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REVIEW

Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis

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Abstract There is conflicting evidence regarding the effect of raised body mass index (BMI) on the outcome of assisted reproductive technology. In particular, there is insufficient evidence to describe the effect of BMI on live birth rates. We carried out a systematic review and meta-analysis of studies to evaluate the effect of raised BMI on treatment outcome following IVF/ICSI treatment. Subgroup analysis on overweight and obese patients was performed. Literature searches were conducted on MEDLINE, EMBASE and the Web of Science from 1966 to 2010. Thirty-three studies including 47,967 treatment cycles were included. Results indicated that women who were overweight or obese (BMI $\geq$ 25) had significantly lower clinical pregnancy (RR = 0.90, $P < 0.0001$) and live birth rates (RR = 0.84, $P = 0.0002$) and significantly higher miscarriage rate (RR = 1.31, $P < 0.0001$) compared to women with a BMI $<$ 25 following treatment. A subgroup analysis of overweight women (BMI $\geq$ 25–29.9) revealed lower clinical pregnancy (RR = 0.91, $P = 0.0003$) and live birth rates (RR = 0.91, $P = 0.01$) and higher miscarriage rate (RR = 1.24, $P < 0.00001$) compared to women with normal weight (BMI $<$ 25). In conclusion, raised BMI is associated with adverse pregnancy outcome in women undergoing IVF/ICSI treatment, including lower live birth rates. This effect is present in overweight as well as obese women.

KEYWORDS: assisted reproduction treatment, body mass index, clinical pregnancy rate, live-birth rate, miscarriage rate, systematic review

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Introduction

Obesity has become a worldwide epidemic, with approximately 1.6 billion adults being overweight and 400 million obese (Prentice, 2006; WHO, 2006). In many European countries, over half of women of reproductive age are either overweight (body mass index (BMI) 25–29.9 kg/m^2) or obese (BMI $\geq$30 kg/m^2) (International Obesity Task Force, 2002; Balen and Anderson, 2007; Koning et al., 2010).

Obesity is associated with a range of health consequences, including a detrimental effect upon reproductive health. Compared with women with normal BMI (18.5–24.9 kg/m^2), women with a raised BMI are known to have a threefold greater risk of infertility due to disturbances in the hypothalamic–pituitary axis, menstrual cycle alterations and anovulation as well as psychological and social factors (van der Steeg et al., 2008; Brewer and Balen, 2010). Obesity is also associated with higher risk of pregnancy complications (Linne, 2004; Catalano and Ehrenberg, 2006; Stothard et al., 2009; Shirazian and Raghaven, 2009; Metwally et al., 2010). Nevertheless, there is conflicting evidence regarding the effect of raised BMI on the outcome of assisted reproduction technology. Although some studies have reported no adverse effect of raised BMI on IVF outcome (Lashen et al., 1999; Winter et al., 2002; Styne-Gross et al., 2005; Dechaud et al., 2006; Bellver et al., 2007; Matalliotakis et al., 2008), others have linked raised BMI with a negative impact on outcome. This included the need for higher doses of gonadotrophins, fewer oocytes collected, higher cancellation rate and reduced pregnancy and live-birth rates, as well as higher miscarriage rates (Wang et al., 2000; Fedorcsak et al., 2000, 2004; Veleva et al., 2008; Robker, 2008; ESHRE Task Force on Ethics and Law, 2010). Two recent systematic reviews found insufficient evidence regarding the impact of raised BMI on the live-birth and miscarriage rates after IVF treatment (Maheshwari et al., 2007; Metwally et al., 2008). Since the publication of these two reviews, numerous studies have been published investigating the link between raised BMI and IVF outcome. The aim of this study was to perform an up-to-date systematic review of existing literature to evaluate the impact of BMI on the pregnancy outcome after IVF treatment and, if possible, to determine the impact of overweight (BMI $\geq$25–29.9 kg/m^2) and obesity (BMI $\geq$30 kg/m^2) on IVF outcome separately.

Materials and Methods

Search strategy and identification of literature

Literature searches were conducted via Medline (1966–2010) and Embase (1966–2010) and the Institute for Scientific Information conference proceedings. A combination of medical subject headings (MeSH) and text words were used to generate two subsets of citations, one including studies of body mass index ('overweight', 'obesity', 'body mass index', 'BMI', 'hip-waist ratio') and the other including studies of IVF and intracytoplasmic sperm injection (ICSI) ('in-vitro fertilization', 'embryo transfer', 'intracytoplasmic sperm injection', 'assisted reproduction techniques'). These subsets were combined with 'AND' to generate a subset of citations relevant to the research question. No language restrictions were placed on any search. The searches were conducted independently by VR and SKS.

Study selection and data extraction

Studies were included if they investigated the effect of BMI on pregnancy outcome in women undergoing IVF treatment with or without ICSI. Studies involving natural cycle conception, oocyte donation, intrauterine insemination or induction of ovulation were excluded. In addition, studies reporting alternative parameters for obesity (e.g. waist/hip ratio) were also excluded.

Studies were selected in a two-stage process. In the first instance, two reviewers (VR and SKS) independently scrutinized the titles and abstracts from the electronic searches and full manuscripts of all citations that definitely or possibly met the predefined selection criteria were obtained. Following examination of the full manuscripts, final inclusion or exclusion decisions were made. Assessment of the manuscripts was performed independently by two reviewers (VR and SKS), and any disagreements about inclusion were resolved by consensus after consultation with two co-authors (SS and TE).For each study included, information was obtained regarding population size, study design, BMI categories used and population numbers in each category, exclusion criteria and outcome measures.

The data collected was initially combined into one study group that had BMI $\geq$25 kg/m^2 (overweight and obese patients) and compared with a control group BMI $<$ 25 kg/m^2. The latter did not exclude underweight women (BMI $<$ 18.5 kg/m^2), as most authors studying this BMI category did not report if underweight women were included in their analysis. Thereafter, a subgroup analysis on overweight (BMI $\geq$25–29.9 kg/m^2) and obese (BMI $\geq$30 kg/m^2) patients was performed and each compared with the normal BMI group (BMI $<$ 25 kg/m^2).

Outcome measures

The outcome measures of interest were clinical pregnancy, miscarriage and live-birth rates. For the purpose of this review, clinical pregnancy was defined as the observation of a pregnancy sac on ultrasound at least 4 weeks after embryo transfer. Miscarriage was defined as any pregnancy loss, including biochemical pregnancies, occurring before 20 weeks of gestation. Other outcome measures, such as duration and dose of gonadotrophin used for ovarian stimulation, number of oocytes retrieved and peak oestradiol concentrations were also studied.

Statistical analysis

Outcome data from each study were pooled and expressed as risk ratio (RR) with 95% confidence interval (CI) by using either a fixed-effect model (Mantel and Haenszel, 1959) or a random-effect model (DerSimonian and Laird, 1986) if statistical heterogeneity in the outcome data was detected. Heterogeneity of treatment effects was evaluated graphically using forest plots (Lewis and Clarke, 2001) and statistically using the I^2 statistic to quantify the variation across studies caused by heterogeneity (Higgins and Thompson,

2002). An I^2 value <50% was considered evidence of significant heterogeneity. Exploration of clinical heterogeneity was conducted using variation in features of the study population, intervention and study quality. Statistical analyses were performed with RevMan 5.0 software.

Results

The search strategy yielded 422 citations, all captured from electronic citations (**Figure 1**). Of these, 346 publications were excluded, as it was clear from the title and/or abstract that they did not fulfill the selection criteria. From the remaining 76 articles, 17 were excluded, as they were duplicate publications, two of which (Munz et al., 2005; Lenoble et al., 2008) were counted twice as they appeared three times in the search (Wittemer et al., 2000; Loveland et al., 2001; Salha et al., 2001; Krizanovska et al., 2002; Wang et al., 2002; Kolibianakis et al., 2003; Nichols et al., 2003; Munz et al., 2005; van Swieten et al., 2005; Dorkras et al., 2006; Lenoble et al., 2008; Martinuzzi et al., 2008; Sneed et al., 2008; Jungheim et al., 2009; Vilarino et al., 2011) and 23 studies were excluded as the WHO criteria for BMI classification was not used. The authors of the three abstracts with insufficient information for inclusion eligibility were contacted via email to obtain more information. No reply was received and therefore these three studies were excluded (Woodford et al., 2006; Novi et al., 2007; Migotto et al., 2010).

For the remaining 33 articles, full manuscripts were obtained for scrutiny and data necessary for the analysis were then extracted. The main characteristics of the studies are presented in **Table 1**.

Study characteristics

There were only two studies that were prospective observational studies and the remaining studies were retrospective. Out of the 33 studies, only one study was a case-control study, the remaining were cohort studies. They were all single-centre studies. There were 25 studies in the group with BMI < 25 versus BMI $\geq 25\ kg/m^2$, 16 studies in the group BMI 18.5–24.9 and BMI 25–29.9 kg/m^2 and 15 studies in the group BMI 18.5–24.9 and BMI ≥ 30. In total, 33 studies including 47,967 IVF/ICSI cycles were included in the review: BMI $< 25\ kg/m^2$, $n = 32,496$; and BMI $\geq 25\ kg/m^2$, $n = 15,471$.

Primary outcome

Live-birth rate per IVF/ICSI cycle

BMI $< 25\ kg/m^2$ versus BMI $\geq 25\ kg/m^2$: the pooled results from nine studies showed a statistically significant reduction in the live-birth rate in women with BMI $\geq 25\ kg/m^2$ compared with women with BMI $< 25\ kg/m^2$ (RR 0.84, 95% CI 0.77–0.92, $P = 0.0002$; **Figure 2**A). There was no significant heterogeneity between the included studies ($I^2 = 21.3\%$).

Normal BMI versus BMI 25–29.9 kg/m^2: the pooled results from five studies showed a statistically significant reduction in the live-birth rate in women with BMI 25–29.9 kg/m^2 compared with women with normal BMI (RR 0.91, 95% CI

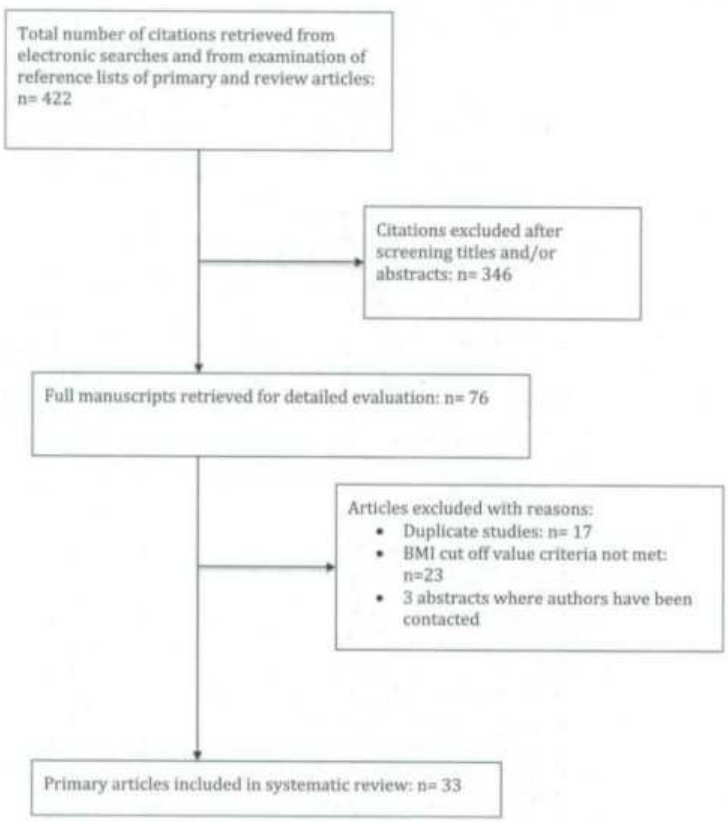

Figure 1 Study selection process for systematic review on effect of body mass index (BMI) on IVF treatment outcome.

Table 1 Characteristics of the included studies.

	BMI group (kg/m²) and numbers	*Exclusion criteria*	*Outcome measures*	*Comments*
Fedorcsak et al. (2000), 383 women, cohort (August 1996–January 1998), IVF/ICSI	<25: 304 Women ≥25: 79 Women	12 patients for incomplete data	Amount of FSH No. of oocytes recovered Abortion before 6 weeks Abortion between week 6 and 12 Abortion after week 12 Life-birth rate	Inclusion of first pregnancy for each couple only Different stimulation cycles (including clomiphene citrate with FSH) 1–3 embryos transferred day 2, 3 or 4 after oocyte collection Measurement of HCG day 14, ultrasound scan at 6 weeks and 12 weeks of gestation
Wittemer et al. (2000), 398 women, retrospective (December 1997–April 1998), IVF/ICSI	<20: 87 Women 20–25: 222 Women ≥25:, 89 Women	None stated	Pregnancy rate Miscarriage rate Delivery rate	Different stimulation cycles (including clomiphene citrate combined with FSH) Pregnancy outcome given for women younger than 38 and analyzed in no. of cycles
Wang et al. (2000), 3586 women, retrospective (1987–1998), IVF/ICSI/GIFT	<20: 441 Women 20–24.9: 1910 Women 25–29.9: 814 Women 30–34.9: 304 Women ≥35: 117 Women	None stated	Probability of achieving at least one clinical pregnancy	Pregnancy determined by ultrasonography of embryonic sac at 4–6 weeks after embryo transfer Outcomes per women, some women underwent more than one cycle
Loveland et al. (2001), 139 women, 180 cycles, retrospective (January 1997–March 1999), IVF only	≤25: 87 Cycles, 70 women >25: 93 Cycles, 69 women	≥40 years of age Blastocyst transfers Frozen embryo transfers Donor cycles	Dose and duration of FSH Cancellation rate Oocyte numbers No. of embryo transfers Clinical pregnancy rate Spontaneous abortion Ongoing pregnancy rate	Long protocol or microdose flare up protocol 26 cycles cancelled for poor response, 154 cycles for overall analysis Biochemical pregnancies considered as failure to conceive Ongoing pregnancy rate implies delivered or ongoing pregnancy >20 weeks

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Table 1 (*continued*)

	BMI group (kg/m²) and numbers	*Exclusion criteria*	*Outcome measures*	*Comments*
Wang et al. (2001), 1018 women, cohort (1987–1999), IVF/ICSI/GIFT	<20: 112 Women 20–24.9: 509 Women 25–29.9: 231 Women 30–34.9: 116 Women ≥35: 50 Women	Women whose PCOS status or BMI was not assessed	Spontaneous abortion	BMI measured <1 year before pregnancy Pregnancy defined as presence of embryonic sac by ultrasound scan at 4–6 weeks after embryo transfer Spontaneous abortion defined as pregnancy <20 weeks of gestation
Wang et al. (2002), 2349 women, retrospective (1987–1999), IVF/ICSI/GIFT	<18.5: 70 Women 18.5–24.9: 1508 Women 25–29.9: 503 Women 30–34.9: 198 Women ≥35: 70 Women	Ectopic pregnancies	Spontaneous miscarriage	Pregnancy defined as presence of fetal heart by ultrasound at 6–8 weeks after last menstrual period Spontaneous abortion defined as pregnancy loss before 20 weeks of gestation BMI measured up to 1 year before start of treatment PCOS women included
Krizanovska et al. (2002), 309 women, retrospective (January 1997–June 1999), IVF/ICSI	<16: 2 Women 18–20: 30 Women 20–25: 173 Women 25–30: 79 Women ≥30: 25 Women	None stated	Average no. of oocytes, fertilization, no. of embryos Clinical pregnancy Miscarriages OHSS	Mean No. of oocytes and embryos No definition of clinical pregnancy
Ferlitsch et al. (2002), 182 women, retrospective (January 1999–December 2000), IVF	<20: 31 Women ≥20–25:104 Women ≥25–30: 31 Women >30: 16 Women	None stated	Pregnancy rate	Different stimulation regimes of two treatment groups Pregnancy defined as positive urinary pregnancy test day 14
Winter et al. (2002), 1123 women, cohort (1994–1999), IVF/ICSI/GIFT	<18.5: 26 Women 18.5–25: 701 Women 25.1–30: 243 Women 30.1–35: 107 Women >35: 46 Women	None stated	Early pregnancy loss	Pregnancy defined as HCG ≥10 IU/l on day 16 after ovulation Pregnancy loss defined as miscarriage before 6 weeks of gestation, either by self reported miscarriage or absence of embryonic sac or gestational sac on ultrasound at 6–7 weeks of gestation

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Table 1 (*continued*)

	BMI group (kg/m^2) and numbers	*Exclusion criteria*	*Outcome measures*	*Comments*
Doody et al. (2003), 822 women, retrospective (March 2000–March 2003), IVF/ICSI	<25: 460 Women 25–29.9: 194 Women 30–34.9: 89 Women >35: 79 Women	Women ≥40 years old	No. of oocytes retrieved Implantation rate Ongoing pregnancy rate	
Ryley et al. (2004), 6827 cycles, retrospective, IVF	<20: 466 Cycles 20–24.9: 3605 Cycles 25–29.9: 1632 Cycles 30–34.9: 724 Cycles >35: 400 Cycles	Women>40 years old	No. of oocytes retrieved Clinical pregnancy rate	
Fedorcsak et al. (2004), 2660 women, 5019 cycles, retrospective (September 1996–May 2002), IVF/ICSI	<18.5: 76 Women, 136 cycles 18.5–24.9,: 1839 Women, 3457 cycles 25–29.9: 504 Women, 963 cycles ≥30: 241 Women, 463 cycles	None stated	Dose and duration of FSH No. of cancelled cycles No. of oocytes collected No. of biochemical pregnancies Early pregnancy loss Miscarriage 6–12 weeks Miscarriage >12 weeks Live-birth rate	Starting FSH dose adapted for age and BMI > 35 kg/m^2 Embryo transfer day 2 or 3 Up to three embryos transferred Pregnancy defined as HCG > 20 U/l on day 14 after oocyte retrieval Early pregnancy loss defined as biochemical pregnancy without ultrasound signs of viable pregnancy BMI measured a median 80 days before treatment cycle
Van Swieten et al. (2005), 162 women, 288 cycles, observational, IVF/ICSI	<25: 101 Women 25–30: 32 Women >30: 29 Women	None stated	Days of stimulation Dose of stimulation No. of oocytes retrieved Endometrial thickness Fertilization rate Clinical pregnancy rate Abortion rate	Cancelled cycles if poor response or OHSS Clinical pregnancy defined as biochemical pregnancy Abortion defined as spontaneous abortion <12 weeks Only first stimulation cycles studied

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Table 1 (*continued*)

	BMI group (kg/m²) and numbers	*Exclusion criteria*	*Outcome measures*	*Comments*
Hammadeh et al. (2005), 52 women, prospective, IVF	≤25: 28 Women >25: 24 Women		Pregnancy rate	Five blood samples were taken from each patient Lipid concentrations were measured in all blood samples
Munz et al. (2005), 52 women, retrospective case–control, IVF/ICSI	<25: 28 Women >25: 24 Women	Women with OHSS grade III or IV	Pregnancy rate OHSS grade I and II rate Mean no. of eggs Mean no. of fertilized eggs	Pregnancy defined as biochemical pregnancy.
Dechaud et al. (2006), 573 women, 789 cycles, retrospective (September 2003–May 2005), IVF/ICSI	<20: 186 Women, 264 cycles 20–25: 283 Women, 394 cycles 25–30: 68 Women, 83 cycles ≥30: 36 Women, 48 cycles	Women with a history of uterine surgery, who had apparent endometrial pathologies or hydrosalpinges, who had 3 or more attempts of IVF and embryo transfer, or who received frozen–thawed embryos Women not on long protocol PGD patients	Duration and dose of FSH No. of oocytes collected Implantation rate Clinical pregnancy rate Miscarriage rate	PCOS patients included BMI at initial consultation
Dorkas et al. (2006), 1293 women, retrospective (January 1995–April 2005), IVF/ICSI	<25: 683 Women 25–29.9: 295 Women 30–39.9: 236 Women ≥40: 79 Women	Women ≥38 years of age Day-2 embryo transfer cycles Cryopreserved embryo transfers Donor oocyte cycles	Cancellation rate Days of stimulation No. of follicles aspirated No. of mature oocytes	Women during their first fresh IVF cycle Long protocol or microdose flare protocol Day-3 or day-5 embryo transfer Miscarriage defined as pregnancy loss up to 20 weeks of gestation

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Table 1 (*continued*)

	BMI group (kg/m²) and numbers	*Exclusion criteria*	*Outcome measures*	*Comments*
		GIFT cycles	Fertilization rate Transfer rate OHSS Clinical pregnancy rate Miscarriage rate Delivery rate	
Mitwally et al. (2006), 183 cycles, cohort, IVF	<25: 102 Cycles ≥25: 81 Cycles		Clinical pregnancy rate	Controlled for confounding variables: women's age, infertility diagnosis and duration, no. of prior IVF cycles, ovarian stimulation protocol
Metwally et al. (2007), 426 cycles, retrospective (January 2001–January 2006), IVF/ICSI	19–24.9: 241 Women 25–29.9: 113 Women ≥30: 72 Women	Women with unknown BMI	Dose and duration of FSH No. of oocytes collected Clinical pregnancy rate	Cycles stratified into two age groups, <35 years and ≥35 years PCOS not excluded
Moini et al. (2008), 287 women, cross-sectional (2002–2003), IVF/ICSI	20–25: 133 Women >25–30: 117 Women >30: 37 Women	Age ≥40 years BMI<20 Hypo/hyperthyroidism, hyperprolactinaemeia, diabetes type 1	No. of oocytes Clinical pregnancy rate Miscarriage rate	Only non-PCOS patients included Day-2 embryo transfer Clinical pregnancy defined as presence of gestational sac with fetal heart activity detected by sonography
Sneed et al. (2008), 1273 cycles, retrospective (January 2005–March 2006), IVF	<18.5: 28 Women >18.5–24.9: 613 Women >25–29.9: 325 Women >30: 307 Women	Frozen embryo transfer Donor oocyte cycles Gestational surrogacy cycles	Cancelled cycles Oocytes retrieved Pregnancies Spontaneous abortion Clinical pregnancies Live births	Only first treatment cycles for each patent analysed Clinical pregnancy defined as presence of gestational sac on ultrasound

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Table 1 (*continued*)

	BMI group (kg/m²) and numbers	*Exclusion criteria*	*Outcome measures*	*Comments*
Lenoble et al. (2008), 846 women, 1444 cycles, retrospective, IVF/ICSI	≤18: 43 Women, 68 cycles 18–25: 607 Women, 1045 cycles ≥25: 196 Women, 331 cycles	Women with unknown BMI and oocyte donation cycles	Pregnancy rate Clinical pregnancy rate Cancelled cycles Miscarriage rate	Different stimulation cycles used Clinical pregnancy defined as presence of gestational sac Early miscarriage defined as <15 weeks of gestation Later miscarriage defined as ≥15 weeks of gestation
Esinler et al. (2008), 775 women, 1113 cycles, retrospective, ICSI	18.5–24.9: 451 Women, 627 cycles 25–29.9: 222 Women, 339 cycles ≥30: 102 Women, 147 cycles	Freeze–thaw cycles Female age > 40 years History of irregular menstrual cycle Presence of PCOS Patients suspected of having a poor ovarian response	Dose and duration of FSH No. of oocytes Fertilization rate Clinical pregnancy rate No. of miscarriages	BMI immediately prior to initiating ICSI cycle Day-3 embryo transfer Clinical pregnancy defined as presence of intrauterine gestational sac with heartbeat at ultrasonography and/or presence of trophoblastic tissue in dilatation and curettage pathology specimen
Martinuzzi et al. (2008), 417 women, retrospective (October 2004–December 2006), IVF/ICSI	<18.5: 21 Women 18.5–24.9: 267 Women 25–29.9: 77 Women ≥30: 52 Women	Women > 35 years old Only women included with cycle day-3 FSH < 10 IU/l and oestradiol < 80 pg/ml	No. of oocytes retrieved Implantation rate Clinical pregnancy rate	First cycles only Clinical pregnancy defined as presence of a gestational sac Ongoing pregnancy defined as the presence of fetal heart tones at 8–9 weeks of gestation Division into PCOS and non-PCOS patients
Orvieto et al. (2009a), 100 cycles, retrospective during a 4-year period, IVF	≤25: 42 Women >25: 58 Women	Non-PCOS patients excluded	No. of oocytes Fertilization rate Pregnancy rate	Only PCOS patients undergoing either agonist or antagonist stimulation Clinical pregnancy defined as visualization of gestational sac and fetal cardiac activity on ultrasound

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Table 1 (*continued*)

	BMI group (kg/m²) and numbers	*Exclusion criteria*	*Outcome measures*	*Comments*
Bellver et al. (2010), 6500 cycles, retrospective (January 2001–April 2007), IVF/ICSI	<20: 1070 Cycles 20–24.9: 3930 Cycles 25–29.9: 1081 Cycles ≥30: 419 Cycles	None stated	Gonadotrophin dose Implantation rate Pregnancy rate Early pregnancy loss rate Clinical miscarriage rate Live-birth rate	Embryo transfer day 2, 3, 5 or 6 Miscarriage defined as pregnancy failing to reach 22nd week of gestation Life birth defined as fetus born alive beyond 22nd week
Rittenberg et al. (2011), 413 women, cohort (January 2006–March 2010), IVF/ICSI	18.5–24.9: 244 Women ≥25: 169 Women	<18.5 Women > 40 years old PGD cycles Donated oocyte cycles Embryos frozen for fertility preservation Pregnancies in women with Müllarian duct anomalies Pregnancies resulting in monozygotic twin gestation	Dose and duration of FSH No. of oocytes retrieved Fertilization rate Embryo quality Clinical pregnancy rate Implantation rate Miscarriage rate Ongoing pregnancy rate	Single blastocyst transfers only following fresh and cryo–thawed cycles Only first pregnancy during the study period included Miscarriage defined as pregnancy loss <20 weeks Clinical pregnancy defined as gestational sac with fetal heart beat on ultrasound scan week 4–5 after embryo transfer BMI measured within 1 month of starting treatment
Farhi et al. (2010), 233 cycles, retrospective (2006–2007), IVF	≤25: 160 Cycles >25: 73 Cycles	Women ≥38 years old ≥3 previous IVF attempts Other than 2 high-quality embryos Women with hydrosalpinx, fibroid uterus, congenital uterine anomaly, chronic illness	Dose and duration of gonadotrophins No. of oocytes retrieved Implantation rate Pregnancy rate	Only data for first cycle included Different stimulation cycles used Day-2 or -3 embryo transfers Clinical pregnancy defined as intrauterine gestational sac with fetal pole with heart beat on scan 4 weeks after embryo transfer Only embryo transfers included when 2 top-quality could be transferred (two 4-cell grade I on day 2 or two 7–8 cell on day 3)

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Table 1 (*continued*)

	BMI group (kg/m²) and numbers	*Exclusion criteria*	*Outcome measures*	*Comments*
Zhang et al. (2010), 2628 women, retrospective (January 2002–May 2008), IVF/ICSI	18.5–25: 2222 Women >25–29.9: 379 Women ≥30: 27 Women	Endometriosis stage III or IV >2 failed IVF or ICSI cycles PGD cycles Frozen–thawed embryo transfers	Days and dose of stimulation No. of oocytes retrieved Pregnancy rate Miscarriage rate Ongoing pregnancy rate Live-birth rate	Long stimulation protocols only PCOS patients included Only first treatment cycles included Clinical pregnancy defined by visualization of gestational sac and cardiac activity 6 weeks after embryo transfer Miscarriage defined as pregnancy loss <12 full weeks of gestation Only Chinese women
Kilic et al. (2010), 1970 women, retrospective (January 2006–September 2008)	18–24.9: 718 Women 25–29.9: 470 Women ≥30: 782 Women	Endometriosis stage III or IV PCOS Hypogonotrophic hypogonadism	Clinical pregnancy rate	Also subdivided groups to look at poor responders Clinical pregnancy defined as fetal cardiac activity seen at ultrasound 4–6 weeks after embryo transfer
Chueca et al. (2010), 5719 cycles, retrospective (January 2000–December 2008), IVF	<20: 1289 Cycles 20–25: 3382 Cycles >25–30: 755 Cycles >30: 293 Cycles	FSH > 13 mIU/ml	No. of oocytes retrieved Implantation rate Clinical pregnancy rate Miscarriage rate	
Sathya et al. (2010), 308 women, retrospective, IVF	<25: 88 Women 25–30: 147 Women >30: 73 Women	Donor cycles Women > 40 years Women with FSH > 10 mIU/ml	Gonadotrophin dose Clinical pregnancy rate Miscarriage rate	Only long agonist protocols were used
Vilarino et al. (2010), 385 women, 488 cycles, retrospective, IVF/ICSI	<25: 257 Women, 321 cycles ≥25: 128 Women, 167 cycles		Duration of stimulation Pregnancy rate Miscarriage rate Live-birth rate	Patients with PCOS included Pregnancy defined as positive serum hCG 12 days after embryo transfer Clinical pregnancy defined as gestational sac with a embryo and fetal heartbeat seen on scan after 5 weeks gestation Miscarriage defined as a pregnancy loss before 22 weeks gestation

BMI = body mass index; GIFT = gamete intra-Fallopian transfer; HCG = human chorionic gonadotrophin; ICSI = intracytoplasmic sperm injection; OHSS = ovarian hyperstimulation syndrome; PCOS = polycystic ovary syndrome PGD = preimplantation genetic diagnosis.

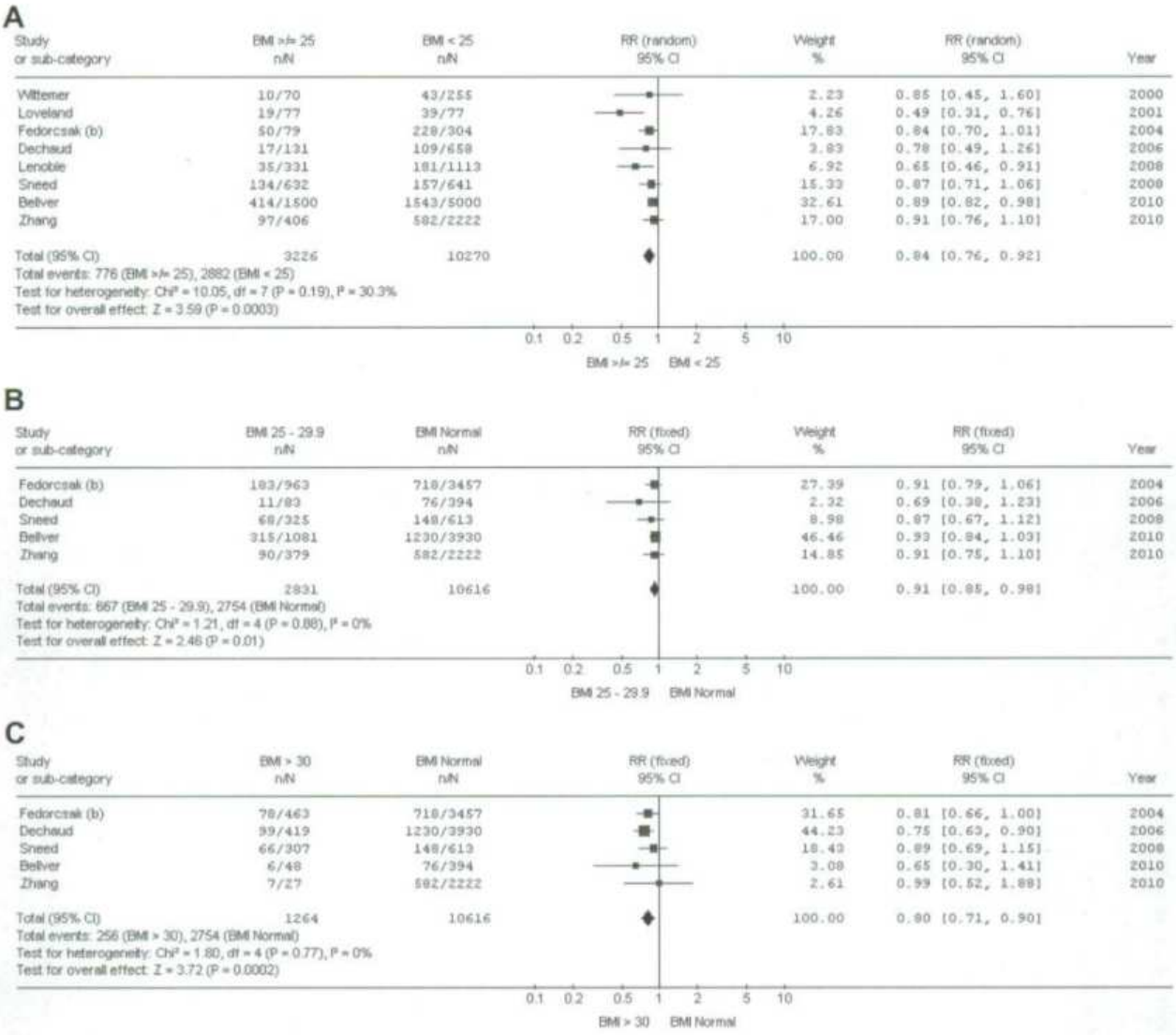

Figure 2 Meta-analysis of live-birth rate data for different body mass index (BMI) categories: (A) BMI $< 25\ kg/m^2$ versus BMI $\geq 25\ kg/m^2$; (B) normal BMI versus BMI 25–29.9 kg/m^2; and (C) normal BMI versus BMI $\geq 30\ kg/m^2$.

0.85–0.98, $P = 0.01$; **Figure 2**B). There was no significant heterogeneity between the included studies ($I^2 = 0\%$).

Normal BMI versus BMI $\geq 30\ kg/m^2$: pooling the results from five studies that reported live birth as an outcome showed a statistically significant reduction in the live-birth rate in women with BMI $\geq 30\ kg/m^2$ compared with women with normal BMI (RR 0.80, 95% CI: 0.71–0.90, $P = 0.0002$; **Figure 2**C). There was no significant heterogeneity between the included studies ($I^2 = 0\%$).

Secondary outcome

Clinical pregnancy rate

BMI $< 25\ kg/m^2$ versus BMI $\geq 25\ kg/m^2$: pooled analysis from 25 studies showed a significant reduction in the clinical pregnancy rate in women with BMI $< 25\ kg/m^2$ compared with women with BMI $\geq 25\ kg/m^2$ (RR 0.90, 95% CI 0.85–0.94, $P < 0.0001$; **Figure 3**A). There was significant heterogeneity between the included studies ($I^2 = 50.8\%$, $P = 0.002$).

Normal BMI versus BMI 25–29.9 kg/m^2: pooled analysis from 16 studies showed a significant reduction in the clinical pregnancy rate in women with BMI 25–29.9 kg/m^2 compared with women with normal BMI (RR 0.91, 95% CI 0.86–0.96, $P = 0.0003$; **Figure 3**B). There was no significant heterogeneity between the included studies ($I^2 = 34.6\%$).

Normal BMI versus BMI $\geq 30\ kg/m^2$: pooled studies from 15 studies showed that there was a significant reduction in the clinical pregnancy rate in women with BMI $\geq 30\ kg/m^2$ compared with those with normal BMI (RR 0.87, 95% CI 0.80–0.95, $P = 0.002$; **Figure 3**C). There was significant heterogeneity between the included studies ($I^2 = 61.8\%$, $P = 0.0008$).

Miscarriage rate

BMI $< 25\ kg/m^2$ versus BMI $\geq 25\ kg/m^2$: pooled analysis from 22 studies showed a statistically significant increase in the miscarriage rate in women with BMI $\geq 25\ kg/m^2$ compared with women with BMI $< 25\ kg/m^2$ (RR 1.31, 95% CI 1.18–1.45, $P < 0.00001$; **Figure 4**A). The I^2 value was 47.9%

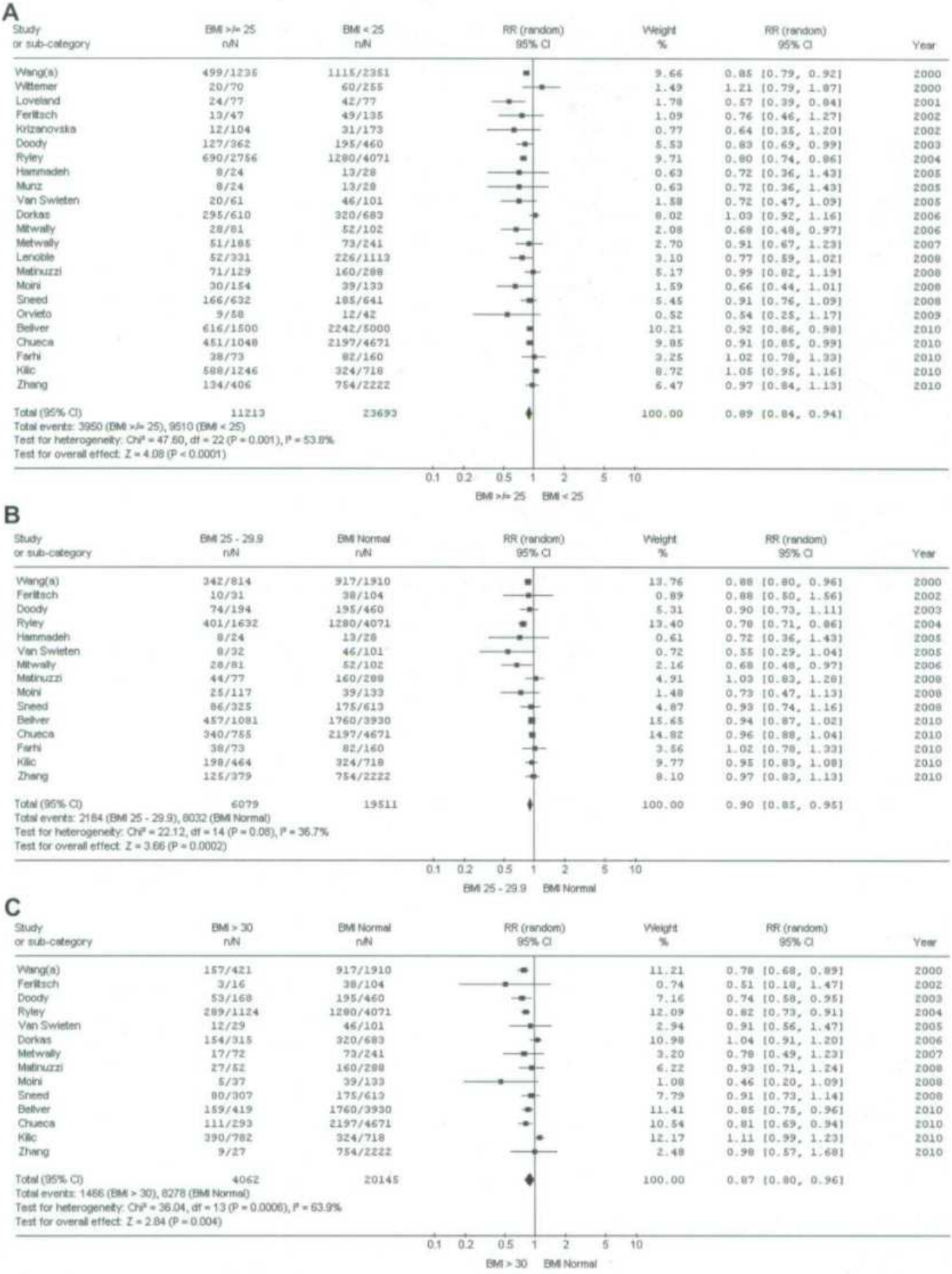

Figure 3 Meta-analysis of clinical pregnancy rate data for different body mass index (BMI) categories: (A) BMI $< 25\ kg/m^2$ versus BMI $\geq 25\ kg/m^2$; (B) normal BMI versus BMI 25–29.9 kg/m^2; and (C) normal BMI versus BMI $\geq 30\ kg/m^2$.

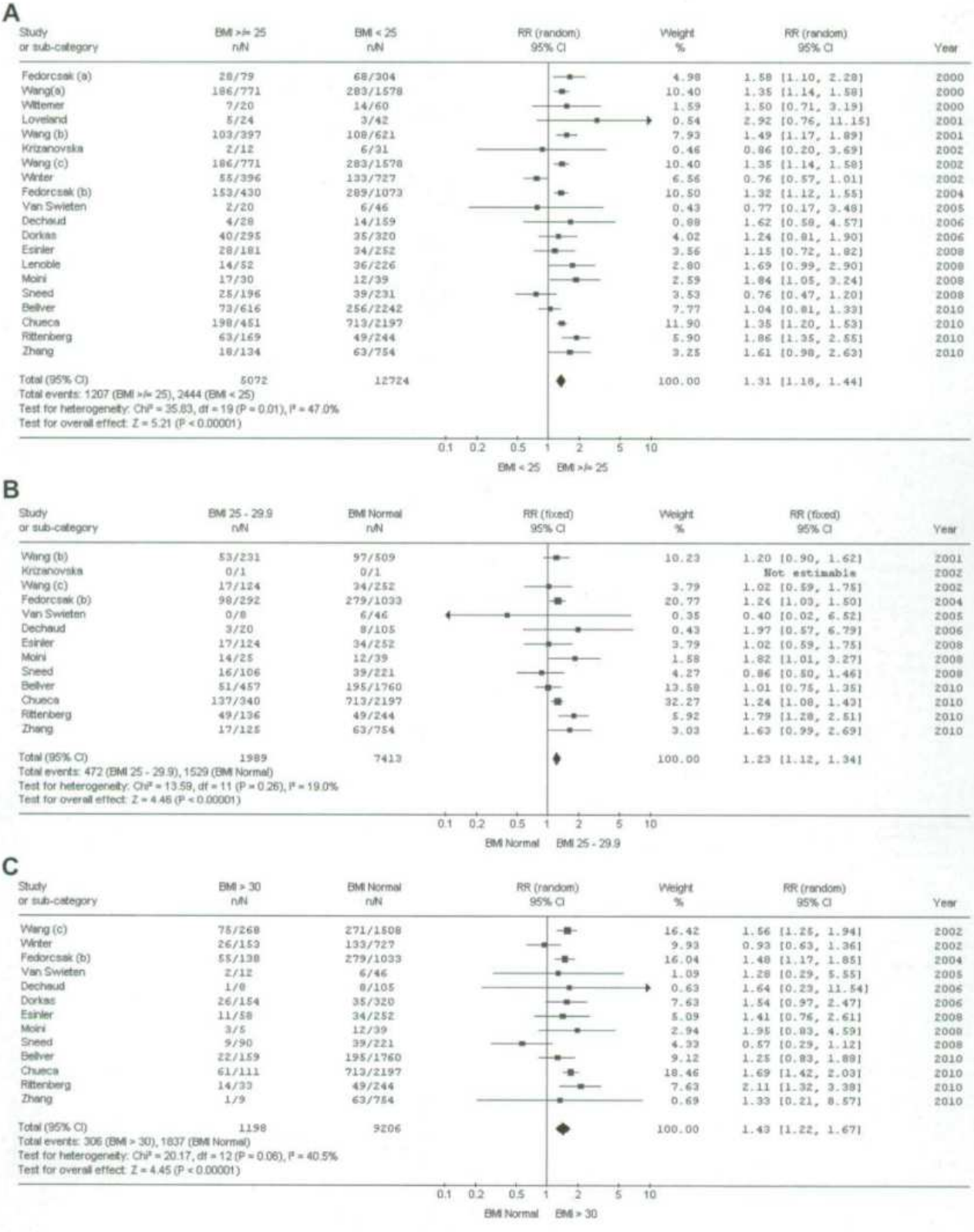

Figure 4 Meta-analysis of miscarriage rate data for different body mass index (BMI) categories: (A) BMI $< 25\ kg/m^2$ versus BMI $\geq 25\ kg/m^2$; (B) normal BMI versus BMI 25–29.9 kg/m^2; and (C) normal BMI versus BMI $\geq 30\ kg/m^2$.

indicating no significant heterogeneity in the included studies.

Normal BMI versus BMI 25–29.9 kg/m^2: pooled analysis from 14 studies showed a statistically significant higher rate of miscarriage in women with BMI 25–29.9 kg/m^2 compared with women with normal BMI (RR 1.24, 95% CI 1.13–1.35, $P = 0.001$; **Figure 4**B). There was no significant heterogeneity between the included studies ($I^2 = 22.4\%$).

Normal BMI versus BMI $\geq$30 kg/m^2: pooled analysis from 14 studies showed that the miscarriage rate was significantly higher in the group with BMI $\geq$30 kg/m^2 (RR 1.36, 95% CI 1.13–1.64, $P = 0.001$ **Figure 4C**). There was significant heterogeneity between the included studies ($I^2 = 56.4\%$, $P = 0.005$).

Other outcome measures

Duration of gonadotrophin stimulation

BMI < 25 kg/m^2 versus BMI $\geq$25 kg/m^2: pooled analysis from two studies (Farhi et al., 2010; Rittenberg et al., 2011) showed that the duration of gonadotrophin stimulation was significantly longer in women with BMI $\geq$25 kg/m^2 compared with women with BMI < 25 kg/m^2 (Weighted mean difference (WMD) 0.88, 95% CI 0.49–1.27, $P < 0.0001$). There was no significant heterogeneity between the included studies ($I^2 = 0\%$).

Normal BMI versus BMI 25–29.9 kg/m^2: pooled analysis from five studies (van Swieten et al., 2005; Dechaud et al., 2006; Dorkras et al., 2006; Esinler et al., 2008; Zhang et al., 2010) showed that the duration of gonadotrophin stimulation was significantly longer in women with BMI 25–29.9 kg/m^2 compared with women with normal BMI (WMD 0.22, 95% CI 0.21–0.23, $P < 0.00001$). There was no significant heterogeneity between the included studies ($I^2 = 0\%$).

Normal BMI versus BMI $\geq$30 kg/m^2: pooled analysis from five studies (van Swieten et al., 2005; Dechaud et al., 2006; Dorkras et al., 2006; Esinler et al., 2008; Zhang et al., 2010) showed that the duration of gonadotrophin stimulation was significantly longer in women with BMI $\geq$30 kg/m^2 compared with women with normal BMI (WMD 0.27, 95% CI 0.26–0.28, $P < 0.00001$). There was no significant heterogeneity between the included studies ($I^2 = 0\%$).

Dose of gonadotrophin stimulation

BMI < 25 kg/m^2 versus BMI $\geq$25 kg/m^2: pooled analysis from two studies (Farhi et al., 2010; Vilarino et al., 2010) showed that there was no statistically significant difference in the dose of gonadotrophin stimulation in women with BMI $\geq$25 kg/m^2 compared with women with BMI < 25 kg/m^2.

Normal BMI versus BMI 25–29.9 kg/m^2: pooled analysis from five studies (Dechaud et al., 2006; Esinler et al., 2008; Bellver et al., 2010; Sathya et al., 2010; Zhang et al., 2010) showed a higher dose of gonadotrophin stimulation in women with BMI 25–29.9 kg/m^2 compared with women with normal BMI (WMD 137.92, 95% CI 41.25–234.60, $P = 0.005$). There was a significant heterogeneity between the included studies ($I^2 = 61.2\%$).

Normal BMI versus BMI $\geq$30 kg/m^2: pooled analysis from five studies (Dechaud et al., 2006; Esinler et al., 2008; Bellver et al., 2010; Sathya et al., 2010; Zhang et al., 2010) showed a higher dose of gonadotrophin stimulation in women with BMI $\geq$30 kg/m^2 compared with women with normal BMI (WMD 406.77, 95% CI 169.26–644.2, $P = 0.0008$). There was significant heterogeneity between the included studies ($I^2 = 80.8\%$).

Number of oocytes retrieved

There was no significant difference in number of ooctyes retrieved in the different study groups.

Peak oestradiol concentrations

There was no significant difference in peak oestradiol concentrations in the different study groups.

Discussion

Obesity has become a worldwide epidemic. Consequently, an increasing number of overweight and obese women are seeking fertility through assisted reproduction technology. Thus, the impact of raised BMI on the outcome of IVF treatment is of interest to patients, clinicians and policy makers.

The results of this review indicate that women who are overweight or obese (BMI $\geq$25 kg/m^2) have a poorer outcome following IVF treatment compared with women with normal BMI. Unlike the previous systematic reviews (Maheshwari et al., 2007; Metwally et al., 2008), the current review and meta-analysis is able to clearly demonstrate that raised BMI is associated with a significantly reduced live-birth rate and increased miscarriage rate after IVF treatment.

This review has also allowed separate evaluation of the impact of being overweight or obese on IVF outcome. The results demonstrate that the poorer outcome of IVF treatment is not limited to women with BMI $\geq$30 kg/m^2; overweight women (BMI 25–29.9 kg/m^2) also have significantly lower pregnancy and live-birth rates and higher miscarriage rate after IVF treatment compared with women with normal BMI. The study results also confirm the trend towards a poorer outcome with rising BMI. This dose–effect relationship has been previously suggested (Ferlitsch et al., 2004; Van der Steeg et al., 2008; Bellver et al., 2010). The current data show that, on average, the live-birth rate is reduced by 9% (95% CI 2–15%) in overweight women compared with a 20% reduction (95% CI 12–29%) in the obese group.

The validity of the current results depends on the quality of individual studies included in this review. Data were aggregated from a considerable number of large observational studies and only studies which adopted the WHO classification of BMI were included. However, like previous reviews, these results are not completely free from bias and should be interpreted with caution. For example, considerable methodological and clinical heterogeneity was encountered amongst the included studies, particularly in relation to study population characteristics and definition of the relevant outcome measures.

In addition, this study was not able to adjust for important confounders such as patient age, cause and duration of infertility, ovarian stimulation protocol used and number and quality of embryos transferred, all of which varied among the included studies. In an attempt to reduce heterogeneity, 23 studies that did not follow the WHO classification of BMI or did not have any results in the overweight or obese group analysis that could be used for analysis were excluded (Hédon et al., 1991; Lashen et al., 1999; Salha et al., 2001; Nichols et al., 2003; Kolibianakis et al., 2003; Merryman et al., 2003; Frattarelli and Kodama, 2004; Spandorfer et al., 2004; Ku et al., 2006; Thum et al., 2007; Veleva et al., 2008; Matalliotakis et al., 2008; Ashkenazi et al., 2009; Jungheim et al., 2009; Awartani et al., 2009; Orvieto et al., 2009b; Kumbak et al., 2010; Xing et al., 2010; Guan et al., 2010; Li et al., 2010; Kjotrod et al., 2010; Chen et al., 2010; Kahraman et al., 2010).

Although it was not possible to exclude women who had BMI < 18.5 kg/m^2 from the group of women who were reported as having BMI < 25 kg/m^2 from the data provided in 18 studies (Fedorcsak et al., 2000; Loveland et al., 2001; Ferlitsch et al., 2002; Doody et al., 2003; Ryley et al., 2004; van Swieten et al., 2005; Hammadeh et al., 2005; Munz et al., 2005; Dechaud et al., 2006; Dorkras et al., 2006; Mitwally et al., 2006; Moini et al., 2008; Orvieto et al., 2009a; Farhi et al., 2010; Bellver et al., 2010; Chueca et al., 2010; Vilarino et al., 2010; Sathya et al., 2010), including these women in the current analysis has probably resulted in underestimation of the detrimental effect of raised BMI, as a low BMI (<18.5 kg/m^2) is known to be associated with a poorer IVF outcome (Veleva et al., 2008). Furthermore, the subgroup analysis followed the WHO criteria for overweight (BMI ≥25–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) in order to provide an accurate comparison of normal versus increased BMI (Wang et al., 2000–2002; Doody et al., 2003; Ryley et al., 2004; Fedorcsak et al., 2004; Dorkras et al., 2006; Metwally et al., 2007; Sneed et al., 2008; Esinler et al., 2008; Martinuzzi et al., 2008; Bellver et al., 2010; Zhang et al., 2010; Kilic et al., 2010).

Despite the methodological shortcomings of the available literature, there was limited statistical heterogeneity in this study's results, which corroborates those of previous reviews and confirms the detrimental effect of raised BMI on IVF outcome. In support of the current findings, the negative impact of raised BMI on IVF outcome was also confirmed in a recent meta-analysis of randomized controlled trails evaluating the use of single-embryo transfer in IVF (McLernon et al., 2010), which showed that for every unit increase in BMI the odds of a preterm birth ≤32 weeks increased by 16% (1.16, 1.04–1.30, $P = 0.01$).

Successful implantation and continuation of pregnancy depend on close interactions between the embryo and the endometrium. Raised BMI is associated with a variety of key endocrine and paracrine changes which could adversely affect oocyte maturation and embryonic competence. These include hyperandrogenaemia (Brewer and Balen, 2010), insulin resistance (Dumesic et al., 2008), abnormal leptin concentrations and LH hypersecretion (Qiao and Feng, 2011). In addition, alterations in serum concentrations of insulin-like growth factors, which are involved in cell proliferation and differentiation, and their binding proteins could influence folliculogenesis, oocyte maturation and embryo development (Wang et al., 2006; Fowke et al., 2010). Furthermore, BMI correlates with endometrial and intra-follicular concentrations of the inflammatory markers, interleukin 6 and tumor necrosis factor α, both of which have been associated with poor oocyte quality, impaired implantation and increased risk of miscarriage, and thus could mediate the effect of obesity on IVF outcome (Lee and Loke, 2000; Gosman et al., 2006; Ma et al., 2010; Dimitriadis et al., 2010).

Future studies examining the relationship between BMI and IVF outcome should strictly conform with WHO standardized classification of BMI categories and account for important confounders such as age, cause of infertility, particularly polycystic ovary syndrome, and quality of embryos transferred (Anderson et al., 2000; van der Spuy and Dyer, 2004; Hourvitz et al., 2006; Homburg, 2006; Lambers et al., 2006; Maconochie et al., 2007). In addition, since only one cycle per women should be included in these studies, reporting rates per woman rather than per cycle would provide a more robust analysis.

The findings of this review can empower clinicians to provide more detailed advice regarding the impact of raised BMI on treatment outcome before starting an IVF cycle. Ideally, the advice given can be complemented with information on the effect of weight loss on IVF treatment outcome. Ferlitsch et al. (2004) have reported that for each unit reduction in BMI the odds of achieving a pregnancy following IVF could improve by 19%. Therefore, weight loss should be encouraged in overweight and obese women, while at the same time clinicians should facilitate access to effective weight-loss programmes to enable women to achieve a better treatment outcome.

In conclusion, this systematic review and meta-analysis clearly demonstrates that raised BMI has an adverse effect on IVF treatment outcome. It significantly reduces pregnancy and live-birth rates and increases miscarriage rate. This effect is present in overweight as well as obese women. Further studies are needed to enhance the understanding of the underlying mechanisms for this effect.

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