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META-ANALYSIS ***Infertility***

IVF outcomes in obese donor oocyte recipients: a systematic review and meta-analysis

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STUDY QUESTION: Does obesity influence the chance of pregnancy after IVF in donor oocyte recipients?

SUMMARY ANSWER: The chance of pregnancy after IVF is no different in obese donor oocyte recipients versus those in the normal BMI range.

WHAT IS KNOWN ALREADY: Obesity is associated with decreased chances of pregnancy in women undergoing IVF with autologous oocytes. Prior studies have investigated the impact of obesity on IVF outcomes in donor oocyte recipients, with disparate results. This is the first systematic review and meta-analysis to address this topic.

STUDY DESIGN, SIZE, DURATION: A systematic review and meta-analysis of published literature identified in Medline, EMBASE and Scopus through December of 2011 were performed to address the association between BMI and outcomes for donor oocyte recipients. The primary outcome of this study was implantation.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Two authors conducted the searches independently, selected the studies and abstracted the data. Studies in English of first donor oocyte cycles with reported recipient BMI were included. Primary data collected from the IVF program at Washington University were also included as one study ($n = 123$ donor oocyte recipients). Studies limited to frozen embryo transfer were excluded. Data were synthesized using DerSimonian–Laird random effects models for implantation, clinical pregnancy, miscarriage and live birth.

MAIN RESULTS AND THE ROLE OF CHANCE: Of 475 screened articles, 7 were reviewed and 5 were included together with primary data from Washington University, giving a total of 4758 women who were included for the assessment of the primary outcome. No associations between obesity (BMI $\geq$ 30 kg/m^2) and chance of pregnancy after IVF were noted in women using donor oocytes [risk ratio (RR): 0.98, 95% confidence intervals (CI): 0.83–1.15, I^2: 61.6%]. Additional analyses assessing associations between recipient obesity and embryo implantation (RR: 0.93, 95% CI: 0.80–1.07, I^2: 0%), miscarriage (RR: 1.12, 95% CI: 0.83–1.50, I^2: 0%) and live birth (RR: 0.91, 95% CI: 0.65–1.27, I^2 47.9%) also failed to show a negative effect.

LIMITATIONS, REASONS FOR CAUTION: Included studies were small and they were performed in a variety of locations and practice settings where stimulation and laboratory protocols may differ, and extremes of BMI may also differ. Furthermore, included studies had different inclusion and exclusion criteria. These factors could not be controlled for in this meta-analysis and statistical heterogeneity was noted for some outcomes.

WIDER IMPLICATIONS OF THE FINDINGS: These data suggest obesity does not affect IVF outcomes in women using donor oocytes. Oocyte quality rather than endometrial receptivity may be the overriding factor influencing IVF outcomes in obese women using autologous oocytes.

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Introduction

Obesity is associated with adverse reproductive outcomes including subfertility and increased risk of miscarriage (Boots and Stephenson, 2011). Obese women who conceive naturally are at increased risk of adverse pregnancy outcomes, such as pre-eclampsia, gestational diabetes and stillbirth (Chu *et al.*, 2007). Children born to obese women are at increased risk of congenital and growth abnormalities (Stothard *et al.*, 2009). Obese women who conceive with the assistance of IVF face similar risks in pregnancy as women who conceive naturally (Dokras *et al.*, 2006; Rittenberg *et al.*, 2011). What is different is that the precise timing of events and close follow up involved in the care of women undergoing IVF provide a unique opportunity to observe associations between preconception exposures and various steps of the reproductive process including implantation, clinical pregnancy, miscarriage and live birth.

There has been a longstanding debate about which components of the reproductive process are affected most by obesity. Whereas some have focused on adverse effects of obesity on oocyte quality, others have focused on the endometrium (Jungheim and Moley, 2010). A number of studies have evaluated associations between obesity and adverse reproductive outcomes in women undergoing donor oocyte IVF and embryo transfer as a way to separate out the effects of obesity on the oocyte versus the endometrium and implantation. Taken alone, these studies are limited by sample size. Our objective was to estimate the associations between BMI and IVF outcomes in donor oocyte recipients through a systematic review and meta-analysis.

Methods

The conduct and reporting of this systematic review closely adhered to guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher *et al.*, 2009). We used a predesigned protocol for the literature search, study selection and data synthesis.

Search strategy

Our literature search included Medline, EMBASE and Scopus through 2011 using MeSH headings: (*In vitro* Fertilization (IVF) OR assisted reproductive techniques) AND 'Donor Oocytes' AND (Obesity OR BMI) AND Human. The reference list was screened and relevant articles retrieved. If there was a question about an article's relevance it was also retrieved for further review. Reference lists in identified articles were manually searched for other potentially relevant publications.

Study selection criteria

Studies were limited to those published in English analyzing the first cycle of donor IVF. Studies were required to report BMI for the donor oocyte recipients. Studies including the use of frozen embryos were excluded. If more than one study included overlapping data, the largest of the studies was kept and the other was excluded. Study design was not limited.

Primary data collection

Institute Review Board approval was obtained and primary data from the IVF program at Washington University were also collected and included as one of the studies. Medical and laboratory charts were reviewed to collect patient BMI, age and IVF outcome including embryo implantation, clinical pregnancy and live birth. Our program has strict selection criteria for anonymous oocyte donors in that they must be <35 years of age, non-smokers, have a BMI in the normal range and no significant medical issues. Our donors all undergo standard gonadotrophin stimulation protocols as previously described (Jungheim *et al.*, 2009) and our oocyte recipients receive GnRH agonists for ovarian suppression, where appropriate, along with oral estrogen and i.m. progesterone for uterine lining preparation.

Study selection and data abstraction

Each eligible article was reviewed and data were extracted for study design and location, year of publication, for the number of patients in each of the four standard World Health Organization (WHO) BMI categories: (i) <20 kg/m^2, (ii) 20–24.9 kg/m^2, (iii) 25–29.9 kg/m^2 and (iv) ≥ 30 kg/m^2. Data were also extracted for donor oocyte recipient age, oocyte donor age, embryo implantation, clinical pregnancy, miscarriage and live birth. Information regarding selection and preparation for oocyte donors and preparation for oocyte donor recipients was also collected along with relevant study inclusion and exclusion criteria. The published data for two studies did not specify the outcomes for first donor oocyte cycles using the BMI groups described above (Bodri *et al.*, 2010; DeUgarte *et al.*, 2010). The authors of these studies were contacted and were able to provide the relevant data necessary for incorporation into this meta-analysis. The primary outcome for this study was implantation (defined as the number of gestational sacs seen on first trimester ultrasound divided by the total number of embryos transferred) while clinical pregnancy, miscarriage and live birth were secondary outcomes. The quality of each study was assessed using methods described by Downs and Black (1998). Briefly, this consists of a checklist of 27 items aimed at assessing the methodological quality of observational studies with regard to the quality of reporting, internal validity, power and external validity. Only 19 of the items from the Downs and Black (1998) checklist were relevant to the studies we assessed. All steps were performed independently by E.S.J. and S.B.S.

Data analysis

Abstracted data and primary data were analyzed using STATA 12 (Stata, College Station, TX, USA). Heterogeneity was assessed using χ^2 test for heterogeneity (Cochran's Q statistic), and the magnitude of heterogeneity quantified using I^2 [($I^2 = Q -$ degrees of freedom) $\times$ 100/Q], where degrees of freedom $= k - 1$, $Q =$ Cochran's Q statistic and k the number of studies) (Higgins and Thompson, 2002). Pooled risk ratios (RR) and 95% confidence intervals (CI) from the studies were calculated for implantation, clinical pregnancy, miscarriage and live birth using a random effects model (DerSimonian and Laird, 1986).

Results

A flow diagram of study identification for the meta-analysis is shown in Fig. 1. Twenty-five publications were identified and reviewed from our initial search (Carrell *et al.*, 2001; Bellver *et al.*, 2003; Thum *et al.*, 2003; Wattanakumtornkul *et al.*, 2003; Zenke and Chetkowski, 2004; Styne-Gross *et al.*, 2005; Bellver *et al.*, 2007; Budak *et al.*, 2007; Maheshwari *et al.*, 2007; Nelson and Fleming, 2007; Soares *et al.*, 2007; Campos *et al.*, 2008; Howards and Cooney, 2008; Metwally *et al.*, 2008; Soares *et al.*, 2008; Dessolle *et al.*, 2009; Lash and Armstrong, 2009; Bodri *et al.*, 2010; Brewer and Balen, 2010; DeUgarte *et al.*, 2010; Huddleston *et al.*, 2010; van der Hoorn *et al.*, 2010; Rittenberg *et al.*, 2011; Luke *et al.*, 2011a, b). Eleven of these studies were excluded because they did not have useable BMI data (Thum *et al.*, 2003; Zenke and Chetkowski, 2004; Budak *et al.*, 2007; Soares *et al.*, 2007; Campos *et al.*, 2008; Howards and Cooney, 2008; Soares *et al.*, 2008; Lash and Armstrong, 2009; Brewer and Balen, 2010; Huddleston *et al.*, 2010;

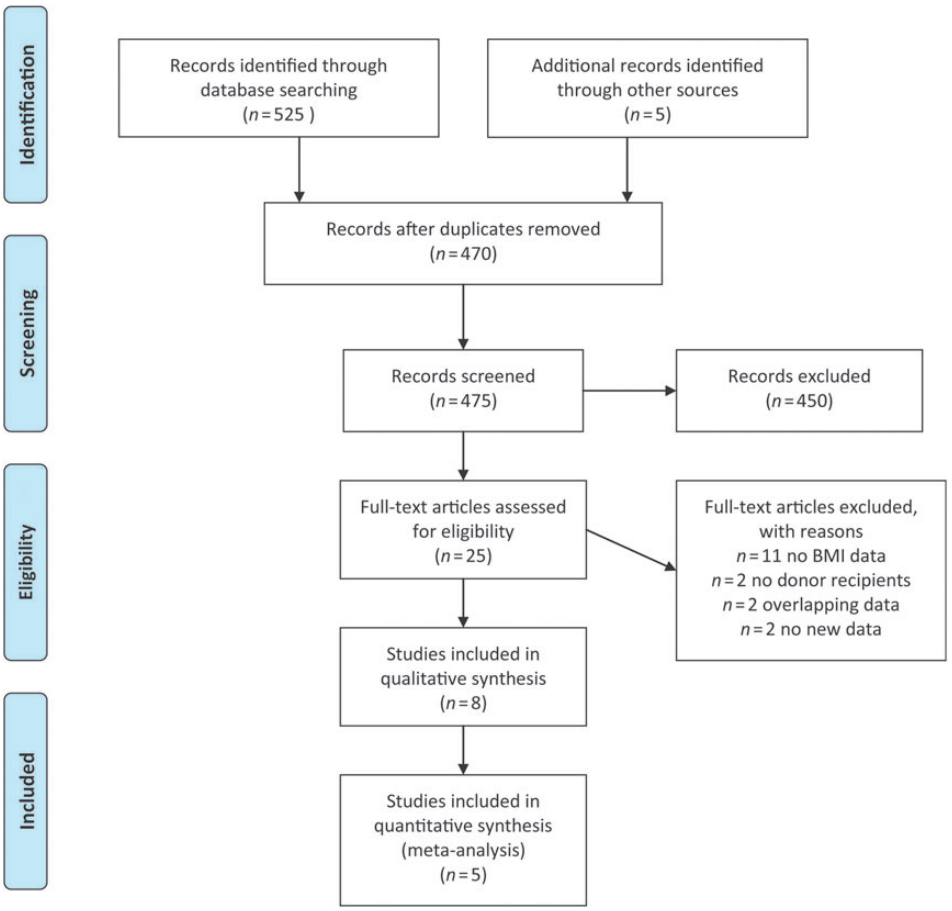

Figure 1 PRISMA 2009 flow diagram. From Moher *et al.* (2009). For more information, visit www.prisma-statement.org.

van der Hoorn *et al.*, 2010) and two were excluded because they did not involve oocyte recipients (Maheshwari *et al.*, 2007; Nelson and Fleming, 2007). Two additional studies were excluded because they incorporated data that overlapped with other included publications (Bellver *et al.*, 2003; Luke *et al.*, 2011b). Two more articles were excluded because they were review articles containing no previously unidentified publications or data (Metwally *et al.*, 2008; Rittenberg *et al.*, 2011). Eight articles were reviewed in depth. One of the eight articles was excluded from the meta-analysis because it included multiple cycles per donor oocyte recipient (Luke *et al.*, 2011a). Another was excluded because it used frozen donor embryo cycles only (Dessolle *et al.*, 2009) and a third was excluded because it used unconventional BMI categories (Carrell *et al.*, 2001). Five of the eight articles were included in the meta-analysis along with our primary data (Wattanakumtornkul *et al.*, 2003; Styne-Gross *et al.*, 2005; Bellver *et al.*, 2007; *et al.*, 2010; DeUgarte et.al., 2010) The characteristics of these five studies and the primary data collected in our IVF unit are outlined in Table I along with tabulated quality scores (Downs and Black, 1998). All five studies specified the characteristics of the donors in their programs, all specified the uterine preparation protocols for oocyte recipients and all had useable data for the four standard WHO categories for BMI. Three studies did not report their oocyte donor-controlled ovarian hyperstimulation protocols (Styne-Gross *et al.*, 2005; Bodri *et al.*, 2010; DeUgarte *et al.*, 2010). All five studies had data for embryo implantation. Four had data available for clinical pregnancies and for miscarriage (Styne-Gross *et al.*, 2005; Bellver *et al.*, 2007; Bodri *et al.*, 2010; DeUgarte *et al.*, 2010), and two had information regarding live births (Wattanakumtornkul *et al.*, 2003; DeUgarte *et al.*, 2010).

Study quality scores ranged from 14 to 18 out of a total of 19 possible points. Points were deducted from the studies for failing to report details of stimulation protocols that the donors underwent and/or details regarding how the endometrium was prepared in the donor oocyte recipients. Several studies also lost points for failing to adequately describe characteristics of their donor oocyte recipients. On the other hand, given that there are only a handful of different methods for stimulating oocyte donors and for preparing the uterine endometrium for embryo transfer and given that donors are typically young and chosen for good reproductive potential, we believe the studies were of similar methodological quality.

From the meta-analysis, obesity (BMI $> 30\ kg/m^2$) was not associated with a difference in implantation (RR: 0.93, 95% CI: 0.80–1.07) or clinical pregnancy (RR: 0.98, 95% CI: 0.83–1.15) rates compared with a BMI in the normal range. However, overall there was significant heterogeneity among studies for clinical pregnancy (I^2 value: 61.6%) (Fig. 2). Primary data collected from our center for this meta-analysis were the only data to show a beneficial effect of obesity on clinical

Table I Characteristics and quality scores of studies[a] comparing BMI and IVF outcomes in women receiving donor oocytes.

Study	Year	Location	Design	Inclusion and exclusion criteria	Characteristics of oocyte donors described	COH protocol described	Donor oocyte recipient protocol described	Quality score (out of 19 possible points)	Population BMI (kg/m^2)			
									<20	20–24.9	25–29.9	≥30
Bellver *et al.*	2007	Spain	RC	I: Donor oocyte recipients, recent BMI, good embryo quality E: RPL, APA, no uterine pathology or severe sperm pathology	Yes	Yes	Yes	18	471	1613	450	122
Bodri *et al.*	2010	Spain	RC	I: Donor oocyte recipients, Black, East Asian and Caucasian E: Frozen embryo cycles	Yes	No	Yes	14	195	544	92	67
DeUgarte *et al.*	2010	CA, USA	RC	I: Donor oocyte recipients E: Smokers, PCOS, RPL, DM, HTN, rescue ICSI	Yes	No	Yes	16	9	125	112	103
Styne-Gross *et al.*	2005	NJ, USA	RC	I: Donor oocyte recipients E: None specified	Yes	No	Yes	15	101	284	74	77
Wattanakumtornkul *et al.*	2003	MN, USA	RC	I: Donor oocyte recipients E: No BMI data	Yes	Yes	Yes	15	7	52	25	12
Jungheim	2012	MO, USA	RC	I: Donor oocyte recipients E: None	Yes	Yes	Yes	–	8	47	39	29

RC, retrospective cohort; COH, controlled ovarian hyperstimulation; I, inclusion criteria; E, exclusion criteria; RPL, recurrent pregnancy loss; APA, antiphospholipid antibodies; PCOS, polycystic ovary syndrome; DM, diabetes mellitus; HTN, hypertension; ICSI, intracytoplasmic sperm injection.

[a]As the original search was in 2011, an additional search was performed and no further suitable papers were identified for inclusion.

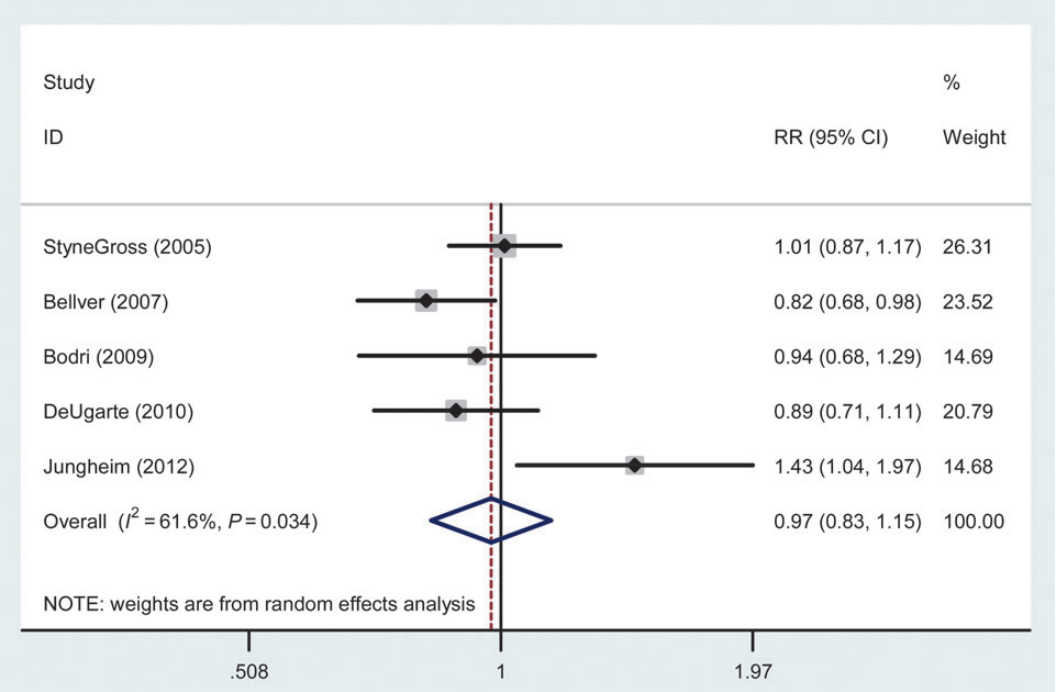

Figure 2 Forest plot comparing clinical pregnancy in obese versus normal weight women using donor oocytes.

pregnancy rates (RR: 1.43, 95% CI: 1.04–1.97). Given this, we performed the analysis again excluding our primary data and still found no association between obesity and clinical pregnancy rates (RR: 0.92, 95% CI: 0.83–1.02). Excluding our data resulted in a dramatic reduction of the heterogeneity seen previously (I^2 value: 12.2%). In addition, we found that obesity was not associated with a difference in the chances of miscarriage or live birth compared with normal BMI. Characteristics of underweight and overweight were also not associated with differences in IVF outcomes (implantation, clinical pregnancy, miscarriage, live birth) compared with women of normal BMI. The results for all BMI groups and each of the outcomes evaluated are outlined in Table II.

Discussion

Obesity is common among women of reproductive age and it is associated with significant reproductive sequelae and adverse pregnancy outcomes, although the mechanisms involved are largely unknown. Significant debate exists as to which components of the reproductive process are affected most by obesity. Some have focused on the adverse effects of obesity on oocyte quality, whereas others have focused research efforts on a study of the endometrium (Jungheim and Moley, 2010). The donor oocyte model has been proposed as a model to investigate the effects of various patient characteristics and exposures on endometrial receptivity and contribution to adverse outcomes of assisted reproduction techniques (ARTs), as oocytes are often obtained from healthy young women with no known reproductive problems (Check, 1994). In this meta-analysis, we pooled the results of five studies investigating obesity in donor oocyte recipients with the primary data collected from our donor IVF program. Two of these published studies demonstrate a mild effect of obesity on embryo implantation, clinical pregnancy, miscarriage and live birth in women receiving donor oocytes, whereas the other two published studies show no effect. Collectively, the pooled results of these studies in our meta-analysis show that obesity does not significantly affect embryo implantation or the chance of clinical pregnancy. There was also no significant effect of obesity on miscarriage and live birth rates.

The two studies demonstrating a mild effect of obesity on ART outcomes in women receiving donor oocytes differed from the other two included studies showing no effect in that they excluded women with recurrent pregnancy loss and they had other exclusion criteria (Bellver *et al.*, 2007; DeUgarte *et al.*, 2010). It is possible that these exclusions biased the outcomes in the two studies toward showing an effect by improving the outcomes in the women without obesity or other comorbidities. It would be beneficial if these studies had provided information on the distribution of the excluded women among the BMI groups in order to make this determination.

While this meta-analysis demonstrates no significant effect of obesity on measured ART outcomes in women receiving donor oocytes, it is important to note that live birth rates were not reported by all of the studies thus limiting our power to investigate this outcome, and adverse pregnancy outcomes were not reported in any of the studies. This is not uncommon in published clinical studies on ART. Ultimately, a healthy live birth is the goal of any ART intervention. Admittedly, we do not have adverse pregnancy event outcomes for our own patient population either. The larger body of obstetric literature demonstrates a significant negative impact of obesity on the chance of live birth and this should not be ignored when counseling obese women on the potential risks of pregnancy using donor oocytes (Chu *et al.*, 2007).

Whereas we did not find an association between donor oocyte recipient obesity and adverse ART outcomes in our meta-analysis, large

Table II Meta-analysis of included data (to 2011): BMI and IVF outcomes in women using donor oocytes.

BMI category (kg/m^2)	Number of studies[a]	Sample size	Statistical model	RR (95%CI)	Statistical heterogeneity (I^2, %)
Implantation ($n = 4758$)					
<20	6	791	Random effects	1.01 (0.91–1.12)	0
20–24.9		2665	–	Reference	
25–29.9	6	892	Random effects	0.92 (0.822–1.02)	0
>30	6	410	Random effects	0.93 (0.80–1.07)	0
Clinical pregnancy ($n = 4662$)					
<20	5	784	Random effects	1.03 (0.93–1.15)	44.8
20–24.9		2613	–	Reference	
25–29.9	5	867	Random effects	0.94 (0.88–1.01)	0
>30	5	398	Random effects	0.98 (0.83–1.15)	61.6
Miscarriage ($n = 4662$)					
<20	5	784	Random effects	0.92 (0.73–1.17)	0
20–24.9		2613	–	Reference	
25–29.9	5	867	Random effects	0.90 (0.59–1.34)	45.3
>30	5	398	Random effects	1.12 (0.83–1.50)	0
Live birth ($n = 568$)					
<20	3	24	Random effects	0.83 (0.57–1.21)	0
20–24.9		224	–	Reference	
25–29.9	3	176	Random effects	1.02 (0.82–1.25)	0
>30	3	144	Random effects	0.91 (0.65–1.27)	47.9

RR, risk ratio; CI, confidence intervals.
[a]Data were available for each outcome from the following studies as listed:
Implantation: Wattanakumtornkul *et al.* (2003); Styne-Gross *et al.* (2005); Bellver *et al.* (2007); Bodri *et al.* (2010); DeUgarte *et al.* (2010; Washington University IVF center data; Clinical pregnancy and miscarriage: Styne-Gross *et al.* (2005); Bellver *et al.* (2007); Bodri *et al.* (2010); DeUgarte *et al.* (2010), Washington University IVF center data; Live birth: Wattanakumtornkul *et al.* (2003); DeUgarte *et al.* (2010), Washington University IVF center data.

cohort and cross-sectional studies of obese women using their own oocytes have shown an association (Luke *et al.*, 2011a,b). Meta-analyses on this topic have concurred (Metwally *et al.*, 2008; Rittenberg *et al.*, 2011). Because ART offers the opportunity to separate out events of the reproductive process and donor oocyte cycles offer the opportunity to isolate preconception exposures on oocytes and the endometrium, the donor oocyte model would seem the ideal model for investigating the effect of obesity on the endometrium. On the other hand, one needs to consider how, and if, this model can be used to draw conclusions regarding what happens in natural conception or even in fresh ART cycles among women using their own oocytes. In fresh ART cycles among women receiving their own oocytes, the monitoring and preparation or stimulation are usually focused on the goal of achieving optimal ovarian follicle size, whereas in donor oocyte recipients the goal is reaching optimal endometrial thickness and morphology. It is possible that the way in which the endometrium is prepared and monitored in donor oocyte cycles may override any adverse effects that obesity may have on it.

Another difficulty in using published studies to investigate the donor oocyte recipient model is that most women using donor oocytes are doing so because they are older and not eligible to go through IVF using their own oocytes. Older women often have other medical conditions that place them at higher risk for pregnancy complications and, as a result, many IVF programs place restrictions on who they will accept. For fear that obesity may decrease their published IVF success statistics, some clinics also place BMI and weight restrictions on who they will accept. Consequently, women who are morbidly obese or who have co-morbidities associated with their obesity may not be represented in the published data.

It may be argued that the studies included here are not only evaluating recipient characteristics. Donor BMI may indeed affect oocyte quality and could have biased the results presented here. Although specific data were not available for oocyte donors we would argue that, in general, most clinical practices limit oocyte donation to healthy young women who are likely to have good quality oocytes. This is the assumption we made for our meta-analysis and was based on the fact that all of the studies included in our meta-analysis stated that oocytes were from healthy young women. Thus, a difference in recipient characteristics is not likely to be a confounding factor among the studies —rather it is consistent and controlled for.

In conclusion, the pooled results of studies in our meta-analysis show that obesity is not associated with decreased embryo implantation or clinical pregnancy. There was also no effect on miscarriage and live birth rates. However, it is difficult to apply the results of this work to women conceiving naturally or through IVF using their own oocytes. A prospective study of obesity and its associations with outcomes in natural and ART conceptions will be helpful in moving this forward.

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Authors' roles

E.S.J. was involved in conception and design, acquisition of data, analysis and interpretation of data, drafting and revision of article and final approval of submitted manuscript. S.B.S., M.B.S., D.A.D.U. and S.A.F. were involved in acquisition of data, drafting and revision of article and final approval of submitted manuscript. M.G.T. was involved in conception and design, drafting and revision of article and final approval of submitted manuscript.

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Conflict of interest

None declared.

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