Human Reproduction Update, Vol.25, No.4 pp. 439–451, 2019
Advanced Access publication on March 4, 2019 doi:10.1093/humupd/dmz011

human reproduction update

Female obesity is negatively associated with live birth rate following IVF: a systematic review and meta-analysis

Nathalie Sermondade[1], Stéphanie Huberlant[2], Vanessa Bourhis-Lefebvre[3], Elisangela Arbo[4], Vanessa Gallot[5], Marina Colombani[3], and Thomas Fréour [6,*]

[1]Service de Biologie de la Reproduction, Hôpital Tenon, Hôpitaux Universitaires Est Parisien, Assistance Publique—Hôpitaux de Paris, PARIS 75020, France [2]Département de Gynécologie Obstétrique et Médecine de la Reproduction, CHU Carémeau, NIMES 30029, France [3]Institut de Médecine de la Reproduction, Marseille 13008, France [4]Gedeon Richter France, Paris 75009, France [5]Service de Médecine de la Reproduction et Préservation de la Fertilité, Hôpital Antoine Béclère, Assistance Publique—Hôpitaux de Paris, Clamart 92140, France [6]Service de biologie et médecine de la reproduction, CHU de Nantes, NANTES 44093, France—Faculté de médecine, Université de Nantes, France—INSERM UMR1064, Nantes 44093, France

*Correspondence address. Pr Thomas FREOUR, Service de biologie et médecine de la reproduction, CHU de Nantes, Nantes 44093, France. Tel: +33 2 40 08 32 34. E-mail: thomas.freour@chu-nantes.fr orcid.org/0000-0002-7243-7709

Submitted on November 14, 2018; resubmitted on February 19, 2019; editorial decision on February 27, 2019; accepted on February 28, 2019

TABLE OF CONTENTS

BACKGROUND: A worldwide increase in the prevalence of obesity has been observed in the past three decades, particularly in women of reproductive age. Female obesity has been clearly associated with impaired spontaneous fertility, as well as adverse pregnancy outcomes. Increasing evidence in the literature shows that obesity also contributes to adverse clinical outcomes following *in vitro* fertilization (IVF) procedures. However, the heterogeneity of the available studies in terms of populations, group definition and outcomes prevents drawing firm conclusions. A previous meta-analysis published in 2011 identified a marginal but significant negative effect of increased female body mass index (BMI) on IVF results, but numerous studies have been published since then, including large cohort studies from national registries, highlighting the need for an updated review and meta-analysis.

OBJECTIVE AND RATIONALE: Our systematic review and meta-analysis of the available literature aims to evaluate the association of female obesity with the probability of live birth following IVF. Subgroup analyses according to ovulatory status, oocyte origin, fresh or frozen-embryo transfer and cycle rank were performed.

SEARCH METHODS: A systematic review was performed using the following key words: ('obesity', 'body mass index', 'live birth', 'IVF', 'ICSI'). Searches were conducted in MEDLINE, EMBASE, Cochrane Library, Eudract and clinicaltrial.gov from 01 January 2007 to 30 November 2017. Study selection was based on title and abstract. Full texts of potentially relevant articles were retrieved and assessed for inclusion by two reviewers. Subsequently, quality was assessed using the Newcastle-Ottawa Quality Assessment Scales for patient selection, comparability and assessment of outcomes. Two independent reviewers carried out study selection and data extraction according to Cochrane methods. Random-effect meta-analysis was performed using Review Manager software on all data (overall analysis), followed by subgroup analyses.

OUTCOMES: A total of 21 studies were included in the meta-analysis. A decreased probability of live birth following IVF was observed in obese (BMI ≥ 30 kg/m^2) women when compared with normal weight (BMI 18.5–24.9 kg/m^2) women: risk ratio (RR) (95% CI) 0.85 (0.82–0.87). Subgroups analyses demonstrated that prognosis was poorer when obesity was associated with polycystic ovary syndrome, while the oocyte origin (donor or non-donor) did not modify the overall interpretation.

WIDER IMPLICATIONS: Our meta-analysis clearly demonstrates that female obesity negatively and significantly impacts live birth rates following IVF. Whether weight loss can reverse this deleterious effect through lifestyle modifications or bariatric surgery should be further evaluated.

Key words: female obesity / IVF / BMI / live birth rate / ART / meta-analysis

Introduction

A worldwide increase in the prevalence of obesity has been observed in the past three decades (Finucane *et al.*, 2011, Ng *et al.*, 2014), with 13% of the general population being obese in 2016 (WHO, 2018). This increase concerns both sexes and all age groups, with more than half of women of reproductive age being overweight (defined by BMI ≥ 25 kg/m^2) or obese (BMI ≥ 30 kg/m^2) (Flegal *et al.*, 2012; Gallus *et al.*, 2015).

Female obesity has been clearly associated with several adverse pregnancy outcomes, such as miscarriage, hypertension, pre-eclampsia and diabetes (Jungheim *et al.*, 2011; Hawkins Bressler *et al.*, 2015). Obesity also leads to impaired fertility, mainly due to anovulation (Rich-Edwards *et al.*, 2002). Yet other factors may also be involved, since time to conception for obese women is longer than in normal weight women, even in the case of regular menstrual cycles (Gesink Law *et al.*, 2007).

The obese infertile female population is characterized by poorer *in vitro* fertilization (IVF) outcomes, such as use of higher doses of gonadotrophins, increased cycle cancellation rate, lower oocyte recovery and increased miscarriage rate (Maheshwari *et al.*, 2007; Koning *et al.*, 2012). Growing evidence in the literature shows that obesity impacts clinical outcomes following IVF procedures. However, the heterogeneity of available studies in terms of populations, group definitions and outcomes described prevents drawing firm conclusions. A previous meta-analysis published in 2011 concluded that increased female BMI was associated significantly with adverse pregnancy outcomes following IVF (Rittenberg *et al.*, 2011). Numerous studies have been published since then, including large cohort studies from national registries, highlighting the need for an updated review and meta-analysis.

This systematic review and meta-analysis aims to evaluate the association between female obesity and live birth rates (LBRs) following IVF. Subgroups analyses were performed according to ovulatory status, oocyte origin, fresh or frozen-embryo transfer and cycle rank. The association between female overweight and LBR was also studied secondarily.

Methods

Literature search strategy and eligibility criteria

The search strategy, selection criteria, data extraction, quality assessment and statistical analyses described below were defined *a priori*. The conduct and reporting of this review was guided by PRISMA guidelines and prospectively registered (PROSPERO: CRD42018090645). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used while writing this review. Cohort studies comparing IVF patients identified as obese according to the World Health Organization (WHO, 2000) (BMI ≥ 30 kg/m^2) versus normal weight (BMI in 18.5–24.9 kg/m^2) were included. As live birth was the outcome of interest, studies were required to report values of live birth for obese and normal weight females. Studies describing only overweight, underweight and/or obese with another cut-off point than BMI ≥ 30 kg/m^2 were excluded.

PubMed, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews were searched for relevant literature. The search strategy was limited to articles published in English or French between 01 January 2007 and 21 June 2017 for all electronic databases, except for Pubmed (end date: 30 November 2017). Further efforts were made to identify all available studies, including searching clinical-trial registries (ClinicalTrials.gov and EU Clinical-trial register) and conference abstracts from ESHRE, and the American Society for Reproductive Medicine, both in 2015 and 2016. The search strategy for electronic databases used the following combined search terms: ('obesity'[MeSH Terms] OR 'obesity'[Title/Abstract] OR 'obese'[Title/Abstract] OR 'body mass index'[MeSH Terms] OR 'body mass index'[Title/Abstract] OR BMI [Title/Abstract]) AND ('live birth'[MeSH Terms] OR 'live birth'[Title/Abstract]) AND ('in vitro fertilization'[Title/Abstract] OR 'fertilization in vitro'[Title/Abstract] OR 'fertilization in vitro'[MeSH Terms] OR 'fertilization in vitro'[Title/Abstract] OR 'in vitro fertilization'[Title/Abstract] OR 'ivf' [Title/Abstract] OR 'sperm injections, intracytoplasmic'[MeSH Terms] OR 'intracytoplasmic sperm injections'[Title/Abstract] OR 'sperm injections, intracytoplasmic'[Title/Abstract] OR 'icsi'[Title/Abstract]) AND (English[lang] OR French[lang]) AND ('humans'[MeSH Terms] OR 'Hum Reprod'[Journal] OR ('women'[MeSH Terms] OR 'women'[All Fields] OR 'woman'[All Fields])).

Study selection and data extraction

Two reviewers (MC and TF) independently performed a screening of titles and abstracts of all articles, clinical studies and abstracts of congresses to exclude citations deemed irrelevant by both observers. Based on the pre-established inclusion criteria, full texts of potentially relevant articles were retrieved and assessed for inclusion by two reviewers (NS and VG, SH and TF, VBL and MC). Any disagreement or uncertainty was resolved by discussion with a third reviewer. The methodological quality of the selected studies was assessed using the Cochrane Handbook methods: patient selection, baseline comparability and outcomes selection and measurement with a total of nine stars were judged using the Newcastle-Ottawa Quality Assessment Scale for cohort studies (Stang, 2010). Data were extracted from included articles by two independent reviewers (NS and VG, SH and TF, VBL and MC) using a data extraction form developed for the present review. All qualifying articles with quantitative data for LBR, with documented numbers for obese females (BMI $\geq$ 30 kg/m^2) and for normal weight females (BMI in [18.5 kg/m^2; 24.9 kg/m^2]) were included in the meta-analysis. No replacement of missing data has been done. When only percentages were available, and when possible, the number of events was derived from total number of cycles/transfer in each population group. Data were not extracted for clinical studies and conference abstracts.

Data synthesis and meta-analysis

The following study details were extracted to characterize the included studies: study authors, publication year, study time frame, country, study design, eligibility criteria, cycle rank, oocyte donation, women with polycystic ovary syndrome (PCOS), fertilization method, type of embryo transfer. For each group (normal weight and obese), the sample size, age, percentage and/or number of live births were noted. When data were dispatched by subgroups in the article (e.g. PCOS and non-PCOS), extracted data were pooled for overall meta-analysis. Dichotomous variables were expressed as risk ratios (RR) and the precision of the estimates was evaluated by the 95% CI. The clinical relevance of all comparisons was assessed based on the precision of the estimates. A random effects model was used to address the differences in true effect size across studies, since it is unlikely that observed differences among study results are due solely to the role of chance.

The software Review Manager 5.3.5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to combine and analyse the results for the meta-analysis. Meta-analysis was performed using a random-effect model with the Mantel–Haenszel (M-H) method. Pooled effect sizes were deemed statistically significant at $P < 0.05$. In addition to computed estimates of between-study variance (Tau2), the statistic heterogeneity across the studies was calculated by chi-square statistic, and inconsistency was judged by the value of I^2 statistic. $I^2 \geq 50\%$ indicates substantial heterogeneity (Higgins *et al.*, 2003). For each study included in the meta-analysis, risk of bias was assessed by two independent reviewers (NS and VG, SH and TF, VBL and MC) using ROBIN-I tools (Sterne *et al.*, 2016): confounding, selection of participants, intervention classification, intervention deviations, missing data, outcome measurement and selection of reported results. Each study was assigned a 'low', 'high' or 'unclear' risk of bias. A funnel plot was used to assess the presence of small-study effects suggestive of publication bias.

Sensitivity analysis

Several pre-specified sensitivity analyses were performed. To explore statistical heterogeneity, meta-analysis using a fixed-effect model was also performed to compare the estimates of the intervention effect of fixed- and random-effect models. Furthermore, sensitivity analysis was performed by excluding the outliers identified in the Funnel plot. To assess the possible impact of study weights, sensitivity analyses were performed. First, a forest plot was displayed in ascending order of study weight and checked visually. Second, studies with a high number of patients were analysed, after lowering their weight under 20%. To verify whether the conclusion would have been different if eligibility was restricted to studies with low risk of bias, another sensitivity analysis was performed though omitting all studies with at least one high risk of bias. Subgroup analyses were performed to separate the distinct kinds of embryo transfer, cycle rank of the IVF, oocyte source and patients diagnosed with PCOS or not.

Results

Study selection

The search strategy identified a total of 486 articles, including duplicates and articles irrelevant to the primary research questions. After removing duplicates, 407 abstracts were reviewed, and 54 full-text articles were assessed for eligibility for quantitative analysis. Among them, 21 articles seemed potentially appropriate to be included in the meta-analysis (Fig. 1).

All 21 eligible studies were cohort studies. The study sample sizes ranged from 117 (Hill *et al.*, 2011) to 494 097 (Kawwass *et al.*, 2016) cycles, for a total of 682 532 cycles (Table I). Study participants were mainly from the USA (McCormick *et al.*, 2008; Sneed *et al.*, 2008; Hill *et al.*, 2011; Luke *et al.*, 2011; Chavarro *et al.*, 2012; Bailey *et al.*, 2014; Schliep *et al.*, 2015; Zhang *et al.*, 2015; Kawwass *et al.*, 2016;

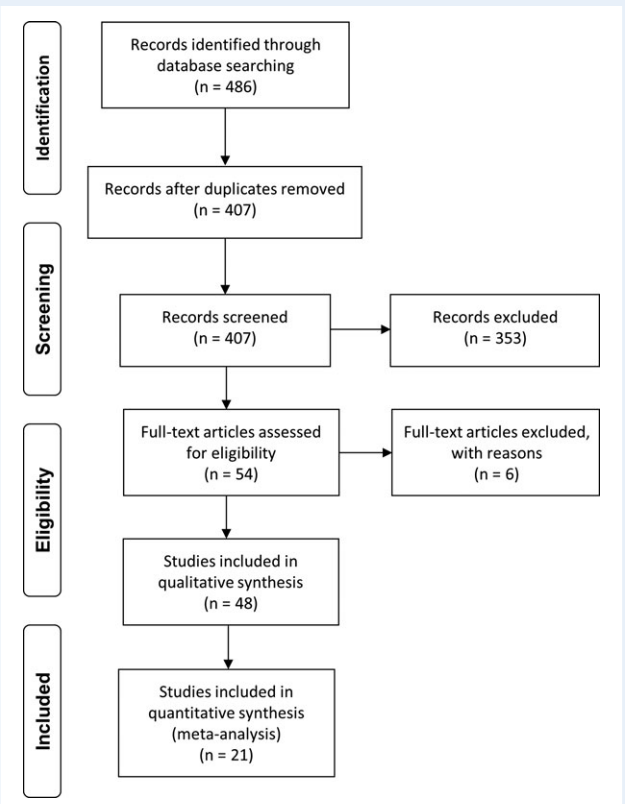

Figure 1 Flow chart of study selection for systematic review and meta-analysis.

Table I Characteristics of studies included in the meta-analysis.

Author, year country	BMI groups[a] and number of cycles			Inclusion criteria	Exclusion criteria	Cycle rank	Autologous or donor oocytes cycle	Ovarian status of the patients	Type of embryo transfer
	Normal 18.5–24.9 kg/m^2	Overweight 25.0–29.9 kg/m^2	Obese ≥ 30.0 kg/m^2						
Bailey *et al.* (2014), USA	51	19	31	Age <40 years, PCOS, IVF	IVM cycles, FSH >10 IU/L, uncontrolled thyroid disease, previous chemotherapy or radiotherapy, recurrent pregnancy loss, uterine factor, translocation, endometriosis or pelvic inflammatory disease, adenomyosis, myoma	All	Autologous	Only PCOS	Fresh
Bellver *et al.* (2010), Spain	3930*	1081	419	All cycles performed	Not specified	All	Not specified	Not specified	Fresh
Bellver *et al.* (2013), Spain	5706*	1770	653	First donor cycle, donor being of normal BMI and 18–35 years	Not specified	First	Donor	Not specified	Both
Chavarro *et al.* (2012), USA	103*	46	37	Not specified	Not specified	Not specified	Autologous	Both	Fresh
Hill *et al.* (2011), USA	58	38	21	Age 19–42 years, FSH <12 IU/L	FSH ≥12 IU/L, age >42 years	Not specified	Not specified	Not specified	Fresh
Insogna *et al.* (2017), USA	288	106	59	Initial frozen-embryo transfer cycles	Not specified	First	Both	Both	Frozen-thawed
Kawwass *et al.* (2016), USA	271 985	116 788	91 646	All fresh cycles from this time period for which BMI data are available	Cancellation, missing BMI data, cryopreservation with no fresh transfer	All	Autologous	Not specified	Fresh
Luke *et al.* (2011), USA	25 860	10 581	7467	Cycles resulting in transfer of one or more embryos, heigh and weight recorded	Not specified	Not specified	Both	Not specified	Both
McCormick *et al.* (2008), USA	64		30	Age <42 years, fresh non-donor IVF	Not specified	All	Autologous	Both	Fresh
Petanovski *et al.* (2011), Macedonia	533	255	99	First cycle, IVF or ICSI, no donor	Not specified	First	Autologous	Both	Fresh
Pinborg *et al.* (2011), Denmark	702	257	178	IVF, ICSI or frozen-embryo transfer	Not specified	All	Not specified	Not specified	Both
Provost *et al.* (2016a), USA	134 588	54 822	42 508	All fresh cycles from this time period for which physiologically reasonable data had been entered for height and weight	BMI >48; BMI <16	All	Autologous	Both	Fresh
Provost *et al.* (2016b), USA	13 058	5394	3228		Height <48 inches and weight <70 pounds	All	Donor	Not specified	Fresh

Russo *et al.* (2017), USA	294	64	112	First embryo transfer, age <40 years, single top-quality autologous blastocyst transfer	Congenital uterine anomalies, endometrial polyps, intrauterine synechiae, adenomyosis, intra-cavitary fibroids, hydrosalpinges, donor embryo transfer, age >40 years	First	Autologous	Not specified	Both
Schliep *et al.* (2015), USA	407	147	135	Patients undergoing first fresh IVF cycle	Men with non-obstructive azoospermia	First	Not specified	Not specified	Fresh
Sharma (2014), India	208	213	69	Fresh IVF/ICSI cycles, non-donor, age 25–35 years	Age >35 years, frozen-embryo transfer, donor and gestational surrogacy cycles, accompanying medical problem which may lead to abnormal BMI	Not specified	Autologous	Not specified	Fresh
Sneed *et al.* (2008), USA	613	325	307	First fresh non-donor cycle, age 21–44 years	Frozen-embryo transfer, donor oocyte and gestational surrogacy cycles	First	Autologous	Both	Fresh
Sifer *et al.* (2014), France	260	90	59	Age <37 years, first or second IVF cycle, at least two good quality embryos, including at least one top-quality embryo	Single Embryo Transfer for obstetrical cause	All	Not specified	Not specified	Fresh
Zander-Fox *et al.* (2012), Australia	1065	486	506	Gonadotropin-stimulated cycles involving oocyte retrieval and insemination with either partner or donor sperm, age <38 years	Donor cycle, natural cycle	All	Autologous	Not specified	Fresh
Zhang *et al.* (2010), China	2222	379	27	First cycle, receiving aGnRH and r-FSH stimulation protocol	Severe endometriosis, PGD, frozen-embryo transfer	First	Not specified	Both	Fresh
Zhang *et al.* (2015), USA	243	142	52	Male, unexplained, tubal factors	Hypothyroidism, hyperprolactinemia	First	Autologous	Not specified	Both

[a]Normal weight was defined by BMI 20–24.9 kg/m^2. PCOS, polycystic ovary syndrome.

Provost et al., 2016a, 2016b; Insogna et al., 2017; Russo et al., 2017), but also Australia (Zander-Fox et al., 2012), China (Zhang et al., 2010), Denmark (Pinborg et al., 2011), France (Sifer et al., 2014), India (Sharma, 2014), Macedonia (Petanovski et al., 2011) and Spain (Bellver et al., 2010, 2013). Included women were recruited during their first cycle (Sneed et al., 2008; Petanovski et al., 2011; Bellver et al., 2013; Schliep et al., 2015; Zhang et al., 2010, 2015; Insogna et al., 2017; Russo et al., 2017), all of them (McCormick et al., 2008; Bellver et al., 2010; Pinborg et al., 2011; Zander-Fox et al., 2012; Bailey et al., 2014; Sifer et al., 2014; Kawwass et al., 2016; Provost et al., 2016a, 2016b) or not specified (Hill et al., 2011; Luke et al., 2011; Chavarro et al., 2012; Sharma, 2014). Studies concerned either autologous cycles (McCormick et al., 2008; Sneed et al., 2008; Petanovski et al., 2011; Chavarro et al., 2012; Zander-Fox et al., 2012; Bailey et al., 2014; Sharma, 2014; Zhang et al., 2015; Kawwass et al., 2016; Provost et al., 2016a; Russo et al., 2017), oocyte donation cycles (Bellver et al., 2013; Provost et al., 2016b), both (Luke et al., 2011; Insogna et al., 2017) or not specified (Bellver et al., 2010; Zhang et al., 2010; Hill et al., 2011; Pinborg et al., 2011; Sifer et al., 2014; Schliep et al., 2015). Studies included only fresh embryo transfers (McCormick et al., 2008; Sneed et al., 2008; Bellver et al., 2010; Zhang et al., 2010; Hill et al., 2011; Petanovski et al., 2011; Chavarro et al., 2012; Zander-Fox et al., 2012; Bailey et al., 2014; Sharma, 2014; Sifer et al., 2014; Schliep et al., 2015; Kawwass et al., 2016; Provost et al., 2016a, 2016b), frozen-embryo transfers (Insogna et al., 2017) or both (Luke et al., 2011; Pinborg et al., 2011; Bellver et al., 2013; Zhang et al., 2015; Russo et al., 2017) (Table I).

Live birth rates following IVF in obese versus normal weight women

When comparing obese to normal weight women, the RR (95% CI) for live birth following IVF was 0.85 (0.82–0.87) confirming a significant negative association between obesity and live birth (Fig. 2) (n = 609 881 cycles analysed). Heterogeneity was moderate at 48%.

Subgroup analyses performed according to cycle rank (only first cycle, all cycles, unspecified, Fig. 3) or oocyte origin (autologous, oocyte donation, both, unspecified, Fig. 4) did not modify the overall interpretation. Subgroup analyses performed according to embryo transfer type (fresh, frozen, both, Fig. 5) cannot be interpreted due to the selection of only one study evaluating only frozen-embryo transfers. Subgroup analyses performed according to ovarian status (PCOS only, non-PCOS, both, undetermined, Fig. 6) showed significantly lower RR (95% IC) of live birth in obese than in normal weight women when only PCOS patients were selected (0.78, 0.74–0.82), whereas LBR was comparable between obese and normal weight

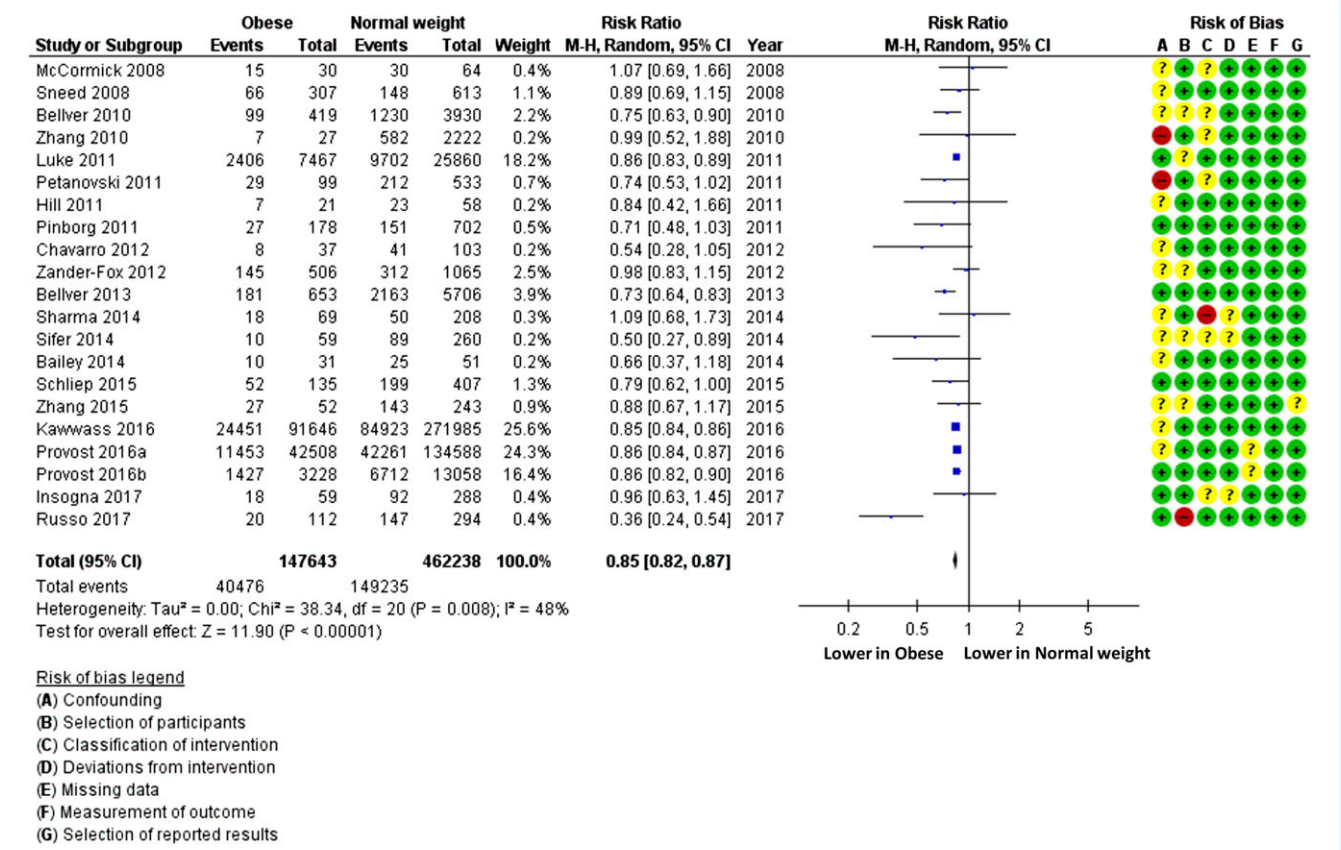

Figure 2 Live birth rate following IVF in obese and normal weight women (random effects model). 'Events' relates to IVF cycles leading to live birth, 'Total' relates to the total number of IVF cycles included in the study. Obesity was considered BMI ≥ 30 kg/m^2, normal weight BMI 18.5–24.9 kg/m^2.

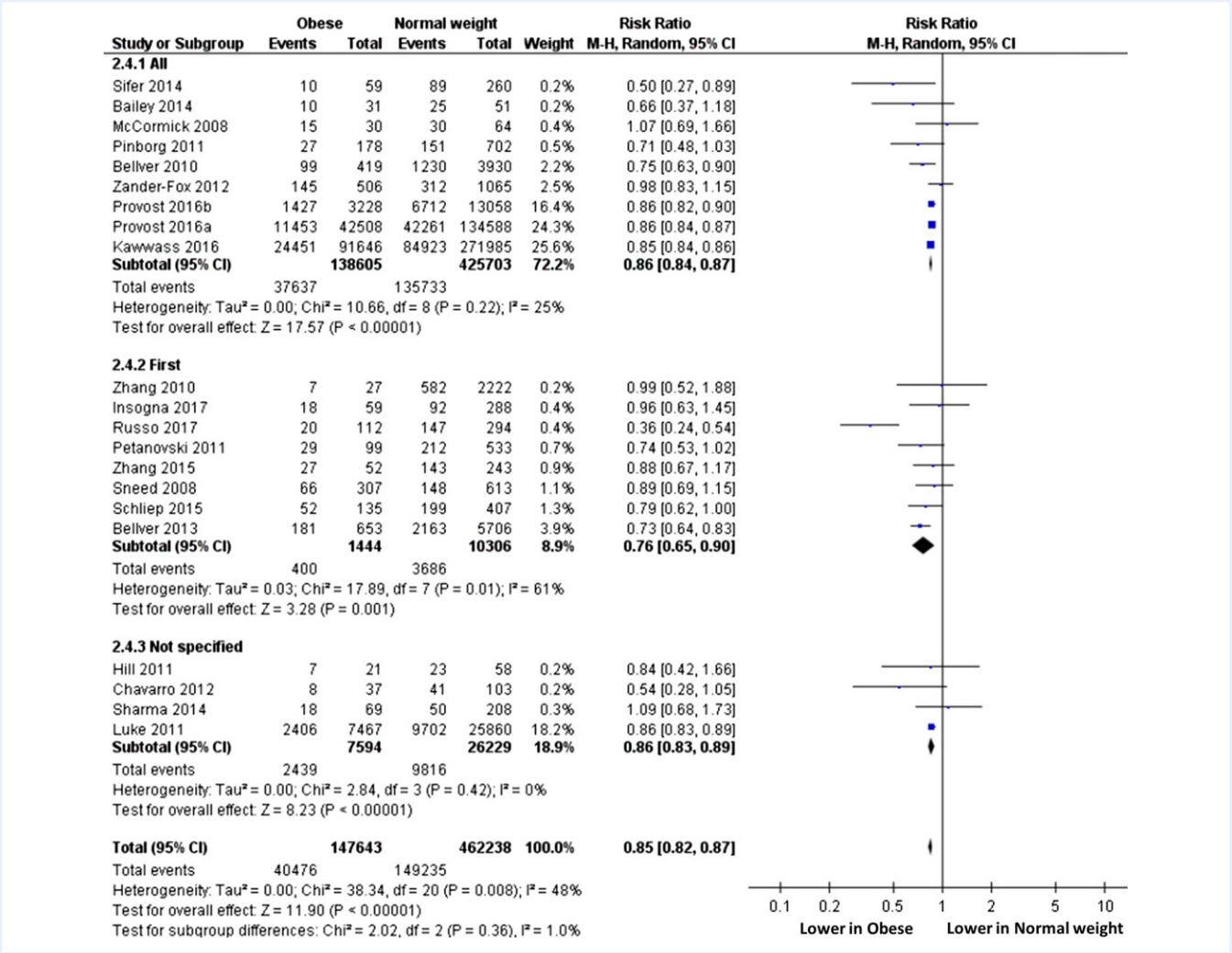

Figure 3 Subgroup analysis according to cycle rank. 'Events' relates to IVF cycles leading to live birth, 'Total' relates to the total number of IVF cycles included in the study.

women when only non-PCOS women were considered (RR, 95% IC: 0.92, 0.68–1.25).

Sensitivity analyses

The use of the fixed effects model did not modify the result (0.85, 0.85–0.86) (data not shown). Sensitivity analyses revealed an outlier publication (Russo *et al.*, 2017) (Supplementary Fig. S1). Excluding data from Russo *et al.* did not influence the results: RR (95% CI) for a live birth following IVF was 0.85 (0.84–0.87) for obese women when compared to normal weight women, with very low heterogeneity (Supplementary Fig. S2).

Live birth rates following IVF in overweight versus normal weight women

When compared to normal weight women, the RR (95% CI) for overweight women to obtain a live birth following IVF was 0.94 (0.91–0.97) (Fig. 7) (n = 266 404 cycles analysed). Heterogeneity was moderate (39%).

Risk of bias within studies

Excluding data from articles presenting at least one high risk of bias (Zhang *et al.*, 2010; Petanovski *et al.*, 2011; Sharma, 2014; Russo *et al.*, 2017) did not influence the results: RR (95% IC) for a live birth following IVF was 0.85 (0.84–0.87) for obese women when compared to normal weight women, with moderate heterogeneity (Supplementary Fig. S3).

Discussion

This meta-analysis based on 682 532 cycles demonstrates that female obesity has a significant deleterious effect on LBR following IVF. Obese women had a significantly decreased chance of giving birth following IVF when compared with normal weight women (RR, IC95%: 0.85, 0.84–0.87). LBR was also significantly lower in overweight women (RR, IC95%: 0.94, 0.91–0.97). These updated results are in accordance with a previous meta-analysis that showed significantly lower chances of clinical pregnancy and live birth in women who were overweight or obese in 47 967 cycles (Rittenberg *et al.*, 2011).

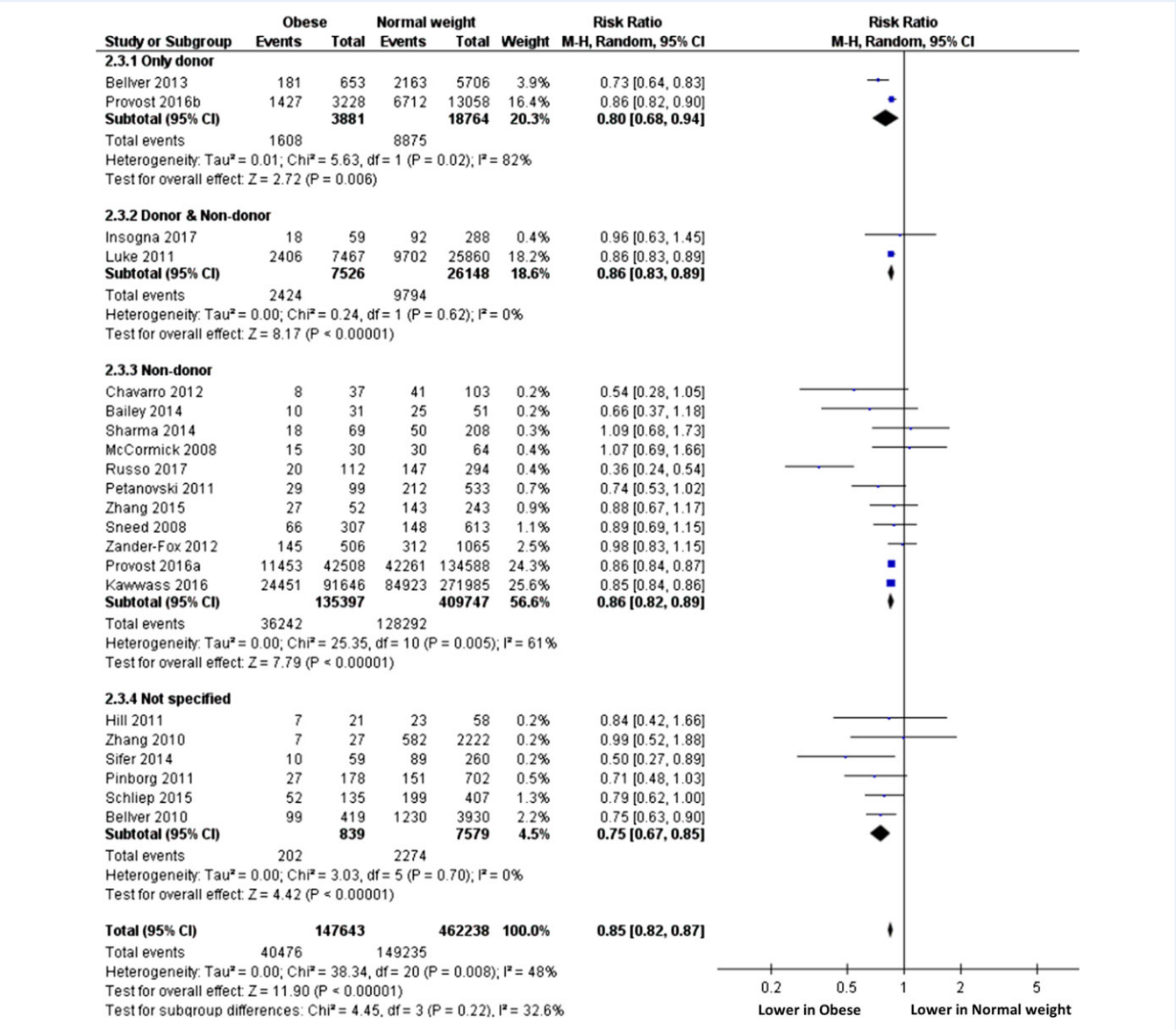

Figure 4 Subgroup analysis according to oocyte origin. 'Events' relates to IVF cycles leading to live birth, 'Total' relates to the total number of IVF cycles included in the study.

Impaired ovarian folliculogenesis, oocyte quality, embryonic development and uterine environment might be involved in poorer reproductive outcomes in obese women. However, their respective impacts still remain unclear. Altered function of the hypothalamic-pituitary axis associated with high insulin, androgen and estrogen levels might participate in impairing ovarian folliculogenesis (Jungheim and Moley, 2010). Oocyte quality is the final result of a long intrafollicular process consisting of adequate and simultaneous nuclear and cytoplasmic oocyte maturation. The oocyte is surrounded by granulosa cells and bathes in follicular fluid throughout its maturation. Therefore, any impairment of granulosa cell function and/or follicular fluid composition might impair oocyte maturation, and subsequently oocyte quality. The association between female obesity and alterations of follicular fluid composition has been extensively documented (reviewed in Broughton and Moley, 2017). These metabolic alterations mainly concern lipids, proteins and growth factors, and are associated with increased oxidative stress and disrupted steroidogenesis (Jungheim *et al.*, 2011; Valckx *et al.*, 2012). Higher leptin levels found in obese women have also been shown to affect oocyte and embryo quality (Catteau *et al.*, 2016), as well as granulosa cell function (Lin *et al.*, 2017). Some authors suggested that blastocyst formation may also be impaired in obese women (Comstock *et al.*, 2015). Whether those suspected alterations of oocyte quality might lead to increased risk of embryo aneuploidy in obese women has been recently evaluated. A study of preimplantation genetic testing for aneuploidies did not find any significant association between obesity and aneuploidy rate or the number of euploid embryos (Goldman *et al.*, 2015), suggesting that obesity does not affect oocyte chromosomal competence.

Although this remains controversial, obesity has also been shown to reduce uterine receptivity (Broughton and Moley, 2017). Impaired

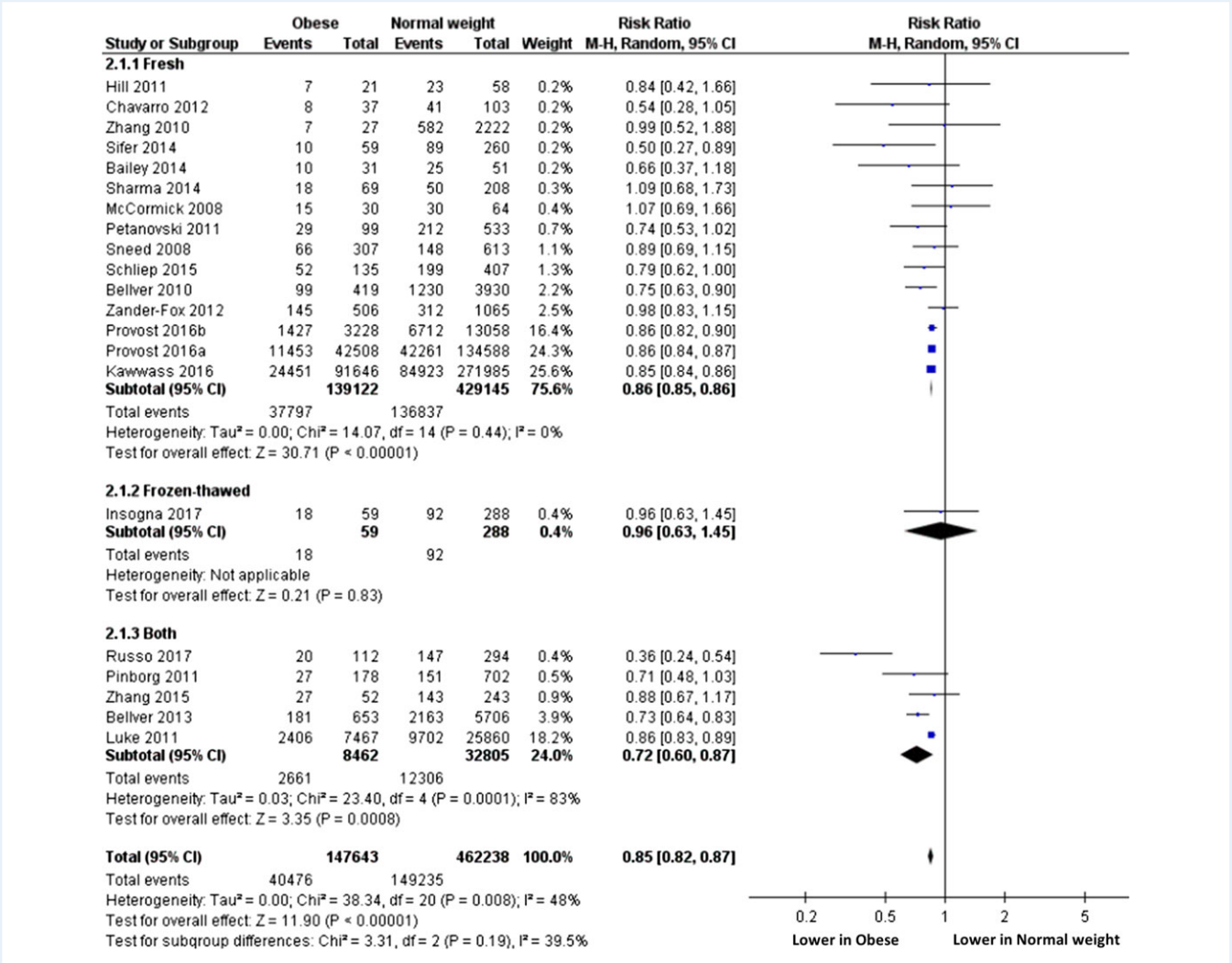

Figure 5 Subgroup analysis according to embryo transfer type. 'Events' relates to IVF cycles leading to live birth, 'Total' relates to the total number of IVF cycles included in the study.

endometrial stromal cell decidualization has been reported in *in vitro* studies and animal models (Rhee *et al.*, 2016). Obesity may alter endometrium—embryo cross-talk, leading to impaired implantation (Broughton and Moley, 2017) and leptin could play a key role in this phenomenon (Catteau *et al.*, 2016). Whether this impaired implantation participates in the increased risk of abnormal placentation and early miscarriage found in obese women can be questioned (Metwally *et al.*, 2008).

Our results might suggest a dose-effect relationship, even if the design of our study cannot ascertain it. According to subgroups analyses, prognosis seems to be poorer when obesity is associated with PCOS. Although this result is based only on four studies, it suggests that PCOS could be an independent deleterious prognosis factor. Obesity and PCOS are very intricate pathophysiological situations. Whether each one is causative of the other still remains unclear (Alvarez-Blasco *et al.*, 2006; Yildiz *et al.*, 2008), but it is usually considered that the association of PCOS with obesity exacerbates their respective metabolic dysregulations (Moran *et al.*, 2015; Broughton and Moley, 2017) and thus enhances their overall impact on reproductive functions. This is in accordance with a study that showed alterations in endometrial gene expression during the window of implantation in obese women, especially when associated with PCOS (Bellver *et al.*, 2011). In contrast, oocyte origin (donor or non-donor) did not modify the overall interpretation, contrary to the results reported in a previous meta-analysis (Jungheim *et al.*, 2013). This result has to be interpreted carefully, especially because it is based on only two studies, including one that did not analyse donors' BMI (Provost *et al.*, 2016b). Importantly, the second study was large, including almost 10 000 first egg donation cycles, and showed a detrimental effect of obesity on reproductive outcome, even after controlling for donor BMI (Bellver *et al.*, 2013). These results could suggest that obesity preferentially negatively alters endometrial receptivity rather that oocyte quality, as also underlined by molecular studies evaluating endometrial gene expression in obese patients (Bellver *et al.*, 2011).

Our study has some limitations. First, LBR being the main outcome, details concerning controlled ovarian stimulation parameters, embryo quality, early pregnancy or miscarriage rates are lacking.

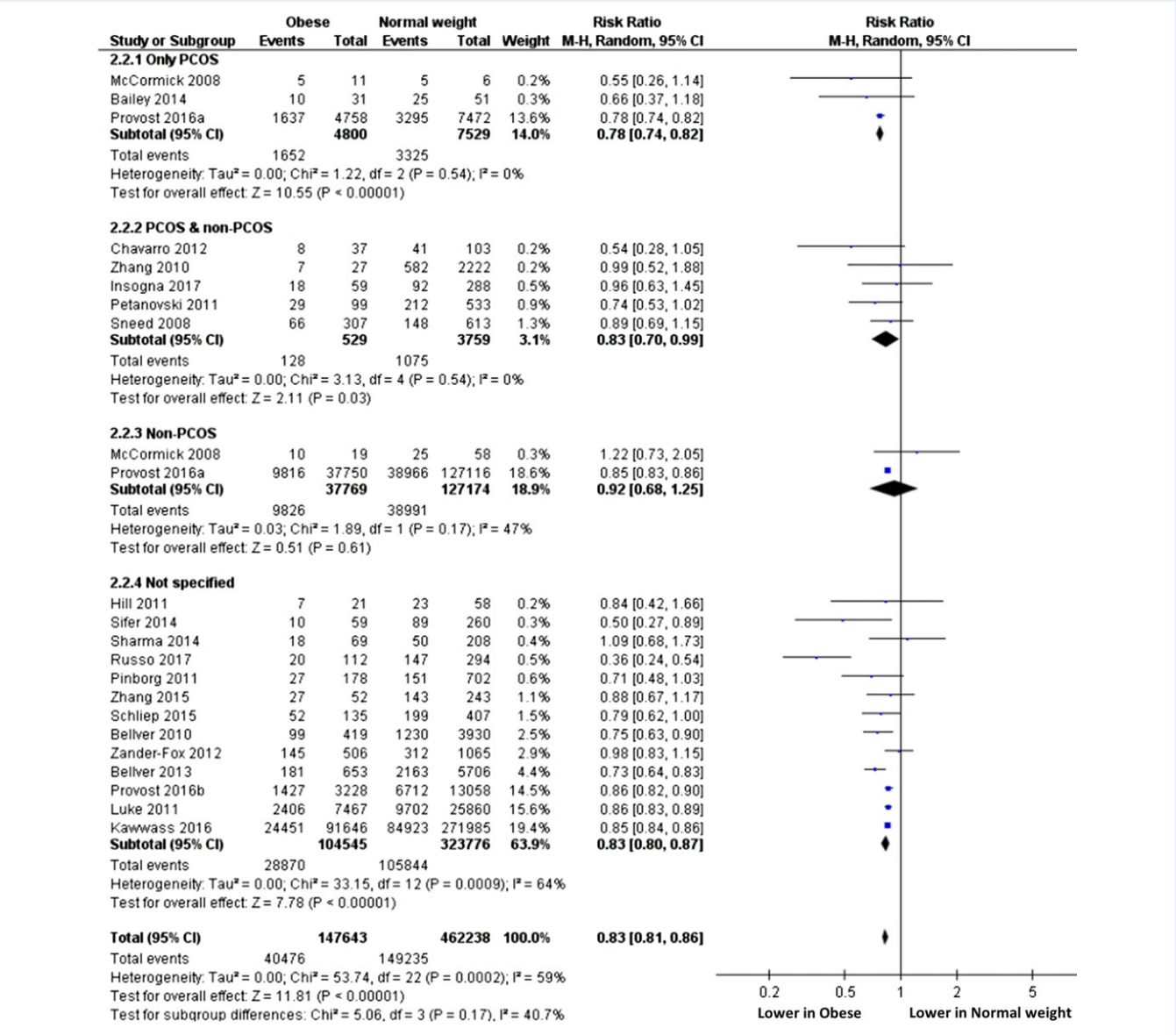

Figure 6 Subgroup analysis according to ovarian status. 'Events' relates to IVF cycles leading to live birth, 'Total' relates to the total number of IVF cycles included in the study.

However, LBR represents the gold standard for the assessment of IVF results, guaranteeing the homogeneity of the results, in particular by avoiding the variations in the definition of 'pregnancy rate'. On the other hand, it has to be underlined that data allowing evaluation of cumulative LBR were not available in the included studies. Second, we used the definition of obesity according to the WHO standardized classification of BMI. Although unable to distinguish body fat distribution, it remains the most widely used marker of adiposity in clinical and research settings. Third, we chose to compare obese to normal weight women for the main analysis. The comparison with overweight women was also performed, but as a secondary analysis, and our study was not designed to evaluate a potential dose-effect of the BMI on LBR. Last, even if the quality of the studies included in the meta-analysis was carefully evaluated, they still present a relatively important heterogeneity in terms of population or outcome definitions. The numerous confounding factors that potentially influence the chance of live birth following IVF treatment could not be included in our study. More specifically, confounding factors potentially associated with obesity should be considered with care, such as patient age (McLernon *et al.*, 2016), parity and obstetric history, male partner BMI (Mushtaq *et al.*, 2018), smoking status and intensity (Wang *et al.*, 2016; Carreras-Torres *et al.*, 2018), ethnicity (Wang *et al.*, 2016; Yu, 2016; Luke, 2017), socio-demographic status (Merino Ventosa and Urbanos-Garrido, 2016; Wang *et al.*, 2016; Bilger *et al.*, 2017), indication for IVF treatment or embryo transfer strategy (McLernon *et al.*, 2016). Nevertheless, our meta-analysis offers several strengths, including the largest sample size ever published and robust statistical analysis with very short CIs, stable RRs and low

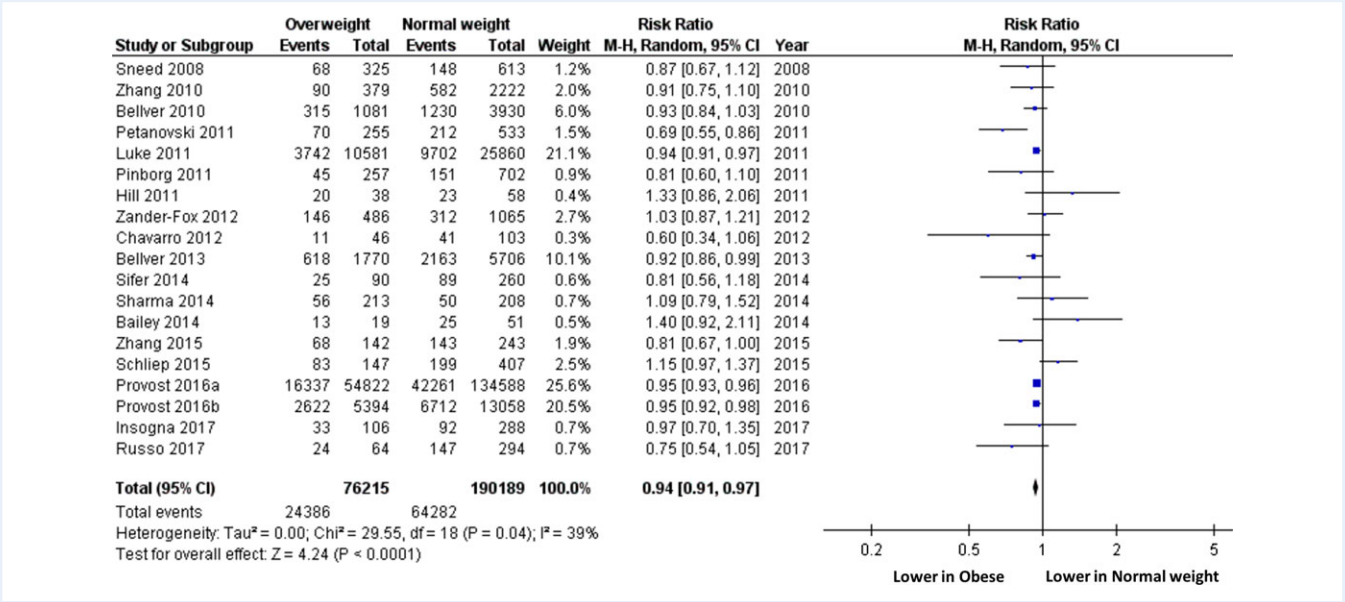

Figure 7 Live birth rate following IVF in overweight and normal weight women (random effects model). 'Events' relates to IVF cycles leading to live birth, 'Total' relates to the total number of IVF cycles included in the study.

heterogeneity after exclusion of an outlier study or studies presenting high risk of bias.

International recommendations state that infertile couples should be informed of the decreased chances of pregnancy and increased obstetrical and fetal risks in case of female obesity (ESHRE, 2010; NICE, 2013; ASRM, 2015). Some of them even do not recommend IVF in case of female morbid obesity (BMI > 35 kg/m^2; RANZCOG, 2014). Although the present meta-analysis does not aim at providing clinical recommendations, our results clearly advocate clear information and counselling of obese infertile women before IVF. Indeed, female obesity has an impact on long-term health of not only mothers but also offspring, as stated by the 'Developmental Origin of Health and Disease' hypothesis (Barker, 2007), and preconception period may represent the optimal moment to act. It is currently unclear whether weight loss may improve this negative effect of female obesity on IVF results. Although weight loss has been clearly associated with improved natural fertility (Legro *et al.*, 2016; Best *et al.*, 2017) and is advised in clinical international recommendations (ESHRE, 2010; NICE, 2013; RANZCOG, 2014; ASRM, 2015), two recent randomized controlled trials were not able to find any pregnancy or LBR improvement following weight loss and assisted reproductive technology (ART) procedures (Mutsaerts *et al.*, 2016; Einarsson *et al.*, 2017). However, a significantly higher rate of pregnancy was observed during the time prior to the IVF cycle in both studies. Although both studies presented limitations, such as a high degree of heterogeneity, and poor coaching and follow-up, ultimately leading to little weight reduction, their results question current weight loss strategies in obese infertile women and highlight the need for more prospective trials in order to determine the optimal care strategy that will guarantee the highest LBR with minimal complications and burden. Concerning bariatric surgery, current data remains sparse and controversial (Christofolini *et al.*, 2014; Tsur *et al.*, 2014; Milone *et al.*, 2017), calling for further studies. In particular, although weight loss achieved by diet seems to be associated with significantly improved pregnancy outcomes (Bogaerts *et al.*, 2015; Kalliala *et al.*, 2017), results seem more nuanced when obtained by surgery. Bariatric surgery was indeed associated with lower risks of gestational diabetes and large-for-gestational-age infants (Galazis *et al.*, 2014; Johansson *et al.*, 2015), but also with higher risk of small-for-gestational-age infants and shorter gestation (Galazis *et al.*, 2014; Johansson *et al.*, 2015) and possibly increased mortality (Johansson *et al.*, 2015). Altogether, these data suggest that bariatric surgery should be considered as a last option, after appropriate lifestyle therapy combined with tailored follow-up has been actively attempted.

In conclusion, our meta-analysis clearly demonstrates that female obesity negatively and significantly impacts LBRs following IVF. Whether weight loss through lifestyle modifications or bariatric surgery may reverse this deleterious effect should be further evaluated.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Acknowledgements

We thank MONITORING FORCE (Dr Bernadette Darné and Mrs Solène Languille) and the Inter-university Library of Medicine (BIUM) of Paris for methodological support. We also thank Professor Paul Barrière and Dr Astrid Finet for critical review of this work.

Authors' roles

NS: data collection and analysis, writing and revising of the manuscript. SH: data collection and analysis, co-writing of the manuscript.

VBL: data collection and analysis, co-writing of the manuscript. EAJ: study design and supervision. VG: data collection and analysis, co-writing of the manuscript. MC: study design, data collection and analysis, co-writing of the manuscript. TF: study design and supervision, data collection and analysis, writing and revising of the manuscript, validation of the final version of the manuscript. All authors approved the final version of the manuscript.

Funding

This work was sponsored by an unrestricted grant from GEDEON-RICHTER France.

References

Alvarez-Blasco F, Botella-Carretero JI, San Millán JL, Escobar-Morreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. *Arch Intern Med* 2006;**166**:2081–2086.

ASRM (American Society for Reproductive Medicine). Obesity and reproduction: a committee opinion. *Fertil Steril* 2015;**104**:1116–1126.

Bailey AP, Hawkins LK, Missmer SA, Correia KF, Yanushpolsky EH. Effect of body mass index on *in vitro* fertilization outcomes in women with polycystic ovary syndrome. *Am J Obstet Gynecol* 2014;**211**:163.e1–6.

Barker DJ. The origins of the developmental origins theory. *J Intern Med* 2007;**261**:412–417.

Bellver J, Ayllón Y, Ferrando M, Melo M, Goyri E, Pellicer A, Remohí J, Meseguer M. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. *Fertil Steril* 2010;**93**:447–454.

Bellver J, Martínez-Conejero JA, Labarta E, Alamá P, Melo MA, Remohí J, Pellicer A, Horcajadas JA. Endometrial gene expression in the window of implantation is altered in obese women especially in association with polycystic ovary syndrome. *Fertil Steril* 2011;**95**:2335–2341. , 2341.e1-8.

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

Best D, Avenell A, Bhattacharya S. How effective are weight-loss interventions for improving fertility in women and men who are overweight or obese? A systematic review and meta-analysis of the evidence. *Hum Reprod Update* 2017;**23**:681–705.

Bilger M, Kruger EJ, Finkelstein EA. Measuring socioeconomic inequality in obesity: looking beyond the obesity threshold. *Health Econ* 2017;**26**:1052–1066.

Bogaerts A, Ameye L, Martens E, Devlieger R. Weight loss in obese pregnant women and risk for adverse perinatal outcomes. *Obstet Gynecol* 2015;**125**:566–575.

Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. *Fertil Steril* 2017;**107**:840–847.

Carreras-Torres R, Johansson M, Haycock PC, Relton CL, Davey Smith G, Brennan P, Martin RM. Role of obesity in smoking behaviour: Mendelian randomisation study in UK Biobank. *BMJ* 2018;**361**:k1767.

Catteau A, Caillon H, Barrière P, Denis MG, Masson D, Fréour T. Leptin and its potential interest in assisted reproduction cycles. *Hum Reprod Update* 2016;**22**:320–341.

Chavarro JE, Ehrlich S, Colaci DS, Wright DL, Toth TL, Petrozza JC, Hauser R. Body mass index and short-term weight change in relation to treatment outcomes in women undergoing assisted reproduction. *Fertil Steril* 2012;**98**:109–116.

Christofolini J, Bianco B, Santos G, Adami F, Christofolini D, Barbosa CP. Bariatric surgery influences the number and quality of oocytes in patients submitted to assisted reproduction techniques. *Obesity* 2014;**22**:939–942.

Comstock IA, Kim S, Behr B, Lathi RB. Increased body mass index negatively impacts blastocyst formation rate in normal responders undergoing in vitro fertilization. *J Assist Reprod Genet* 2015;**32**:1299–1304.

Einarsson S, Bergh C, Friberg B, Pinborg A, Klajnbard A, Karlström PO, Kluge L, Larsson I, Loft A, Mikkelsen-Englund AL *et al*. Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial. *Hum Reprod* 2017;**32**:1621–1630.

ESHRE Task Force on Ethics and Law, including, Dondorp W, de Wert G, Pennings G, Shenfield F, Devroey P, Tarlatzis B, Barri P. Lifestyle-related factors and access to medically assisted reproduction. *Hum Reprod* 2010;**25**:578–583.

Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN *et al*. Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *Lancet* 2011;**377**:557–567.

Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA* 2012;**307**:491–497.

Galazis N, Docheva N, Simillis C, Nicolaides KH. Maternal and neonatal outcomes in women undergoing bariatric surgery: a systelmatic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 2014;**181**:45–53.

Gallus S, Lugo A, Murisic B, Bosetti C, Boffetta P, La Vecchia C. Overweight and obesity in 16 European countries. *Eur J Nutr* 2015;**54**:679–689.

Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. *Hum Reprod* 2007;**22**:414–420.

Goldman KN, Hodes-Wertz B, McCulloh DH, Flom JD, Grifo JA. Association of body mass index with embryonic aneuploidy. *Fertil Steril* 2015;**103**:744–748.

Hawkins Bressler L, Correia KF, Srouji SS, Hornstein MD, Missmer SA. Factors associated with second- trimester pregnancy loss in women with normal uterine anatomy undergoing in vitro fertilization. *Obstet Gynecol* 2015;**125**:621–627.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–560.

Hill MJ, Hong S, Frattarelli JL. Body mass index impacts *in vitro* fertilization stimulation. *ISRN Obstet Gynecol* 2011;**2011**:929251.

Insogna IG, Lee MS, Reimers RM, Toth TL. Neutral effect of body mass index on implantation rate after frozen-thawed blastocyst transfer. *Fertil Steril* 2017;**108**:770–776.e1.

Johansson K, Stephansson O, Neovius M. Outcomes of pregnancy after bariatric surgery. *N Engl J Med* 2015;**372**:2267.

Jungheim ES, Macones GA, Odem RR, Patterson BW, Lanzendorf SE, Ratts VS, Moley KH. Associations between free fatty acids, cumulus oocyte complex morphology and ovarian function during in vitro fertilization. *Fertil Steril* 2011;**95**:1970–1974.

Jungheim ES, Moley KH. Current knowledge of obesity's effects in the pre- and periconceptional periods and avenues for future research. *Am J Obstet Gynecol* 2010;**203**:525–530.

Jungheim ES, Schon SB, Schulte MB, De Ugarte DA, Fowler SA, Tuuli MG. IVF outcomes in obese donor oocyte recipients: a systematic review and meta-analysis. *Hum Reprod* 2013;**28**:2720–2727.

Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, Mitra A, Terzidou V, Bennett P, Martin-Hirsch P, Tsilidis KK *et al*. Obesity and gynaecological and obstetric conditions: umbrella review of the literature. *BMJ* 2017;**359**:j4511.

Kawwass JF, Kulkarni AD, Hipp HS, Crawford S, Kissin DM, Jamieson DJ. Extremities of body mass index and their association with pregnancy outcomes in women undergoing *in vitro* fertilization in the United States. *Fertil Steril* 2016;**106**:1742–1750.

Koning AM, Mutsaerts MA, Kuchenbecker WK, Broekmans FJ, Land JA, Mol BW, Hoek A. Complications and outcome of assisted reproduction technologies in overweight and obese women. *Human Reprod* 2012;**27**:457–467.

Legro RS, Dodson WC, Kunselman AR, Stetter CM, Kris-Etherton PM, Williams NI, Gnatuk CL, Estes SJ, Allison KC, Sarwer DB *et al*. Benefit of delayed fertility therapy with preconception weight loss over immediate therapy in obese women With PCOS. *J Clin Endocrinol Metab* 2016;**101**:2658–2666.

Lin XH, Wang H, Wu DD, Ullah K, Yu TT, Ur Rahman T, Huang HF. High leptin level attenuates embryo development in overweight/obese infertile women by inhibiting proliferation and promotes apoptosis in granule cell. *Horm Metab Res* 2017;**49**:534–541.

Luke B. Adverse effects of female obesity and interaction with race on reproductive potential. *Fertil Steril* 2017;**107**:868–877.

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

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

McCormick B, Thomas M, Maxwell R, Williams D, Aubuchon M. Effects of polycystic ovarian syndrome on in vitro fertilization-embryo transfer outcomes are influenced by body mass index. *Fertil Steril* 2008;**90**:2304–2309.

McLernon DJ, Steyerberg EW, Te Velde ER, Lee AJ, Bhattacharya S. Predicting the chances of a live birth after one or more complete cycles of *in vitro* fertilisation: population based study of linked cycle data from 113 873 women. *BMJ* 2016;**355**:i5735.

Merino Ventosa M, Urbanos-Garrido RMMMVGC. Disentangling effects of socioeconomic status on obesity: a cross-sectional study of the Spanish adult population. *Econ Hum Biol* 2016;**22**:216–224.

Metwally M, Ledger WL, Li TC. Reproductive endocrinology and clinical aspects of obesity in women. *Ann N Y Acad Sci* 2008;**1127**:140–146.

Milone M, Sosa Fernandez LM, Sosa Fernandez LV, Manigrasso M, Elmore U, De Palma GD, Musella M, Milone F. Does bariatric surgery improve assisted reproductive technology outcomes in obese infertile women? *Obes Surg* 2017;**27**:2106–2112.

Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact. *Trends Endocrinol Metab* 2015;**26**:136–143.

Mushtaq R, Pundir J, Achilli C, Naji O, Khalaf Y, El-Toukhy T. Effect of male body mass index on assisted reproduction treatment outcome: an updated systematic review and meta-analysis. *Reprod Biomed Online* 2018;**36**:459–471.

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

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

NICE (National Institute for Health and Care Excellence) *Fertility: assessment and treatment for people with fertility problems*. London: NICE, 2013CG156. [Accessed 06 November 2018.] Available from URL: http://www.nice.org.uk/CG156.

Petanovski Z, Dimitrov G, Ajdin B, Hadzi-Lega M, Sotirovska V, Matevski V, Stojkovska S, Saltirovski S, Suslevski D, Petanovska E. Impact of body mass index (BMI) and age on the outcome of the IVF process. *Prilozi* 2011;**32**:155–171.

Pinborg A, Gaarslev C, Hougaard CO, Nyboe Andersen A, Andersen PK, Boivin J, Schmidt L. Influence of female bodyweight on IVF outcome: a longitudinal multicentre cohort study of 487 infertile couples. *Reprod Biomed Online* 2011;**23**:490–499.

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

Provost MP, Acharya KS, Acharya CR, Yeh JS, Steward RG, Eaton JL, Goldfarb JM, Muasher SJ. Pregnancy outcomes decline with increasing recipient body mass index: an analysis of 22,317 fresh donor/recipient cycles from the 2008–2010 Society for Assisted Reproductive Technology Clinic Outcome Reporting System registry. *Fertil Steril* 2016b;**105**:364–368.

RANZCOG (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists) *Ovarian stimulation in assisted reproduction*. Victoria: RANZCOG, 2014C-Gyn-2. [Accessed 06 November 2018.] Available from URL: https://www.ranzcog.edu.au/college-statements-guidelines.html.

Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rhee JS, Saben JL, Mayer AL, Schulte MB, Asghar Z, Stephens C, Chi MM, Moley KH. Diet-induced obesity impairs endometrial stromal cell decidualization: a potential role for impaired autophagy. *Hum Reprod* 2016;**31**:1315–1326.

Rich-Edwards JW, Spiegelman D, Garland M, Hertzmark E, Hunter DJ, Colditz GA, Willett WC, Wand H, Manson JE. Physical activity, body mass index, and ovulatory disorder infertility. *Epidemiology* 2002;**13**:184–190.

Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. *Reprod Biomed Online* 2011;**23**:421–439.

Russo M, Ates S, Shaulov T, Dahan MH. Morbid obesity and pregnancy outcomes after single blastocyst transfer: a retrospective, North American study. *J Assist Reprod Genet* 2017;**34**:451–457.

Schliep KC, Mumford SL, Ahrens KA, Hotaling JM, Carrell DT, Link M, Hinkle SN, Kissell K, Porucznik CA, Hammoud AO. Effect of male and female body mass index on pregnancy and live birth success after *in vitro* fertilization. *Fertil Steril* 2015;**103**:388–395.

Sharma R. Prospective study of effect of body weight on in vitro fertilization outcome in reproductive age group. *Int J Infertil Fetal Med* 2014;**5**:58–63.

Sifer C, Herbemont C, Adda-Herzog E, Sermondade N, Dupont C, Cedrin-Durnerin I, Poncelet C, Levy R, Grynberg M, Hugues J-N. Clinical predictive criteria associated with live birth following elective single embryo transfer. *Eur J Obstet Gynecol Reprod Biol* 2014;**181**:229–232.

Sneed ML, Uhler ML, Grotjan HE, Rapisarda JJ, Lederer KJ, Beltsos AN. Body mass index: impact on IVF success appears age-related. *Hum Reprod* 2008;**23**:1835–1839.

Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;**25**:603–605.

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

Tsur A, Orvieto R, Haas J, Kedem A, Machtinger R. Does bariatric surgery improve ovarian stimulation characteristics, oocyte yield, or embryo quality? *J Ovarian Res* 2014;**7**:116.

Valckx SD, De Pauw I, De Neubourg D, Inion I, Berth M, Fransen E, Bols PE, Leroy JL. BMI-related metabolic composition of the follicular fluid of women undergoing assisted reproductive treatment and the consequences for oocyte and embryo quality. *Hum Reprod* 2012;**27**:3531–3539.

Wang P, Abdin E, Sambasivam R, Chong SA, Vaingankar JA, Subramaniam M. Smoking and socio-demographic correlates of BMI. *BMC Public Health* 2016;**16**:500.

WHO. Fact sheet "Obesity and overweight" (16 February 2018). Available from URL: http://who.int/news-room/fact-sheets/detail/obesity-and-overweight [Accessed 06 November 2018].

WHO. Obesity: preventing and managing the global epidemic: Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;**894**:8–9.

Yildiz BO, Knochenhauer ES, Azziz R. Impact of obesity on the risk for polycystic ovary syndrome. *J Clin Endocrinol Metab* 2008;**93**:162–168.

Yu Y. Four decades of obesity trends among non-hispanic whites and blacks in the united states: analyzing the influences of educational inequalities in obesity and population improvements in education. *PLoS One* 2016;**11**:e0167193.

Zander-Fox DL, Henshaw R, Hamilton H, Lane M. Does obesity really matter? The impact of BMI on embryo quality and pregnancy outcomes after IVF in women aged ≤38 years. *Aust N Z J Obstet Gynaecol* 2012;**52**:270–276.

Zhang JJ, Feret M, Chang L, Yang M, Merhi Z. Obesity adversely impacts the number and maturity of oocytes in conventional IVF not in minimal stimulation IVF. *Gynecol Endocrinol* 2015;**31**:409–413.

Zhang D, Zhu Y, Gao H, Zhou B, Zhang R, Wang T, Ding G, Qu F, Huang H, Lu X. Overweight and obesity negatively affect the outcomes of ovarian stimulation and *in vitro* fertilisation: a cohort study of 2628 Chinese women. *Gynecol Endocrinol* 2010;**26**:325–332.