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REVIEW

Paternal obesity negatively affects male fertility and assisted reproduction outcomes: a systematic review and meta-analysis

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Abstract This systematic review investigated the effect of paternal obesity on reproductive potential. Databases searched were Pubmed, Ovid, Web of Science, Scopus, Cinahl and Embase. Papers were critically appraised by two reviewers, and data were extracted using a standardized tool. Outcomes were: likelihood of infertility, embryo development, clinical pregnancy, live birth, pregnancy viability, infant development, sperm; concentration, morphology, motility, volume, DNA fragmentation, chromatin condensation, mitochondrial membrane potential (MMP), and seminal plasma factors. Thirty papers were included, with a total participant number of 115,158. Obese men were more likely to experience infertility (OR = 1.66, 95% CI 1.53–1.79), their rate of live birth per cycle of assisted reproduction technology (ART) was reduced (OR = 0.65, 95% CI 0.44–0.97) and they had a 10% absolute risk increase of pregnancy non-viability. Additionally, obese men had an increased percentage of sperm with low MMP, DNA fragmentation, and abnormal morphology. Clinically significant differences were not found for conventional semen parameters. From these findings it can be concluded that male obesity is associated with reduced reproductive potential. Furthermore, it may be informative to incorporate DNA fragmentation analysis and MMP assessment into semen testing, especially for obese men whose results suggest they should have normal fertility.

KEYWORDS: andrology, BMI, fertility, meta-analysis, obesity, systematic review

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Introduction

Male infertility is a significant issue and constitutes approximately 50% of infertility cases (Lamb and Lipshultz, 2000). Defective sperm function affects about 1 in 20 men (McLachlan and de Kretser, 2001) and constitutes the single most common cause of infertility (Hull et al., 1985; McLachlan and de Kretser, 2001). There is also increasing evidence of paternal non-genetic effects on the long-term health of the offspring transmitted through the gamete (Fullston et al., 2013; Linabery et al., 2012; McPherson et al., 2014; Soubry et al., 2013). Therefore, understanding the factors influencing the health of sperm and the underlying mechanisms behind any resultant pathology is paramount.

Obesity is a condition in which excess body fat is accumulated, and has been associated with multiple conditions such as diabetes, cardiovascular disease and certain types of cancer (Proietto and Baur, 2004). Obesity and its associated comorbidities present significant health concerns throughout the world. It is increasingly prevalent in the population of people trying to conceive (Hyattsville, 2009; Visscher and Seidell, 2001), with the prevalence of obesity in young men of reproductive age having tripled since the early 1970s (Hyattsville, 2009).

Although it is clear that maternal obesity reduces fertility, in part through actions on the oocyte, which affect the viability of the resultant pregnancy (Cai et al., 2014; Papachatzi et al., 2013; Pasquali et al., 2007), the potential role of male obesity in infertility has received comparatively little attention. This is surprising given the potential effect of male obesity on the molecular structure of maturing sperm and therefore subsequent embryo and fetal development. Further, the incidence of male infertility (at least in some geographical areas) is on the rise (Katib, 2015; Swan et al., 2000). This is coincident with a worldwide reduction in sperm quality, which to date is unexplained (Andersson et al., 2008), but that some have postulated may in part be attributable to the increasing prevalence of overweight and obesity (Finucane et al., 2011; Setchell, 1997). With an increase in the prevalence of obesity, it is necessary to broaden the understanding of the clinical significance of a male partner being overweight or obese. In general, male health is an under-researched area compared with female health, and there are broad knowledge gaps in the understanding of how the health of the male influences the viability of the sperm and subsequent pregnancy outcomes.

The aim of this systematic review is to critically evaluate and synthesize the current evidence on the effects of paternal obesity on male reproductive potential. While some findings examining the effects of male obesity on reproductive endocrine state and sperm function are now available – specifically systematic reviews have been performed on the effect of paternal obesity on reproductive health as indicated by sperm count (Sermondade et al., 2013), reproductive endocrine state (Teerds et al., 2011), and sperm count, concentration, volume, and motility in conjunction with the reproductive endocrine state (MacDonald et al., 2010) – there has been no review of the effects of paternal obesity on primary fertility outcomes (i.e. attainment of pregnancy and live birth, infant development) or non-conventional parameters of semen quality (i.e. DNA fragmentation, mitochondrial membrane potential [MMP], chromatin condensation). The inclusion of these factors in this review will provide a more complete picture of the influence and mechanisms of obesity on male reproductive potential.

Materials and methods

A systematic review of the literature was performed to identify what effect paternal obesity has on male reproductive potential according to the methodologies of the JBI Database of Systematic Reviews and Implementation Reports (The Joanna Briggs Institute, 2011). An *a priori* published protocol was followed (Campbell and Bakos, 2013). The review was carried out to include both published and grey literature; however, ultimately only published studies were found. No date restrictions were applied, but language was restricted to English. Studies were retrieved up to March 2013, with an updated search performed in April 2015.

Inclusion and exclusion criteria

Studies carried out on male adults aged >18 years without history of reproductive disorders were included in the review. Studies that utilized frozen or donor sperm were excluded, as were those that focused on men who had been exposed to environmental toxicants such as pesticides. Data had to be reported with men categorised by body mass index (BMI), including a normal weight group (BMI $\leq$ 25) and an obese group (BMI $\geq$ 30). All types of quantitative research were eligible for inclusion in the review (with the exception of case series and reports).

Outcomes of interest

This systematic review considered studies that investigated the following outcomes: likelihood of infertility, in-vitro embryo development, clinical pregnancy, live birth, pregnancy viability, infant development, sperm; concentration, normal morphology, progressive motility, volume, DNA fragmentation, chromatin condensation, low mitochondrial membrane potential, and seminal plasma factors.

Search strategy

The search strategy utilized a three-step approach that has previously been described (The Joanna Briggs Institute, 2011). Included databases were Pubmed, Ovid, Web of Science, Scopus and Embase). A full list of keywords and indexing terms is provided in the supplementary materials, **Appendix S1**.

Critical appraisal and data extraction

Critical appraisal was carried out by two independent reviewers using a standardized checklist prior to inclusion in the review (The Joanna Briggs Institute, 2011). Disagreements between reviewers were resolved through discussion. Data was

extracted from included papers using a standardized instrument (Campbell and Bakos, 2013; The Joanna Briggs Institute, 2011). Where data were missing or clarification was needed, authors were contacted by email.

Data synthesis

Data were entered into the statistical software JBI-MAStARI (The Joanna Briggs Institute) by double data entry to ensure the accuracy of the values. Meta-analysis was then performed, with effect sizes expressed as odds ratios (OR) or weighted mean differences (WMD) depending on whether the data were categorical or continuous, with variability expressed as 95% confidence intervals (CI). In one instance where the same outcome was assessed by different measures, the effects size was expressed as standardized mean difference (SMD). The fixed effects model was used unless a significant level of heterogeneity was found (as assessed by the standard chi-squared test), in which case the random effects model was used. Subgroup analysis was used to investigate the influence of data being collected from the clinical population as opposed to the general population on conventional semen parameters. In cases where categorical data were presented only as ORs rather than raw numbers or percentages the Cochrane systematic review tool "RevMan 5" (Cochrane) was utilized to perform meta-analysis by the inverse variance method.

Results

Study characteristics

In total 30 studies were included in this systematic review. Thirty-five studies met the inclusion criteria, but five did not pass critical appraisal due to shortcomings in their statistical analysis or reporting (Al-Ali et al., 2012, 2014; Jamshidi, 2011; Relwani et al., 2011; Sekhavat and Moein, 2010) (**Figure 1** Supplementary **Table S1**). The overall quality of included studies ranged from 4/9 to 8/9. The non-random recruitment of participants (appraisal criteria 1, Supplementary **Table S1**) was a characteristic failing of studies on this topic, with only two of the 35 utilizing any form randomized patient selection. The included studies were conducted in a range of different countries, including: the USA (9) (Chavarro et al., 2010; Colaci et al., 2012; Eisenberg et al., 2014; Hammoud et al., 2008; Jokela et al., 2008; Keltz et al., 2010; Kort et al., 2006; Linabery et al., 2012; Schliep et al., 2015), Denmark (3) (Aggerholm et al., 2009; Petersen et al., 2013; Ramlau-Hansen et al., 2007), the UK (2) (Pacey et al., 2014; Shayeb et al., 2011), Australia (2) (Bakos et al., 2011a; Tunc et al., 2011), Italy (2) (La Vignera et al., 2012; Lotti et al., 2011), The Netherlands (2) (Duits et al., 2010; Hammiche et al., 2012), Brazil (1) (Fariello et al., 2012), China (1) (Qin et al., 2007), New Zealand (1) (Macdonald et al., 2013), Hungary (1) (Koloszar et al., 2005), the Czech republic (1) (Rybar et al., 2011), Argentina (1) (Martini et al., 2010), Norway (1) (Nguyen et al., 2007), Turkey (1) (Umul et al., 2015), Russia (1) (Gutorova et al., 2014), and France (1) (Dupont et al., 2013). A total of 115,158 participants were

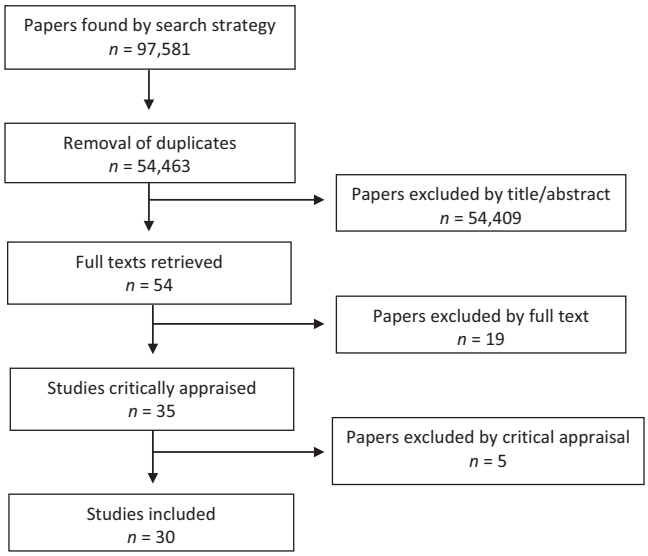

Figure 1 Study identification and selection.

ultimately included in this systematic review, with a range of 81 to 47,835 participants per study. Twenty-one studies were carried out on data collected from participants attending an infertility clinic (Bakos et al., 2011a; Chavarro et al., 2010; Colaci et al., 2012; Duits et al., 2010; Dupont et al., 2013; Fariello et al., 2012; Hammiche et al., 2012; Hammoud et al., 2008; Keltz et al., 2010; Koloszar et al., 2005; Kort et al., 2006; Lotti et al., 2011; Macdonald et al., 2013; Martini et al., 2010; Pacey et al., 2014; Petersen et al., 2013; Rybar et al., 2011; Schliep et al., 2015; Shayeb et al., 2011; Tunc et al., 2011; Umul et al., 2015), while nine studies were carried out on the general population (Aggerholm et al., 2009; Eisenberg et al., 2014; Gutorova et al., 2014; Jokela et al., 2008; La Vignera et al., 2012; Linabery et al., 2012; Nguyen et al., 2007; Qin et al., 2007; Ramlau-Hansen et al., 2007) (**Table 1**).

Fertility

Likelihood of infertility

Two studies were included in the meta-analysis of the effect of male obesity on the likelihood of a couple being infertile (failing to conceive after two or more years) (Nguyen et al., 2007; Ramlau-Hansen et al., 2007). Couples with an obese male partner were found to be statistically significantly more likely to experience infertility than couples with a normal weight male (OR = 1.66, 95% CI 1.53–1.79, Supplementary **Figure S1**). Heterogeneity was non-significant and the fixed effects model was used. Another study investigated the relationship between being obese as a young adult (17 to 24 years) and the likelihood of having a child by 47 years (Jokela et al., 2008). Men who were obese as young adults had an unadjusted risk ratio (RR) of having a child of 0.75 compared with normal weight men (95% CI 0.66–0.84), or (RR = 0.78, 95% CI 0.69–0.88) when data were adjusted for marital status.

In-vitro embryo development

Three studies reported on the effects of male partner obesity on embryo development (Bakos et al., 2011a; Colaci et al.,

Table 1 Characteristics of included studies.

Study	Methods	Participants (sample size)	Obese	Normal weight	Study authors' conclusion	Quality
Aggerholm et al., 2009	Cross-sectional	Participants had no vasectomy, known azoospermia or abnormalities of the reproductive organs (2139)	BMI >30	BMI 20.0–25.0	Reduction in semen quality, if any, was marginal and below the detection limit of this study	5/9
Bakos et al., 2011a	Cross-sectional	IVF patients. No significant symptoms of andrologic dysfunction (315)	BMI >30	BMI 20–24.9	Increased paternal BMI is associated with decreased blastocyst development, clinical pregnancy rates and live birth outcomes	6/9
Chavarro et al., 2010	Cross-sectional	Male partners of subfertile couples (483)	BMI 30–34.9	BMI 18.5–24.9	Obesity was associated with increased sperm DNA damage, morbid obesity was associated with lower sperm count	6/9
Colaci et al., 2012	Cross-sectional	Male partners from couples undergoing ART, aged 18–55 without a history of vasectomy (114)	BMI ≥30	BMI 18.5–24.9	Data suggest a possible deleterious effect of male obesity on the odds of having a live birth among couples undergoing ICSI	6/9
Duits et al., 2010	Cross-sectional	Male partners of infertile couples. No known cause of spermatogenic failure or obstruction, retrograde ejaculate, obstructive azoospermia, Y chromosome deletion, or chromosomal abnormalities associated with infertility (1401)	BMI >30	BMI 20–25	Semen quality was not statistically significantly affected by BMI in a cohort of male partners in subfertile couples	5/9
Dupont et al., 2013	Cross-sectional	Male partners of subfertile couples (330)	BMI ≥30	BMI 18.5–24.9	Male obesity is associated with an increased risk of sperm DNA damage and lower sperm motility and thus reduced sperm quality	5/9
Eisenberg et al., 2014	Cross-sectional	Couples recruited from two different states where the male was 18 + and the female was 18–44 with no physician diagnosed infertility (501)	BMI 30–34.9	BMI <25.0	The report suggests there is an inverse relationship between adiposity and sperm production	6/9
Fariello et al., 2012	Cross-sectional	Men presenting for semen analysis (305)	BMI ≥30	BMI <25	Increased BMI values are associated with decreased mitochondrial activity and progressive motility and increased DNA damage	7/9
Gutorova et al., 2014	Cross-sectional	Volunteers aged 23–58 years without acute disease or exacerbation of a chronic disease or STI (99)	BMI ≥30.1	18.5 ≤ BMI < 25	Higher spermatogenesis values were observed in men with excessive body weight versus men with normal body weight or obesity	6/9
Hammiche et al., 2012	Cross-sectional	Male partners of subfertile couples (450)	BMI ≥30	BMI <25	Sperm concentration and total motile sperm count in men of subfertile couples are detrimentally affected by a high BMI and cen=tral adiposity	6/9

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Table 1 (*continued*)

Study	*Methods*	*Participants (sample size)*	*Obese*	*Normal weight*	*Study authors' conclusion*	*Quality*
Hammoud et al., 2008	Cross-sectional	Infertility patients (472)	BMI ≥30	BMI <25	Male obesity is associated with increased incidence of low sperm concentration and low progressively motile sperm count	6/9
Jokela et al., 2008	Longitudinal	A representative sample of Americans born between 1957 and 1974 (12,073)	BMI >30	18.5 ≤ BMI ≤ 24.9	Obesity may be an important risk factor for infertility	7/9
Keltz et al., 2010	Cross-sectional	ART patients (290 cycles)	BMI ≥30	BMI 18.1–24.9	Overweight decreases clinical pregnancy	4/9
Koloszar et al., 2005	Cross-sectional	Normozoospermic patients attending an infertility clinic, no organic alterations of reproductive organs, no pathogenic bacteria or fungi (290)	BMI 30.1–39	BMI 20.1–25	Obesity is associated with a lower sperm count in cases of normozoospermia	6/9
Kort et al., 2006	Cross-sectional	Normal healthy men aged 26–45 years, no previous surgery (520)	BMI >30	BMI 20–24	Men present with BMI greater than 25 have fewer chromatin-intact normal-motile sperm cells per ejaculate	4/9
Linabery et al., 2012	Longitudinal	European–American parents of infants enrolled *in utero* in the Fels longitudinal study (890)	BMI ≥30	BMI <25	Infants of obese fathers had BMI growth curves distinct from those of normal weight fathers	8/9
Lotti et al., 2011	Cross-sectional	Male partners of infertile couples (222)	BMI ≥30	BMI 18.5–24.9	Higher BMI and BMI class positively correlate with s-IL8, a reliable surrogate marker of prostate inflammatory disease	6/9
Macdonald et al., 2013	Cross-sectional	Men presenting for semen analysis for any reason at participating fertility clinics, without definitive pathological conditions likely to affect sperm quality (511)	BMI ≥30	BMI 18.5–24.99	The strength and consistency of the results of this study add to the growing evidence that any relationship between BMI and the semen parameters assessed in routine semen analysis, if present, is marginal	5/9
Martini et al., 2010	Cross-sectional	Male partners of infertile couples (794)	BMI 30–50	18.5 ≤ BMI < 25	Results support a deleterious effect of obesity on seminal quality, probably by alterations in the function of the epididymis	6/9
Nguyen et al., 2007	Longitudinal	Pregnant couples between 1999 and 2005 where the woman was a native Norwegian speaker, living with the father of the child aged between 18 and 40 (26,303)	BMI ≥30	20 ≤ BMI ≤ 24.99	Male adiposity is associated with increased infertility	7/9

(*continued on next page*)

Table 1 (*continued*)

Study	Methods	Participants (sample size)	Obese	Normal weight	Study authors' conclusion	Quality
Pacey et al., 2014	Cross-sectional	Male patients who visited a fertility clinic, a gynaecology clinic, an andrology laboratory, or made an appointment for a semen analysis and had been attempting conception for 12 months (1970)	BMI >30	BMI 18.5–24.99	An individual's lifestyle has very little impact on sperm morphology	6/9
Petersen et al., 2013	Cross-sectional	Couples receiving ART (12,566)	BMI ≥30	BMI 18.5–24.9	Increased male BMI negatively influenced live birth after IVF treatments. With ICSI the association with BMI was less clear	6/9
Ramlau-Hansen et al., 2007	Longitudinal	Couples, excluding couples where the woman had a disease that could impact her BMI or fecundity (47,835)	BMI ≥30	18.5 ≤ BMI ≤ 24.99	Couples have a high risk of being subfecund if they are both obese	6/9
Qin et al., 2007	Cross-sectional	General population. No chronic disease, genital disease, heavy smoking or regular alcohol consumption (990)	BMI ≥30.0	BMI 18.5–24.9	The association between BMI and semen quality was found to be statistically significant even after adjusting for reproductive hormones	6/9
Rybar et al., 2011	Cross-sectional	Couples who had tried for 12 months or more to achieve pregnancy without success (153)	BMI >30	BMI <24.9	The impact of elevated BMI on the parameters investigated (basic semen parameters, chromatin integrity and chromatin condensation) was not proven in this study	4/9
Schliep et al., 2015	Cross-sectional	Couples undergoing first fresh IVF cycles. Men with nonobstructive azoospermia were excluded (721)	BMI ≥30	BMI ≤24.99	There was no overall association of male and female BMI, individually or in combination, with IVF success after taking into account several important confounding factors, such as male and female age, partner BMI and parity	7/9
Shayeb et al., 2011	Cross-sectional	Male partners of couples attending an infertility clinic. No vasectomy surgery or azoospermia (2035)	BMI >30	BMI 18.5–24.99	Obese men are more likely to have lower semen volume and fewer morphologically normal spermatozoa than men with normal BMI	5/9
Tunc et al., 2011	Cross-sectional	Men presenting for fertility assessment (81)	BMI >30	BMI 20–25	Oxidative stress increased with increasing BMI as well as sperm concentration	5/9
Umul et al., 2015	Cross-sectional	Fresh ICSI cycles with autologous oocytes (155)	BMI ≥ 30	BMI 20–24.9	Increasing paternal BMI has a negative influence on ICSI success, including clinical pregnancy rate and live birth rate	6/9
La Vignera et al., 2012	Cross-sectional	General population, healthy non-smoking (150)	BMI 30.1–44.0	BMI 19.0–24.9	Healthy non-smoking obese men have worse conventional and nonconventional sperm parameters than normal weight controls	7/9

ART = assisted reproduction technology; BMI = body mass index (kg/m^2); ICSI = intracytoplasmic sperm injection; STI = sexually transmitted infection.

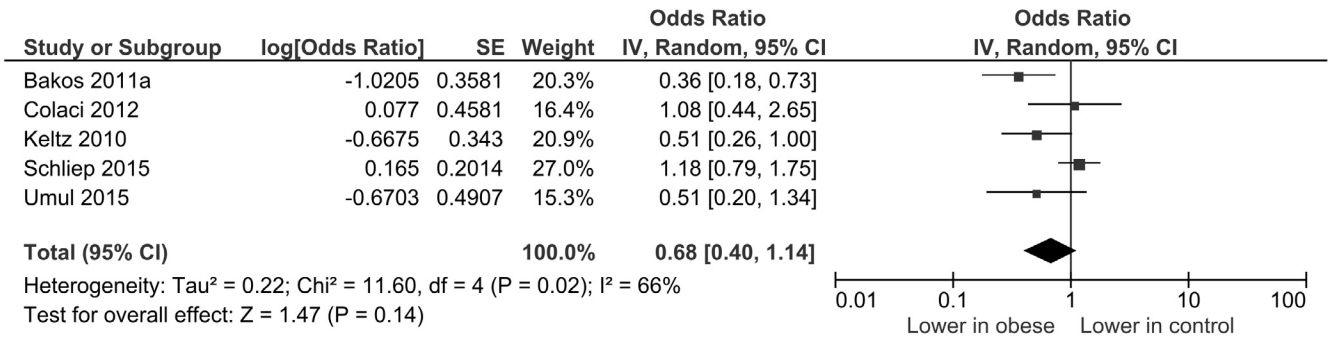

Figure 2 Meta-analysis of the effect of obesity on the likelihood of clinical pregnancy from ART.

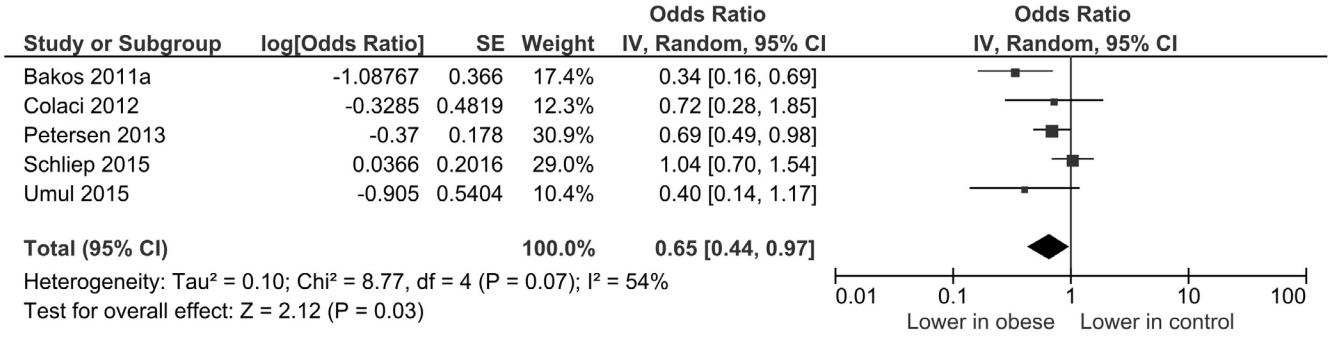

Figure 3 Meta-analysis of the effect of obesity on the likelihood of live birth from ART.

2012; Schliep et al., 2015), but a meta-analysis could not be performed as none of the studies had outcomes in common. The first study found a statistically significant linear decrease in on-time and expanded blastocyst development with increasing BMI, but no significant differences for percentage of grade 1 or grade 2 embryos on day 3 (Bakos et al., 2011a). In the second study embryo development was assessed as poor quality, accelerated cleavage, and slow cleavage on day 3 for 149 cycles. However, no significant differences were found between normal weight and obese men (Colaci et al., 2012). In the final study, no difference was found between normal weight and obese (or morbidly obese) men for the percentage of day 5 embryos that were scored as highest quality (Schliep et al., 2015).

Clinical pregnancy from ART

Five studies were included in the meta-analysis of the effect of male obesity on the OR of couples undergoing assisted reproduction technology (ART; IVF or intracytoplasmic sperm injection [ICSI]) achieving a clinical pregnancy (Bakos et al., 2011a; Colaci et al., 2012; Keltz et al., 2010; Schliep et al., 2015; Umul et al., 2015). Clinical pregnancy rates were reported as: heartbeat detected per oocyte retrieval (Bakos et al., 2011a), ultrasound confirmation (giving no further details) per embryo transfer cycle (Colaci et al., 2012), intrauterine gestational sac on transvaginal sonogram per cycle (Keltz et al., 2010), heartbeat detected per ICSI cycle (Umul et al., 2015), and gestational sac and/or clinical recording of heartbeat (or documentation of birth or termination) per cycle (Schliep et al., 2015). As Colaci et al., 2012 only presented data as OR, a meta-analysis was performed using the inverse variance method. Although Colaci et al. presented OR adjusted for maternal BMI and unadjusted OR the other four studies only presented unadjusted OR. As such, the unadjusted value was used in all cases to protect the homogeneity of the data. A non-statistically significant decrease in clinical pregnancy success rate was found for obese men compared with normal weight men (OR = 0.68, 95% CI 0.40–1.14, **Figure 2**). As data were significantly heterogeneous ($P = 0.02$) the random effects model was used.

Live birth from ART

Five studies were included in the meta-analysis of the effect of male obesity on the OR of couples undergoing ART (IVF or ICSI) achieving a live birth (Bakos et al., 2011a; Colaci et al., 2012; Petersen et al., 2013; Schliep et al., 2015; Umul et al., 2015). Live birth rate was reported according to: oocyte retrieval (Bakos et al., 2011a), embryo transfer cycle (Colaci et al., 2012), treatment cycle (Petersen et al., 2013), ICSI cycle (Umul et al., 2015), and IVF cycle (Schliep et al., 2015). For the same reasons as above the inverse variance method was used to meta-analyse unadjusted data. A statistically significant decrease in live birth success rate was found for obese men compared with normal weight men (OR = 0.65, 95% CI 0.44–0.97, **Figure 3**). Heterogeneity was non-significant and the fixed effects model was used. Additionally, for three studies (Bakos et al., 2011a; Schliep et al., 2015; Umul et al., 2015), data were available that enabled the investigation of the difference between pregnancy rate (detection of a gestational sac) and live birth rate. It was found that the odds of having a non-viable pregnancy (pregnancy that did not result in a live birth) were significantly greater for couples with an obese male partner compared with normal weight partner (OR = 2.87, 95% CI 1.34–6.13, Supplementary **Figure S2A**),

with an absolute risk difference of 10% (95% CI 3–18%, Supplementary **Figure S2B**). Heterogeneity was non-significant and the fixed effects model was used.

Infant development

The one study that was found that met the inclusion criteria and investigated the effect of paternal obesity on offspring development found that paternal obesity significantly altered infant BMI growth curves from birth to 3.5 years compared with normal weight fathers ($P = 0.005$) (Linabery et al., 2012). This effect was still present after adjusting for maternal BMI ($P = 0.02$). Looking only at weight or length, the effect of paternal BMI did not reach significance. However, when the results were adjusted for maternal BMI the difference in offspring length between obese fathers and normal weight fathers was significant ($P = 0.05$).

Conventional semen characteristics

Sperm concentration

Thirteen studies, nine of which were carried out in the clinical ART population (Bakos et al., 2011a; Duits et al., 2010; Fariello et al., 2012; Hammiche et al., 2012; Lotti et al., 2011; Martini et al., 2010; Rybar et al., 2011; Shayeb et al., 2011; Tunc et al., 2011) and four in the general population (Aggerholm et al., 2009; Gutorova et al., 2014; La Vignera et al., 2012; Qin et al., 2007), were included in the meta-analysis of the effect of male obesity on mean sperm concentration. An additional four studies were found that presented data in values that could not be incorporated into the meta-analysis (Chavarro et al., 2010; Dupont et al., 2013; Eisenberg et al., 2014; Macdonald et al., 2013). Due to the presence of significant heterogeneity the random effects model was used in the meta-analysis. No significant differences were found for sperm concentration overall or in either of the subgroups (Supplementary **Figure S3**).

Normal morphology

Nine studies were included in the meta-analysis of the effect of male obesity on the percentage of sperm with normal morphology (Bakos et al., 2011a; Duits et al., 2010; Fariello et al., 2012; La Vignera et al., 2012; Lotti et al., 2011; Martini et al., 2010; Qin et al., 2007; Shayeb et al., 2011; Umul et al., 2015).

Seven assessed morphology by World Health Organization (WHO) criteria (Bakos et al., 2011a; Duits et al., 2010; La Vignera et al., 2012; Lotti et al., 2011; Qin et al., 2007; Shayeb et al., 2011; Umul et al., 2015), while two used Kruger's criteria (Fariello et al., 2012; Martini et al., 2010). Among the WHO studies five were conducted in the clinical ART population (Bakos et al., 2011a; Duits et al., 2010; Lotti et al., 2011; Shayeb et al., 2011; Umul et al., 2015), and two were conducted in the general population (La Vignera et al., 2012; Qin et al., 2007) (Supplementary **Figure S4**). Both of the studies that used Kruger's criteria were conducted in the clinical ART population (Fariello et al., 2012; Martini et al., 2010). An additional five studies were found that presented data in values that could not be incorporated in the meta-analysis (Chavarro et al., 2010; Dupont et al., 2013; Eisenberg et al., 2014; Macdonald et al., 2013; Pacey et al., 2014). Due to heterogeneity the random effects model was used in the meta-analysis of the WHO criteria studies, and a non-significant decrease in the percentage of sperm with normal morphology was found for obese men compared with normal weight men (Supplementary **Figure S4**). However, when analysis was restricted to the clinical ART population the decrease was statistically significant (WMD = −2.08%, 95% CI −3.25 to −0.92, Supplementary **Figure S4**). When Kruger's criteria studies were meta-analysed the results showed no significant difference (Supplementary **Figure S5**). Heterogeneity was non-significant and the fixed effects model was used.

Progressive motility

Twelve studies, nine of which were carried out in the clinical ART population (Bakos et al., 2011a; Duits et al., 2010; Fariello et al., 2012; Hammiche et al., 2012; Lotti et al., 2011; Martini et al., 2010; Rybar et al., 2011; Shayeb et al., 2011; Umul et al., 2015) and three in the general population (Gutorova et al., 2014; La Vignera et al., 2012; Qin et al., 2007), were included in the meta-analysis of the effect of male obesity on the mean percentage of sperm in ejaculate that were progressively motile. Five additional studies could not be included in the meta-analysis due to data incompatibilities (Chavarro et al., 2010; Dupont et al., 2013; Eisenberg et al., 2014; Kort et al., 2006; Macdonald et al., 2013). Due to the presence of significant heterogeneity the random effects model was used in the meta-analyses, which showed a small but significant decrease in motility for obese men overall (WMD = −3.72%, 95% CI −7.11 to −0.33), with a non-significant trend for a decrease in the clinical population (Supplementary **Figure S6**). A potentially larger decrease was found in the general population; however, due to greater variance the effect was not significant.

Ejaculate volume

Ten studies, seven of which were carried out in the clinical ART population (Duits et al., 2010; Fariello et al., 2012; Hammiche et al., 2012; Lotti et al., 2011; Martini et al., 2010; Rybar et al., 2011; Shayeb et al., 2011) and three in the general population (Gutorova et al., 2014; La Vignera et al., 2012; Qin et al., 2007), were included in the meta-analysis of the effect of male obesity on mean ejaculate volume. An additional three studies were found that presented data in values that could not be incorporated in the meta-analysis (Chavarro et al., 2010; Eisenberg et al., 2014; Macdonald et al., 2013). Due to the presence of heterogeneity the random effects model was used in the meta-analyses which showed no significant differences in ejaculate volume for obese men overall or in the subgroup analyses (Supplementary **Figure S7**).

Additional semen characteristics

Sperm DNA fragmentation

Four studies were included in the meta-analysis of the effect of male obesity on the percentage of sperm with DNA fragmentation (Fariello et al., 2012; La Vignera et al., 2012; Rybar et al., 2011; Tunc et al., 2011). Two studies assessed DNA fragmentation by TdT (terminal deoxynucleotidyl transferase)-mediated dUTP nick-end labelling (TUNEL) staining (La Vignera et al., 2012; Tunc et al., 2011), one used the sperm chromatin structure assay (SCSA) (Rybar et al., 2011), and the fourth

used the comet assay (Fariello et al., 2012). An additional study by Kort et al. assessed DNA fragmentation by the SCSA but did not provide population sizes (Kort et al., 2006). Chavarro et al. used the comet assay but presented data in median values (Chavarro et al., 2010). Dupont et al. used TUNEL but presented data as median values and mean differences (Dupont et al., 2013). Eisenberg et al. utilized the SCSA but presented data as median and dichotomized values (Eisenberg et al., 2014). A statistically significant increase in the percentage of sperm with DNA fragmentation was found for obese men compared with normal weight men (WMD = 3.41%, 95% CI 2.08–4.75, Supplementary **Figure S8**). Heterogeneity between studies was non-significant, supporting the idea that although diverse methods were used to assess DNA fragmentation the effect being measured was the same, and meta-analysis was therefore appropriate (additional sensitivity analysis showed that the significant effect was retained when the random effects model was applied, and when the SMD method of meta-analysis was used, data not shown). Three of the studies that could not be included in the meta-analysis reported statistically significant increases in sperm with DNA fragmentation in obese compared with normal weight men (Chavarro et al., 2010; Dupont et al., 2013; Kort et al., 2006), while the fourth found no significant difference in median percentage DNA fragmentation (Eisenberg et al., 2014).

Sperm chromatin condensation

Three studies contained data on the effect of male obesity on the percentage of sperm with decondensed chromatin (La Vignera et al., 2012; Martini et al., 2010; Rybar et al., 2011). One assessed chromatin condensation by propidium iodide staining and found a statistically significant increase in the percentage of spermatozoa with decondensed chromatin in obese men compared with normal weight men (La Vignera et al., 2012), another used aniline blue staining and found a statistically non-significant increase (Martini et al., 2010), and the third used the SCSA and found a statistically non-significant decrease (Rybar et al., 2011). Due to the diversity of methods of staining and results obtained, meta-analysis was not undertaken.

Sperm with low mitochondrial membrane potential

Two studies were found that reported the percentage of sperm with low MMP for obese men compared with normal weight men (Fariello et al., 2012; La Vignera et al., 2012). In one study, MMP was assessed by JC1 staining (La Vignera et al., 2012), and it was demonstrated that the percentage of sperm in the ejaculate of obese men that had low MMP was statistically significantly increased compared with normal weight men. In the other deposition of DAB (diaminobenzidine) was used as a measure (Fariello et al., 2012), and it was demonstrated that both the percentage of sperm with low MMP and the percentage of sperm with no MMP was statistically significantly increased in obese men compared with normal weight men. Due to the presence of heterogeneity and differences in how data were reported, the random effects model was used to assess standardized mean difference (SMD). A statistically significant increase in the percentage of sperm with low MMP was found for obese men compared with normal weight men (SMD = 0.91, 95% CI 0.30–1.53, Supplementary **Figure S9**).

Seminal plasma factors

Three papers reported on the effects of male obesity on the concentrations of different seminal plasma factors (Lotti et al., 2011; Martini et al., 2010; Tunc et al., 2011). However, each paper investigated different factors. As such, meta-analysis was not undertaken.

In Tunc et al., a statistically significant positive correlation was found for increasing concentration of neopterin in seminal plasma and increasing BMI (Tunc et al., 2011). In the study by Lotti et al., being obese was correlated with a statistically significantly increased concentration of interleukin-8 in seminal plasma compared with normal weight men (Lotti et al., 2011). Martini et al. found a statistically significant negative correlation between increasing BMI and the seminal plasma concentration of alpha-glucosidase as well as a statistically significant positive correlation between BMI and seminal plasma concentration of fructose (Martini et al., 2010). Differences for citric acid were not statistically significant.

Discussion

The meta-analyses performed in this systematic review have provided clear evidence that human paternal obesity negatively affects reproductive potential, as shown by significantly reduced fertility in the general population and reduced rates of live birth from ART, as well as increased rates of non-viable pregnancy. A non-significant decrease in rate of clinical pregnancy from ART was also found, which requires additional studies for firm conclusions to be drawn. To the authors' knowledge this systematic review is the first instance where these primary fertility outcomes have been assessed by meta-analysis to demonstrate the negative effect that male obesity has on reproduction. Unfortunately, the majority of studies meta-analysed did not present values adjusted for maternal BMI, leaving open the possibility that these findings could be influenced by assortative mating. Additionally, these findings are based on observational research, and therefore show correlation and not causation. However, that paternal obesity is responsible for decreased fertility is supported by experimental studies performed in animal models (Fullston et al., 2013; Mitchell et al., 2011). Furthermore, there is evidence from both animal and human models that improving the metabolic health of obese males (through exercise and/or controlled diet) can improve fertility (Faure et al., 2014; Hakonsen et al., 2011; McPherson et al., 2013).

The physiological cause of the reduction in reproductive potential found by this review is less clear, with the conventional semen parameters ejaculate volume and concentration showing no statistically significant differences between obese and normal weight men, while the difference found for motility was small. This supports the previous findings of MacDonald et al. (2010), who found no significant association between paternal obesity and mean sperm count, motility and ejaculate volume. It should be noted that sperm concentration is known to have a highly skewed distribution, which may make WMD a suboptimal measure. Supporting this, in a recent meta-analysis where the authors had access to the primary data of all included studies and could classify participants as normospermic, oligospermic or azoospermic, it was shown that obese men were

significantly more likely to be oligo- or azoospermic (Sermondade et al., 2013). However, there were semen parameters reported on in this systematic review that did show significant differences; normal morphology, DNA fragmentation and low MMP were all negatively impacted by paternal obesity. The loss of mitochondrial membrane potential and increased DNA fragmentation in spermatozoa are associated with high concentrations of reactive oxygen species (ROS) (Wang et al., 2003; Zribi et al., 2011). High ROS concentrations have been associated with reduced fertilization and impaired embryonic development (Dada et al., 2010; Gharagozloo and Aitken, 2011; Tunc et al., 2010; Zribi et al., 2011), and have consistently been shown to increase with obesity (Bakos et al., 2011b; Hirao et al., 2010; Tunc et al., 2011). Importantly, ROS concentrations and DNA fragmentation are also associated with pregnancy loss (Dada et al., 2010; Gharagozloo and Aitken, 2011; Imam et al., 2011) and therefore could be the cause of the increased frequency of non-viable pregnancies found for obese men in this meta-analysis. Findings for DNA fragmentation were the strongest as the meta-analysis was based on four studies, with an additional three studies similarly reporting significant increases in DNA fragmentation with paternal obesity. This has potential clinical implications as a case series study found that overweight and obese men from couples with idiopathic infertility and high sperm DNA fragmentation who undertook a weight loss intervention had reduced rates of DNA fragmentation and all subsequently conceived spontaneously or with minimal assistance (intrauterine insemination) (Faure et al., 2014). The finding that paternal obesity was associated with decreased normal morphology was only made in the clinical population when morphology was assessed by WHO criteria. When studies were carried out in the general population, or using Kruger's criteria, the difference in mean sperm morphology for obese and normal weight men became non-significant. As there were only two included studies that assessed sperm morphology in the general population or that used Kruger's criteria, these findings require further investigation before firm conclusions can be made. Interestingly, a study on weight loss carried out in obese men found that sperm morphology was significantly improved in men with the greatest weight loss (Hakonsen et al., 2011). Finally, the percentage of sperm with low MMP increased with paternal obesity. This finding was based on only two studies, but both reported statistically significant effects. As such, it is relatively unlikely that further replication will alter the conclusion that paternal obesity is associated with increased rates of sperm with low MMP. These findings suggest that the reduced reproductive potential that has been shown to be associated with paternal obesity may be mediated by increased rates of sperm with DNA fragmentation, abnormal morphology and low MMP. This suggests that the assessment of conventional semen parameters typically carried out in fertility clinics may be insufficient to detect the cause of some obese men's failure to conceive. As such, it may be useful for pathology laboratories to incorporate DNA fragmentation analysis and/or MMP assessment into their semen testing regimen, especially for obese men whose semen analyses otherwise suggest they should have normal fertility.

The main strength of this systematic review is its numerous novel findings. It is not only the first review to use meta-analysis to investigate the relationship between paternal obesity and primary reproductive outcomes (fertility, clinical pregnancy after ART, live birth after ART, and pregnancy viability), it is also the first systematic review to go beyond conventional semen parameters and meta-analyse sperm morphology, DNA fragmentation, and low MMP.

One limitation of the current review was the high degree of heterogeneity that existed between studies for many measures – which necessitated the use of the random effects model for many meta-analyses and reduced statistical power. Although heterogeneity between observational studies is expected, it is still interesting and suggests differences in the conduct of individual studies. Furthermore, for several outcomes – seminal plasma factors, sperm chromatin condensation and embryo development – meta-analysis could not be performed owing to the included studies not reporting comparable data. Additionally, only one study was found which met the inclusion criteria and reported on the effect of paternal obesity on infant development (Linabery et al., 2012). As the health of the next generation is of the utmost importance, this is a key limitation, especially as the potential for paternal obesity to influence development beyond fertilization is strongly indicated by the increased rate of non-viable pregnancy that has been found.

In conclusion, this systematic review has demonstrated that the reproductive potential of obese men – as indicated by fertility, rate of live birth from ART, and pregnancy viability – is reduced relative to that of normal weight men. The data suggest that this may be due to decreased normal morphology, and increased rates of DNA damage and low MMP. If this observation is upheld by further investigation it has clinical implications for the diagnosis of infertility in obese men.

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Appendix: Supplementary material

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