (9 women) 19.5–26.4 (50 women) ≥26.5 (10 women)	Dose of FSH Pregnancy Miscarriage, successful pregnancy	Clinical pregnancy is defined as no bleeding & rising hCG
Urbancsek *et al*. (2002)	Case control	Women undergoing IVF cycle Excluded Irregular cycle Endocrine disease PCOS	>28 (17 women) 20–25 (17 women)	Number of oocytes collected Pregnancy rate Leptin concentration Inhibin A and B levels Serum estradiol	Cases choosen with BMI of >28, controls with BMI 20–25. No mention of women with BMI between 25 and 28.
Spandorfer *et al*. (2004)	Cohort study	Women undergoing IVF/ICSI Excluded >40 years of age poor ovarian reserve	<27 (702 women) >27 (148 women)	Number of oocytes Dose of FSH Number of 2PN embryo	BMI obtained at initial visit before start of treatment >3 embryos were transferred

All studies have excluded donor cycles and frozen embryo transfer. [a]reported only the miscarriage rate.

Table 2: WHO definition of obesity (http://www.wvdhhr.org/bph/oehp/obesity/define.htm)

	BMI (kg/m^2)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25.0–29.9
Obesity Class I	30.0–34.9
Obesity Class II	35.0–39.9
Obesity Class III	40+

woman). We did not feel that we could combine data on outcomes per cycle with those per woman, as more than one cycle per woman may over-represent women who failed to conceive. Hence, outcomes have been presented per cycle as well as per woman.

Description of outcome measures

Live birth rate

Live birth rate has been reported in a single study (Fedorcsak *et al*., 2004). Two other studies have reported on delivery rate (Wittemer *et al*., 2000; Dokras *et al*., 2006). For the purpose of this review, live birth rate and delivery rate has been combined and have been reported as per patient (Fedorcsak *et al*., 2004; Dokras *et al*., 2006) and per cycle (Wittemer *et al*., 2000; Fedorcsak *et al*., 2004).

Pregnancy rate

There was a wide variation in the definition of clinical/ongoing pregnancy amongst various studies. Krizanovska *et al*. (2002) and van Swieten *et al*. (2005) reported all cases with positive b-hCG as clinical pregnancy, while Wittemer *et al*. (2000) have used 'initiated pregnancies' without a clear definition of this term. Wang *et al*. (2000) measured the probability of achieving at least one clinical pregnancy per woman whereas Nichols *et al*. (2003) defined clinical pregnancy as the presence of a gestational sac at 6–7 weeks gestation, identified via transvaginal scan. For the purpose of this review, we have aggregated all the pregnancies (biochemical, clinical, initiated and ongoing pregnancies) in order to calculate the total pregnancy rate.

Miscarriage rate

Early pregnancy loss has been defined as miscarriage before 6 weeks (Winter *et al*., 2002; Fedorscak *et al*., 2004), before 12 weeks (Fedorcsak *et al*., 2000) and up to 20 weeks (Wang *et al*., 2002; Dokras *et al*., 2006). For the purpose of this review, we have combined all the miscarriages together. Some of the data from Winter *et al*. (2002) and Wang *et al*. (2002) were from the same series of women. Fedorcsak *et al*. (2000) included only miscarriages after first cycle while Winter *et al*. (2002) included more than one cycle per woman. However, in 38% of cycles (1421 cycles), in Winter *et al*. (2002) study, risk of early pregnancy loss could not be determined.

Dose of gonadotrophins used

Data pertaining to the dose of gonadotrophins could only be pooled in a few studies where the mean (SD/SEM) of the total dose was provided (Fedorcsak *et al*., 2004; Deuchad *et al*., 2006).

Number of oocytes recovered

Six studies have reported the number of oocytes retrieved (Nichols *et al*., 2003; Fedorcsak *et al*., 2004; Munz *et al*., 2005; van Swieten *et al*., 2005; Dechaud *et al*., 2006; Dokras *et al*., 2006). Only Dokras *et al*. (2006) reported the number of mature oocytes.

Cancellation rate

Cycle cancellation rate was reported in four studies (Fedorcsak *et al*., 2004; van Swieten *et al*., 2005; Dechaud *et al*., 2006; Dokras *et al*., 2006). Only two studies (Fedorcsak *et al*., 2004; van Swieten *et al*., 2005) differentiated between the cancellations due to poor response and those due to the risk of OHSS. Fedorcsak *et al*. (2004) also mentioned cancellation due to other causes, which were not specified.

Number of embryos obtained

Only two studies have included data on the number of embryos formed (Krizanovska *et al*., 2002; Munz *et al*., 2005). It was not possible to aggregate these data. None of the studies mentioned the quality of embryos obtained.

Ovarian hyperstimulation syndrome

Incidence of OHSS has been investigated in 4 studies (Krizanovska *et al*., 2002; Munz *et al*., 2005; van Swieten *et al*., 2005; Dokras *et al*., 2006). In this review it has not been possible to differentiate between mild, moderate or severe OHSS.

Results of the aggregated data

Pooled results are described separately for BMI $\geq$25 versus <25 and for BMI $\geq$30 versus <30. Results, wherever possible, have been presented per woman. In addition, outcomes per cycle have been aggregated together and described separately.

Live birth rate

In women with BMI of <25, the odds of live birth per woman (Supplementary Fig.2a) were 1.08 (95%: CI 0.92, 1.26), and per cycle were 0.74 (95% CI: 0.27, 2.01) when compared with women with BMI of $\geq$25 (Data not shown). In women with BMI of <30, the odds of live birth per woman (Supplementary Fig. 2b) were 1.12 (95% CI: 0.91, 1.37) when compared with women with BMI of $\geq$30. There was significant statistical heterogeneity in results from the different studies ($P = 0.003$).

Pregnancy rate

In women with BMI of <25, the odds of pregnancy rate per woman (Fig. 1a) were 1.24 (95% CI: 1.02, 1.50) and per cycle were 0.99 (95% CI: 0.88, 1.12) (data not shown) when compared with women with BMI of $\geq$25. Again the results showed significant statistical heterogeneity ($P = 0.03$).

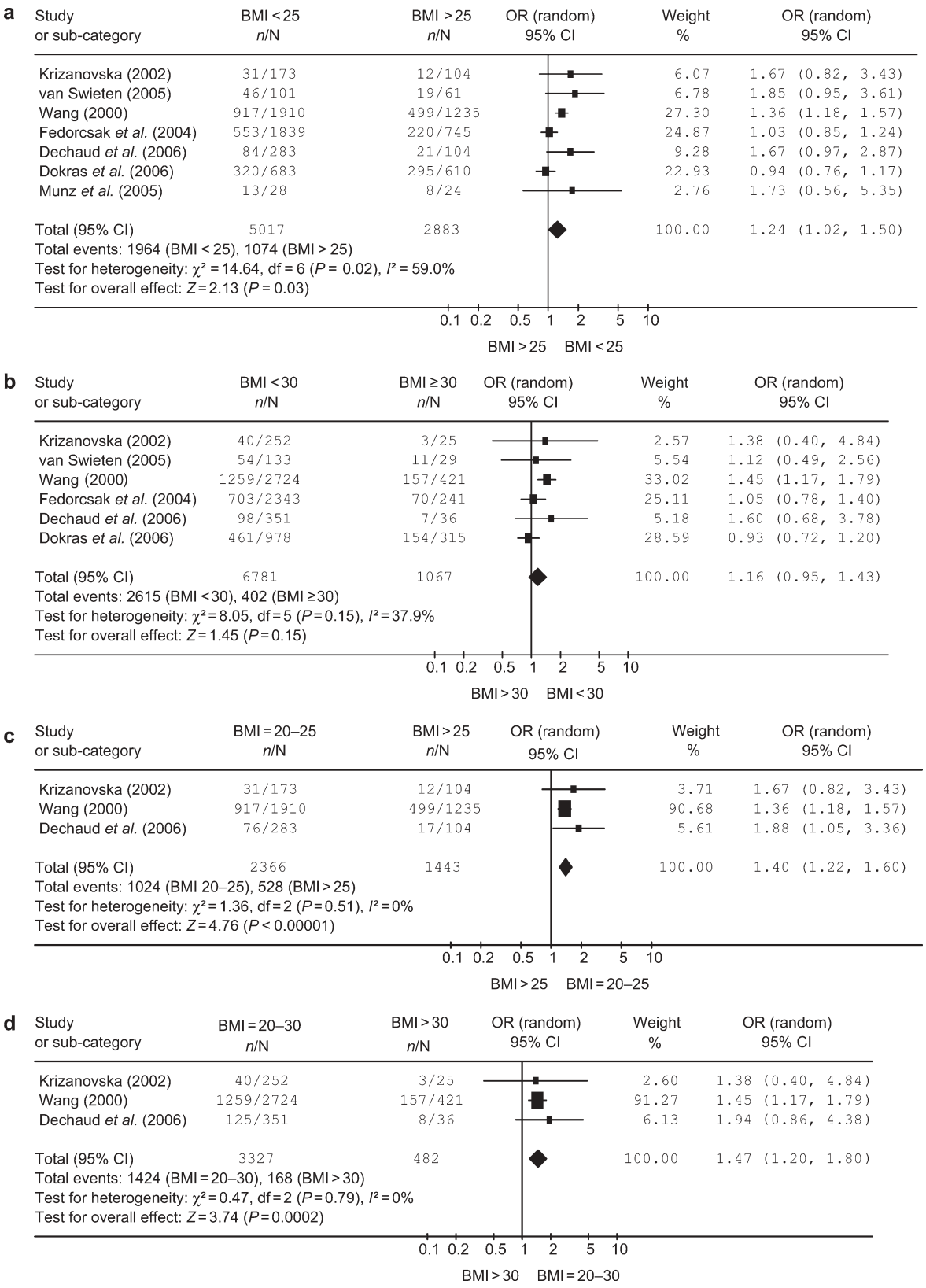

Figure 1: Pregnancy rate per woman
(**a**) BMI <25 versus BMI ≥25; (**b**) BMI <30 versus BMI ≥30; (**c**) BMI 20–25 used for normal weight; (**d**) BMI 20–25 used for normal weight

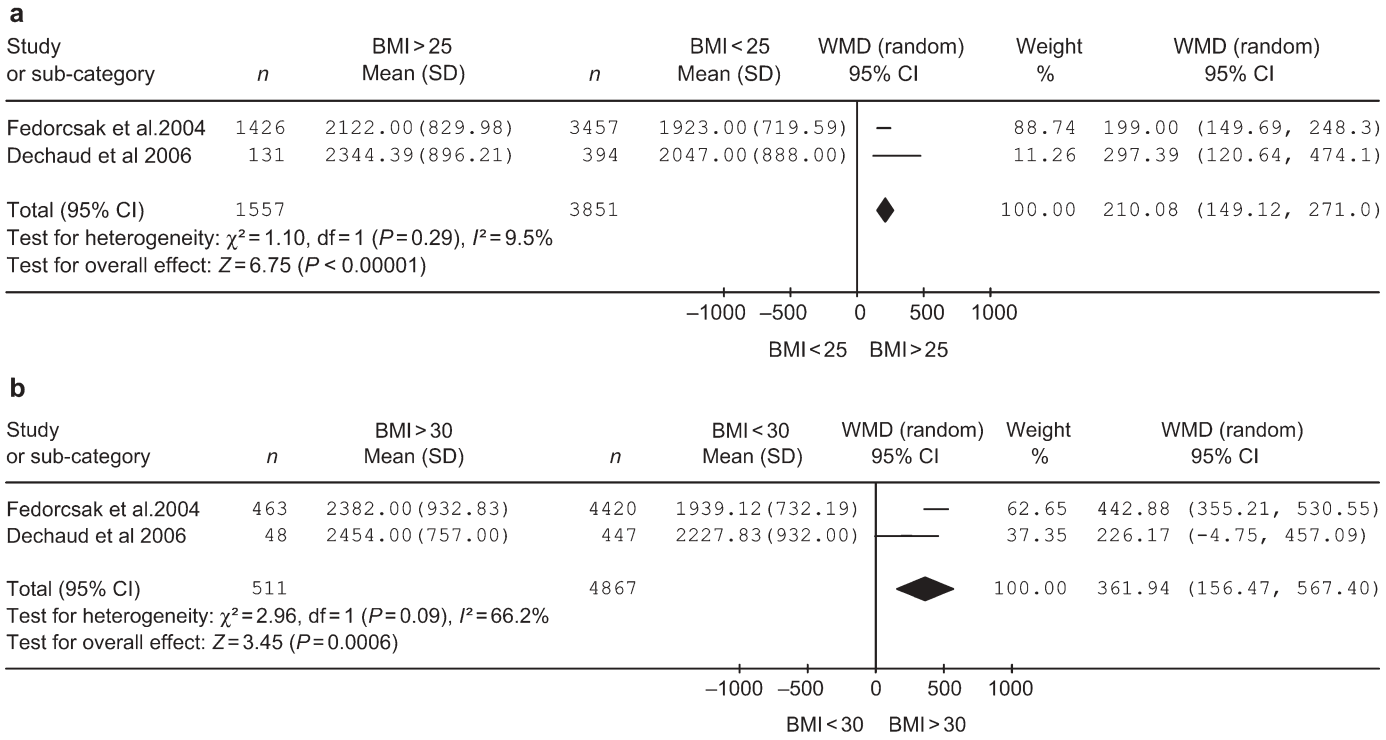

Figure 2: Dose of gonadotrophin per cycle
(**a**) BMI <25 versus BMI ≥25; (**b**) BMI ≥30 versus BMI <30

In women with a BMI of <30, the odds of pregnancy per woman (Fig. 1b) were 1.16 (95%: CI 0.95, 1.43), and per cycle were 1.05 (95% CI: 0.87, 1.28) (data not shown) when compared with women with a BMI of ≥30.

When only normal weight (BMI 20–25) women were included, the odds of pregnancy per woman were 1.40 (95% CI: 1.22, 1.60) as compared to woman with a BMI ≥25. Odds of pregnancy were 1.47 (95% CI: 1.20, 1.80) for a woman with a BMI <30 as compared to women with BMI of ≥30 (Fig. 1c and d).

Dose of gonadotrophins used

The dose of gonadotrophins was higher in women with BMI of ≥25 (WMD 210.08, 95% CI: 149.12, 271.05) in comparison with those with BMI of <25 (Fig. 2a). The requirement for gonadotrophins was higher (WMD 361.94, 95% CI: 156.47, 567.40) in obese women (BMI ≥30 versus BMI <30) (Fig. 2b).

Number of oocytes retrieved

The WMD of the number of oocytes recovered in women with BMI <25 was 0.58 (95% CI: 0.22, 0.94) in comparison with women with BMI ≥25. The WMD of the number of oocytes retrieved in women with BMI <30 was 0.68 (95% CI: 0.11, 1.25) as compared to women with BMI of ≥30 (Fig. 3a and b).

Pooled data from studies which have chosen to report the outcomes per cycle (data not shown), show no difference (WMD −0.30, 95% CI: −1.62, 1.02 & WMD 0.46, 95% CI: −0.55, 1.47) in the number of oocytes recovered in a cycle in either comparison, i.e. BMI <25 versus ≥25 and BMI <30 versus ≥30.

Cancellation rate

In women with BMI of ≥25, the odds of cycle cancellation were 1.32 (95% CI: 0.96, 1.82), as compared to women with BMI of <25 (Supplementary Fig.3a). When the data from studies which have reported the outcomes per cycle were pooled, the odds of cycle cancellation in women with BMI of ≥25 were 1.83 (95% CI: 1.36, 2.45), as compared to women with BMI <25 (data not shown). The results displayed evidence of significant statistical heterogeneity ($P = 0.05$). BMI of ≥30 was associated with higher odds of cycle cancellation 1.35 (95% CI: 0.99, 1.84), than that of BMI of <30 (Supplmentary Fig.3b). When the data from studies which have reported the outcomes per cycle were pooled, the odds of cycle cancellation in women with BMI of ≥30 were 1.59 (95%CI: 0.53, 4.80), as compared to women with BMI <30 (Data not shown).

Ovarian hyperstimulation rate

In a woman with BMI of ≥25, the odds of OHSS were 1.12 (95% CI: 0.74, 1.68), as compared to women with a BMI of <25 (Supplementary Fig. 4a). In a woman with BMI of ≥30, the odds of OHSS were 1.16 (95% CI: 0.69, 1.96), as compared to women with BMI of <30 (Supplementary Fig.4b).

Miscarriage rate

In women with BMI of <25, the odds of miscarriage (Fig. 4a) were 1.33 (95% CI: 1.06, 1.638), compared to women with BMI of ≥25. The results showed evidence of statistical heterogeneity ($P = 0.05$). The risk of miscarriage was higher (Fig. 4b) (OR = 1.53, 95% CI: 1.27, 1.84), in women with BMI ≥30 versus BMI <30.

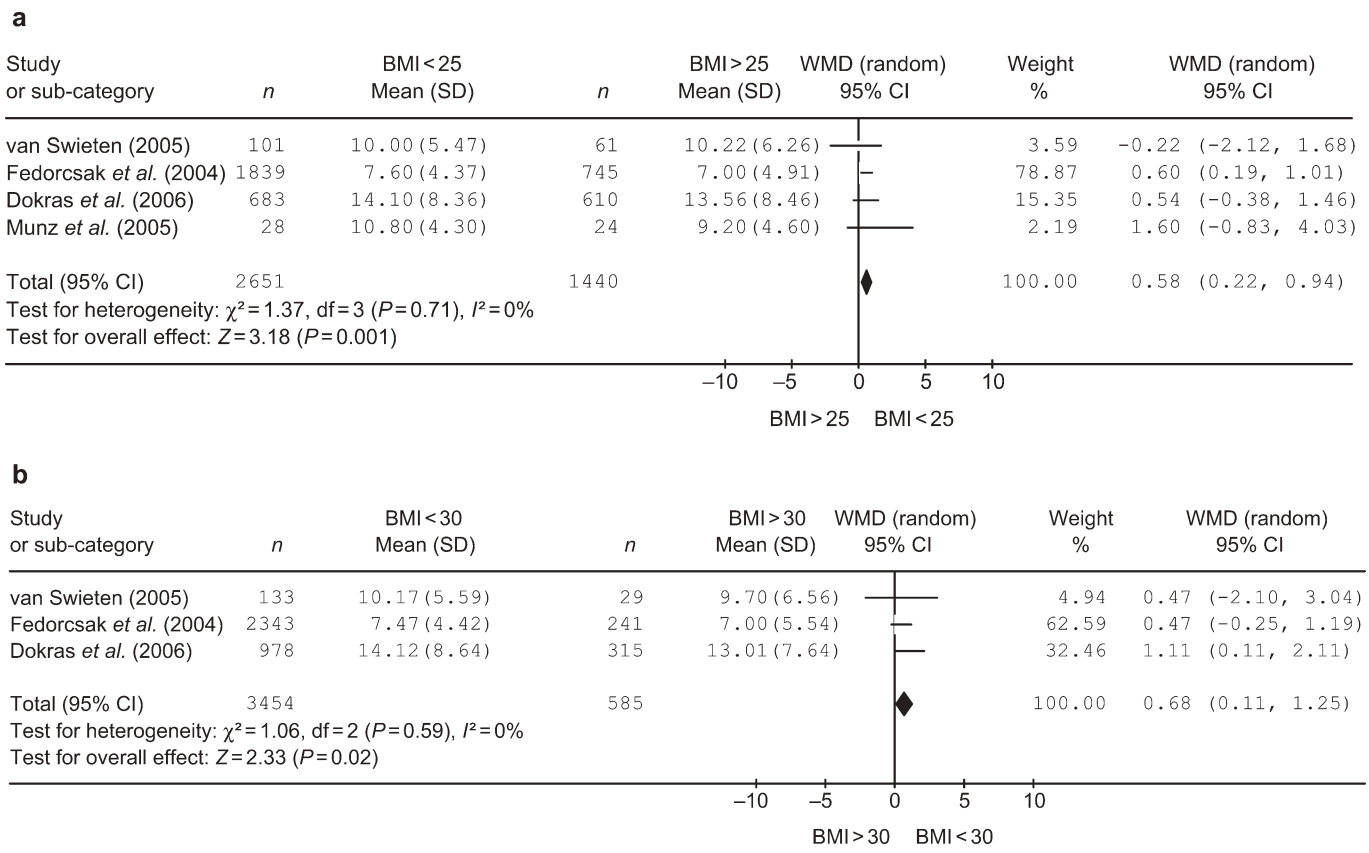

Figure 3: Number of oocytes retrieved (results reported per woman) (**a**) BMI <25 versus BMI ≥25; (**b**) BMI <30 versus BMI ≥30

Discussion

Our results show that overweight women face a lower likelihood of pregnancy and an increased risk of miscarriage after IVF. They also have reduced number of oocytes retrieved despite requiring higher doses of gonadotrophins. There is insufficient evidence of a difference in other outcomes including live birth, OHSS and cycle cancellation rates.

The strength of this systematic review lies in its comprehensive nature and ability to compare pooled data from a number of large studies according to the WHO classification of BMI. However, as a systematic review based on observational data, these results are not free from bias. The studies included in the review display considerable clinical, methodological and statistical heterogeneity. Despite fulfilling all the inclusion criteria, eight studies could not be included in the meta-analysis due to differences in their classification of overweight and obesity. Our meta-analysis, based on reported data, was unable to adjust for potential confounders such as age. Finally, the possibility of publication bias cannot be excluded. It was not feasible to generate a funnel plot based on live birth due to paucity of studies which reported this as an outcome.

The studies included in this review showed a wide variation in their choice of subjects. Some included all women undergoing assisted conception (Wang *et al*., 2000; Krizanovska *et al*., 2002; Fedorcsak *et al*., 2004), while others excluded those with a poor prognosis (Wittemer *et al*., 2000; van Swieten *et al*., 2005; Dechaud *et al*., 2006; Dokras *et al*., 2006). Women with PCOS were excluded by Wittemer *et al*. (2000). This may be relevant as PCOS (which is associated with obesity) has been shown to have an independent effect on pregnancy rates (Wang *et al*., 2000). Two studies excluded women on the basis of age (van Swieten *et al*., 2005; Dokras *et al*., 2006). Others adjusted for confounding factors such as age, year of treatment and diagnosis of PCOS (Wang *et al*., 2000; Nichols *et al*., 2003; Dokras *et al*., 2006).

Clinical protocols used for pituitary down-regulation and controlled ovarian hyperstimulation varied among studies and sometimes even within the same study. This could have had an impact on ovarian response and cancellation rates (Al-Inany *et al*., 2006). The starting dose of gonadotrophins was based on results of preliminary tests of ovarian reserve (Dokras *et al*, 2006), BMI and age (Fedorcsak *et al*., 2004; Dechaud *et al*., 2006) in some studies, but not in others (van Swieten *et al*., 2005).

Live birth, as an outcome measure, was only reported by a minority of studies. It is, however, possible to extrapolate from the available data and argue that a combination of higher miscarriage and lower pregnancy rates in overweight and obese women could result in a reduced expectation of live birth rate. Interpretation of our results is further complicated by differences in the definitions used for outcome measure such as miscarriage, pregnancy rate (Table 1) in individual studies. For instance, there is no consensus regarding the definition of poor response (van Swieten *et al*., 2005; Dechaud *et al*., 2006; Dokras *et al*., 2006) or clear criteria for cancellation due to the threat of OHSS.

Many studies have reported live birth/pregnancy rates per cycle rather than per woman. Using the latter as denominator is the more

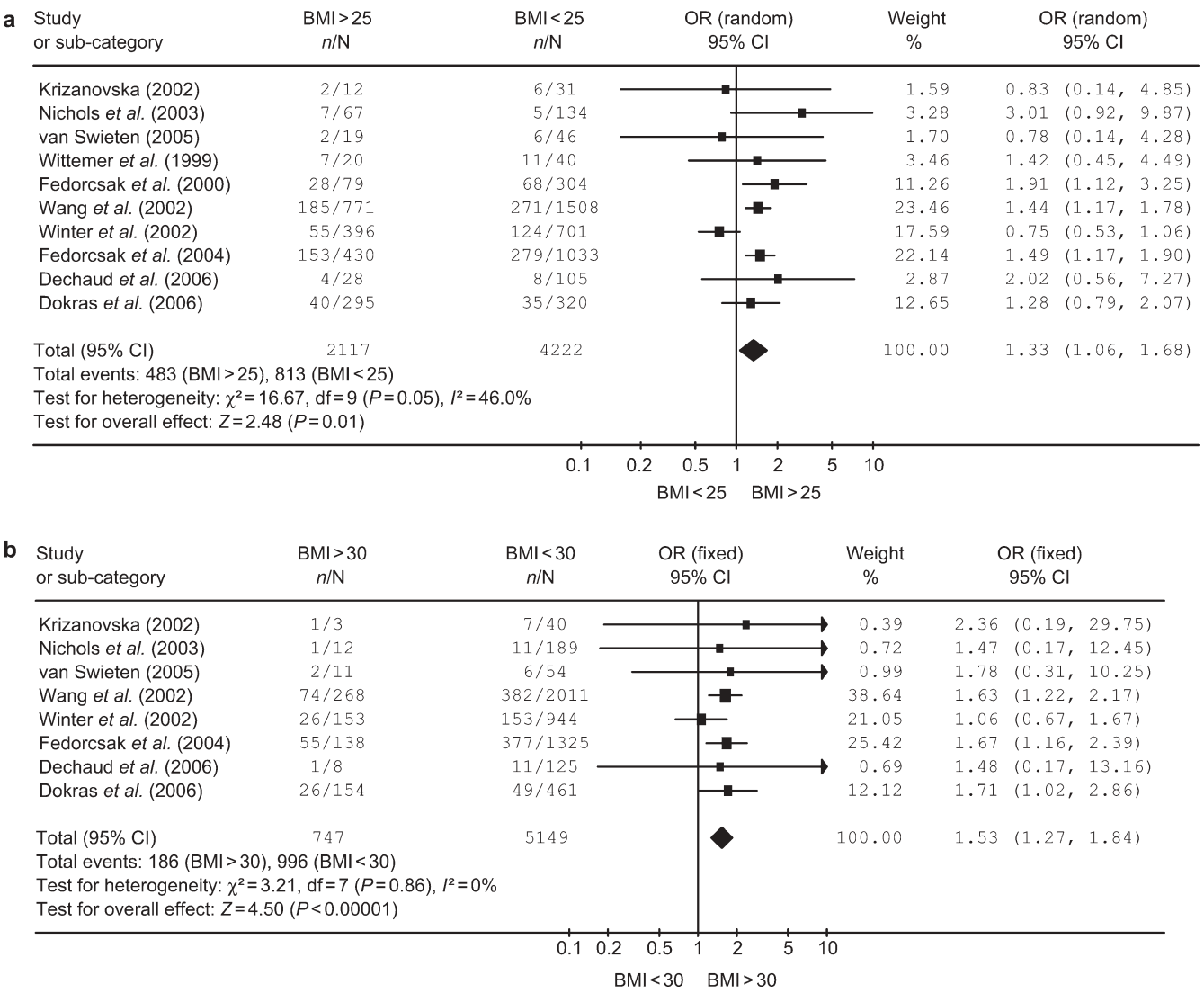

Figure 4: Miscarriage per pregnancy rate
(**a**) BMI <25 versus BMI ≥25; (**b**) BMI <30 versus BMI ≥30

methodologically robust method (Johnson *et al*., 2003; Vail and Gardener, 2003) as it is the woman who is generally accepted to be the unit of analysis. Expressing outcomes per cycle can lead to significant bias—especially as many women can undergo more than one treatment cycle.

We were limited by the need to work with reported results from published papers rather than raw data from individual women. Thus, while some of the individual studies were able to adjust for confounders such as age, parity and duration of infertility, we were unable to adjust for these factors in our meta-analysis. Some of the studies measured the mean number of oocytes or units of gonadotrophins, but failed to provide any measure of the spread of the data (SD/SEM). This again influenced our ability to aggregate data.

Previously, individual studies on the outcome of IVF in women with high BMI showed conflicting results. There was sufficient concerns about risks in overweight/obese women to prompt organizations such as the British Fertility Society (BFS) to suggest withholding IVF from women with BMI of >35 (Kennedy *et al*., 2006). The BFS has also suggested that women with BMI of >30 should be referred to a weight loss programme. Our results show poorer outcomes even in women with a BMI of 25 and over—a group which includes ∼50% of women in the UK. The need to address this issue may have substantial resource implications.

We have been able to provide the estimate of difference in only two BMI groups (BMI <25 versus ≥25 and <30 versus ≥30). Few women in the higher BMI categories currently receive IVF, and this number is destined to shrink in future as clinics adopt a strict weight linked policy for access to IVF. Most of the units in UK have a cut-off of BMI <35 for women to be able to access IVF (Zachariah *et al*., 2006).

In this review, we have considered BMI as a marker of obesity. There are suggestions that WHR is a better predictor of reproductive outcome (Wass *et al*., 1997; Zaadstra *et al*., 1993) as BMI does not differentiate between android and gynaecoid fat distribution.

More research in this area is needed with clearly defined patient populations, using standardized BMI criteria and uniform outcome measures. Access to individual patient data may allow more refined methods of analysis including the ability to adjust for confounders in generating combined OR. Further research is needed in determining the best measure of obesity for reproductive outcome.

Conclusion

Obesity and overweight is associated with decreased pregnancy rates, increased requirement for gonadotrophins and a higher miscarriage rate. These differences are evident even at a BMI $\geq$25. More evidence is required in order to make a judgement about the effect on live birth. More prospective studies with clear entry criteria and uniform reporting of outcomes are needed. Meanwhile, weight loss should be considered in overweight women (i.e. BMI $\geq$25) before initiating assisted reproduction.

Supplementary material

Supplementary material is available at http://humupd.oxfordjournals.org

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