Complications and outcome of assisted reproduction technologies in overweight and obese women†

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BACKGROUND: Based on a presumed negative impact of overweight and obesity on reproductive capacity and pregnancy outcome, some national guidelines and clinicians have argued that there should be an upper limit for a woman’s BMI to access assisted reproductive technologies (ART). However, evidence on the risk of complications or expected success rate of ART in obese women is scarce. We therefore performed a systematic review on the subject.

METHODS: We searched the literature for studies reporting on complications or success rates in overweight and obese women undergoing ART. Articles were scored on methodological quality. We calculated pooled odds ratios (ORs) to express the association between overweight and obesity on the one hand, and complications and success rates of ART on the other hand. We only pooled results if data were available per woman instead of per cycle or embryo transfer.

RESULTS: We detected 14 studies that reported on the association between overweight and complications during or after ART, of which 6 reported on ovarian hyperstimulation syndrome (OHSS), 7 on multiple pregnancies and 6 on ectopic pregnancies. None of the individual studies found a positive association between overweight and ART complications. The pooled ORs for overweight versus normal weight for OHSS, multiple pregnancy and ectopic pregnancy were 1.0 [95% confidence interval (CI) 0.77–1.3], 0.97 (95% CI 0.91–1.04) and 0.96 (95% CI 0.54–1.7), respectively. In 27 studies that reported on BMI and the success of ART, the pooled ORs for overweight versus normal weight on live birth, ongoing and clinical pregnancy following ART were OR 0.90 (95% CI 0.82–1.0), 1.01 (95% CI 0.75–1.4) and OR 0.94 (95% CI 0.69–1.3), respectively.

CONCLUSIONS: Data on complications following ART are scarce and therefore a registration system should be implemented in order to gain more insight into this subject. In the available literature, there is no evidence of overweight or obesity increasing the risk of complications following ART. Furthermore, they only marginally reduce the success rates. Based on the currently available data, overweight and obesity in itself should not be a reason to withhold ART.

Key words: assisted reproduction / body mass / ectopic pregnancy / OHSS / multiple pregnancy

Introduction

Obesity is a growing problem throughout the Western world with more than half of the women in the UK and USA being overweight or obese, and up to 25% of women in their reproductive age being obese (Haslam and James, 2005; Balen and Anderson, 2007). Several studies have shown that obesity is associated with a reduced fecundity (Jensen et al., 1999; Ramlau-Hansen et al., 2007; Van der Steeg et al., 2007). In addition, obese women are more prone to anovulation (Pasquali et al., 2007) and symptoms of polycystic ovarian syndrome (PCOS) are aggravated by obesity. Pregnancy in overweight and obese women is associated with an increased risk of complications, leading to higher maternal and neonatal morbidity and mortality and increased costs (Sebire et al., 2001; Cedergren, 2004; Linné, 2004; Weiss et al., 2004; Usha Kiran et al., 2005).
Due to the worldwide epidemic of obesity, an increasing proportion of women seeking medical help for subfertility will be overweight or obese. In their analysis, Vahdatan and Smith (2009) found that, in comparison to normal weight women, obese women seek medical attention for their subfertility more often. They receive, however, the least fertility-related services. Guidelines that regulate access to fertility care for overweight and obese women vary worldwide. In New Zealand, for example, women with a BMI of $>32 \text{ kg/m}^2$ are excluded from any fertility treatment. Almost all clinics in the UK have an upper BMI limit for access to assisted reproductive technologies (ART), ranging from 25 to 40 kg/m$^2$ (Gillet et al., 2006; Zachariah et al., 2006; Awartani et al., 2009). The UK national guideline recommends that women with a BMI above 29 kg/m$^2$ should be informed about their lower pregnancy chances but does not explicitly prescribe a BMI cut-off point for treatment (NICE, 2004).

Recently, the ESHRE Task Force on Ethics and Law (2010), reported on lifestyle-related factors, i.e. alcohol consumption, smoking and obesity, and access to medically assisted reproduction. It was argued that if a high risk of serious harm for the future child is anticipated, fertility treatment should be denied. Although this risk is obvious for alcohol consumption and smoking, it is unclear whether this recommendation can be applied in daily clinical practice with respect to adipose subfertile women.

Data regarding the impact of overweight and obesity on fertility treatment outcome are conflicting, with some studies showing a negative impact on pregnancy rates, whereas others report no impact (Fedorcak et al., 2004; Balen et al., 2006; Dokras et al., 2006). In a systematic review of the literature on overweight and ART, Maheshwari et al. (2007) concluded that there is insufficient evidence of the effect of BMI on the outcome of ART to justify denial of treatment for overweight and obese women.

Apart from the impact of overweight and obesity on spontaneous pregnancy rates and the course of pregnancy, little is known about the impact of BMI on complications of ART. Some have suggested that women with a high BMI are more prone to complications during their fertility treatment and fertility treatment should therefore be denied.

The aim of the present systematic review was to investigate the association between overweight or obesity and the occurrence of complications of ART, as well as the expected outcome in terms of clinical and ongoing pregnancy and live birth rates. To do so, we updated the review of Maheshwari et al. (2007), and added a new review with data on the impact of overweight and obesity on the risk of complications of ART.

Materials and Methods

We searched the literature from January 1999 till July 2011 for studies that reported on the association between overweight and obesity on complications of ART, as well as for studies that reported on the association between overweight and obesity and the effectiveness of ART. We searched PubMed, Embase, DARE and the Cochrane Library for studies reporting on the association between BMI and complications of ART. Only studies in English were included. To do so, we combined the keywords (‘obesity’, ‘overweight’ or ‘body mass index’), (‘complication’, ‘ovarian hyperstimulation syndrome’, ‘ectopic pregnancy’, ‘multiple pregnancy’, ‘infection’, ‘haemorrhage’ or ‘injury’) and (‘in vitro fertilisation’).

In the search for studies on the association between overweight and obesity and the outcome of ART, we added the keywords (‘outcome’, ‘pregnancy rate’, ‘live birth rate’). Additionally, we checked the references of the selected articles for relevant articles.

Since overweight and obese women are more prone to PCOS, which has an increased risk of ovarian hyperstimulation syndrome (OHSS) after ART (Tummon et al., 2005), we searched and described this group separately using keywords mentioned above in combination with (‘polycystic ovarian syndrome’).

Study quality

Two reviewers independently screened titles and abstracts of all retrieved studies (A.M.H.K. and M.A.Q.M.). We obtained full-text reports of studies that were likely to evaluate the association between BMI and complications or BMI and success rates of ART. If the title did not contain any of our keywords, it was excluded. Reviews were excluded. If not enough data were available for a 2 × 2 table, studies were excluded. Studies reporting on fertility treatment other than IVF/ICSI were excluded. Studies that did not report sufficient data for a 2 × 2 table, but for which data could possibly be obtained from the authors, were also evaluated.

We extracted data on study characteristics, study quality and 2 × 2 tables of test accuracy using a predefined data extraction form. In the case of multiple publications on the same data set, we used all publications to acquire complete data. The most recent and complete results were included in the analysis. If data on test accuracy or on other relevant characteristics were missing, we contacted the corresponding author. Disagreement on data was resolved by discussion and consensus. If consensus could not be reached, a third reviewer (B.W.M.) was consulted.

Methodological quality of selected papers was evaluated using QUADAS, a tool for quality assessment of studies of diagnostic accuracy (Whiting et al., 2003). We adjusted the original QUADAS list in order to evaluate items that we considered of specific importance for this systematic review. Included studies were evaluated on 15 items concerning patient selection, verification, description of the tests and of the study population. A comprehensive list of items on which the methodological study quality was assessed is available from the authors on request.

We defined complications of ART as OHSS, multiple pregnancy, ectopic pregnancy, haemorrhage, infection or injury to pelvic structures. We defined success rates of ART as clinical pregnancy rate, ongoing pregnancy rate, live birth rate and delivery rate.

If data on live birth rates were available, we used these data to calculate odds ratios (ORs) with 95% confidence intervals (CIs). If live birth rates were not available, we used pregnancy rates (clinical or ongoing pregnancy) for the calculations. Some studies report outcome per cycle, with several cycles per woman included. This would suggest better results in terms of pregnancy rates. Therefore, we report outcome (per first cycle) per woman where possible. In order to obtain clinically useful outcome, we chose to only pool data if results per woman were available.

Data synthesis

From each article, we calculated the OR from a 2 × 2 table cross-classifying BMI and one of the aforementioned outcomes. We used the WHO definitions for overweight (BMI $>25 \text{ kg/m}^2$) and obesity (BMI $>30 \text{ kg/m}^2$), where possible. Data of each outcome were pooled if the data were analysed per woman and if there were at least two studies with similar definition of the outcome and similar range of BMI for the comparison groups. Combined ORs and 95% CI were calculated using the Review Manager (RevMan 5.1) software of the Cochrane Collaboration. The heterogeneity was assessed with the $I^2$-statistic for
inconsistency. A value of > 50% was considered as substantial heterogeneity (Higgins et al., 2003). In the case of statistical homogeneity, we used a fixed-effect model. In the case of substantial heterogeneity, we used the random-effect model instead of the fixed-effect model.

Results

Our literature search resulted in 91 studies on the association between BMI and complications of ART and 242 studies on the association between BMI and the effectiveness of ART, respectively. The separate search on the association between overweight women with PCOS and complications after ART or the effectiveness of ART yielded a total of 77 articles in total.

Based on titles and abstracts derived from the search on studies between BMI and complications, 24 articles were identified as potentially eligible for the review (Fig. 1).

Eleven studies were excluded because they were solely concerned with women with PCOS and another 8 because they lacked adequate data; however, another 9 studies were identified by cross-referencing making 14 available for analysis.

Table I shows the characteristics of the 14 studies and the results per woman if available, otherwise per cycle for each complication. Only 2 out of the 14 studies were prospective. It was unclear whether a BMI threshold was used for access to ART. None of the researchers reported blinding for BMI status in the assessment of endpoints. Of the 14 studies, 6 reported on the relationship between OHSS and BMI, 7 reported on the relationship between multiple pregnancies and BMI and 6 reported on the relationship between ectopic pregnancies and BMI. We found no studies that reported on the complications infection, haemorrhage or injury to pelvic structures in relation to BMI in women undergoing ART. Three out of the 14 studies used a different definition than the WHO definition for overweight (Table I legend).

None of the six studies that reported on OHSS found a significant difference between the risk of OHSS in normal and overweight women. The pooled OR for overweight women was 1.0 (95% CI 0.77–1.3) (Fig. 2).

Of the seven studies that reported on the relation between BMI and multiple pregnancies for women undergoing ART, the retrospective cohort study of Spandorfer et al. (2004) found a significantly higher risk of multiple pregnancies in women with normal weight following ART, whereas six other studies did not. The pooled OR expressing the association between overweight and the risk of multiple pregnancies was 0.97 (95% CI 0.91–1.04) (Fig. 3).

Six studies reported on the association between BMI and ectopic pregnancies. None of these studies revealed a significant difference between normal and overweight women. The pooled OR expressing the association between overweight and the risk of ectopic pregnancy was 0.96 (95% CI 0.54–1.7) (Fig. 4).

After screening of titles and abstracts derived from the search on 242 studies reporting on the association between BMI and the effectiveness of ART, 39 articles were identified as potentially eligible for the review. After exclusion of papers that studied only patients with PCOS and those with insufficient data, 25 papers remained and a further 2 were identified by cross-referencing yielding 27 suitable for analysis (Fig. 5).

Of the 27 included studies, 4 were prospective (Table II). Eleven studies reported on live birth rates, 2 on delivery rates, whereas 14 studies reported on pregnancy rates. The definition of delivery rate given in Dokras et al. (2006) is delivery after 20 weeks of gestation, whereas no definition is provided in Wittemer et al. (2000). Nine studies reported on clinical pregnancy rate, four on ongoing pregnancy rate and one reported on fecundity. Definitions of these outcome measures differed between studies. Six out of the 27 studies used a different definition for overweight and obesity than the WHO definition (Table II legend).

In 4 of the 27 included studies, a significant negative effect of an increased BMI on outcome was found, 22 studies did not find a significant association between BMI and ART outcome, and 1 study reported significantly more pregnancies in obese women. In 17 studies, results were presented per woman, and in 10 studies, results were presented per cycle or per embryo transfer (ET). Therefore, not all study results were comparable, and as a result, only seven studies could be pooled for the live birth rate per woman, our primary interest.

Overweight women undergoing ART had a significant lower live birth rate after ART than women with a normal weight [OR 0.90 (95% CI 0.82–1.0)] (Fig. 6), whereas obesity did not show a statistically significant difference in six studies including almost 10 000 women [OR 0.89 (95% CI 0.76–1.03)]. Clinical pregnancy rates were not different for overweight and normal weight women [OR 0.94 (95% CI
## Table I  Incidence of complications following ART in overweight\(^a\) versus normal weight women.

<table>
<thead>
<tr>
<th>Study</th>
<th>ART</th>
<th>n</th>
<th>Per</th>
<th>OHSS HR</th>
<th>Multiple pregnancy HR</th>
<th>Ectopic pregnancy HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>Incidence % (p/p) OR (95% CI)</td>
<td>Incidence % (p/p) OR (95% CI)</td>
</tr>
<tr>
<td>Luke et al. (2011)</td>
<td>IVF</td>
<td>451</td>
<td>63</td>
<td>NA</td>
<td>NA</td>
<td>32</td>
</tr>
<tr>
<td>Farhi et al. (2010)</td>
<td>IVF</td>
<td>233</td>
<td>Woman</td>
<td>2.7</td>
<td>3.8</td>
<td>0.7 (0.1 to 3.7)</td>
</tr>
<tr>
<td>Sathya et al. (2010)</td>
<td>IVF</td>
<td>308</td>
<td>Woman</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zhang et al. (2010)</td>
<td>IVF/ICSI</td>
<td>2628</td>
<td>Woman</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Maheshwari et al. (2009a)</td>
<td>IVF</td>
<td>1756</td>
<td>Woman</td>
<td>10.3</td>
<td>10.2</td>
<td>1.0 (0.7 to 1.4)</td>
</tr>
<tr>
<td>Sreed et al. (2008)</td>
<td>IVF/ICSI</td>
<td>1273</td>
<td>Woman</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mataliotakis et al. (2008)</td>
<td>IVF/ICSI</td>
<td>278</td>
<td>Woman</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Esinler et al. (2008)</td>
<td>ICSI</td>
<td>775</td>
<td>ET</td>
<td>0.8</td>
<td>1.0</td>
<td>0.9 (0.2 to 3.0)</td>
</tr>
<tr>
<td>Dokras et al. (2006)</td>
<td>IVF/ICSI</td>
<td>1291</td>
<td>Woman</td>
<td>4.8</td>
<td>4.8</td>
<td>1.0 (0.6 to 1.6)</td>
</tr>
<tr>
<td>Van Swieten et al. (2005)(^c)</td>
<td>IVF/ICSI</td>
<td>162</td>
<td>Woman</td>
<td>4.9</td>
<td>5.0</td>
<td>1.0 (0.2 to 4.3)</td>
</tr>
<tr>
<td>Spandorfer et al. (2004)</td>
<td>IVF/ICSI</td>
<td>828</td>
<td>Cycle</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fedorcsak et al. (2004)</td>
<td>IVF/ICSI</td>
<td>2660</td>
<td>Woman</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Witters et al. (2000)</td>
<td>IVF/ICSI</td>
<td>325</td>
<td>Cycle</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lashen et al. (1999)(^c)</td>
<td>IVF</td>
<td>228</td>
<td>Woman</td>
<td>2.6(^e)</td>
<td>5.3(^e)</td>
<td>0.5 (0.1 to 2.4)</td>
</tr>
</tbody>
</table>

OHSS, ovarian hyperstimulation syndrome; p/p, per pregnancy; NA, not available.

\(^a\)Comparisons as stated except where indicated \(^b\)BMI > 24, \(^c\)BMI > 27, \(^d\)BMI > 28 versus BMI 20–25.

\(^e\)Prospective study, others were retrospective.
0.69–1.3]) or for obese women when compared with normal weight women [OR 0.97 (95% CI 0.59–1.6)]. For ongoing pregnancy rates, the pooled ORs were 1.01 (95% CI 0.75–1.4) and 0.96 (95% CI 0.64–1.4) for overweight and obesity, respectively (data not shown).

Our search retrieved 77 studies on the association between overweight women with PCOS and the effectiveness of ART. Two studies report on complications in PCOS women with respect to their BMI. Ozgun et al. (2011) report on multiple pregnancy rate, showing no difference between BMI 30 versus 30 kg/m² (P = 1). Liberty et al. (2010) describe women with haemorrhage after oocyte retrieval, in which they conclude that lean women with PCOS (BMI 19–21 kg/m²) are at more risk of this complication (4.5 versus 0%) than obese women with PCOS.

Four studies reported on BMI and outcome in PCOS women (Table III). All studies showed better outcome for normal weight women, with an extreme OR 0.2 (95% CI 0.01–1.9) for live birth rates for overweight woman in McCormick et al. (2008).

**Discussion**

In this systematic review, we assessed the association between overweight and obesity on the one hand and complications and success...
rates of ART on the other hand. We summarized the current evidence on complications following ART with respect to BMI. We found no impact of overweight or obesity on OHSS, multiple pregnancies or ectopic pregnancies. A slight negative effect on live birth rate is found in overweight and obese women. Literature specifically reporting on the effect of BMI on the aforementioned complications in women with PCOS was lacking.

One of the drawbacks of our review is the lack of publications on complications following ART in general. The articles we found did not study complications of ART in relation to BMI as their primary outcome; as a consequence, not one was powered to show a significant difference. Also with exception of two studies, all were retrospective with the possible selection bias and confounding effect. As our research has been based on this limited and of moderate quality data, the outcome of our study should be put in this perspective. Serious complications like infection, haemorrhage, thromboembolism or even mortality are not documented in relation to BMI. The Safety Interest Group (SIG) Safety and Quality of the ESHRE recommended registering mortality following ART worldwide because of this lack of information. Following this review of the literature, we underscore the importance of achieving better data collection of morbidity following ART.

Furthermore, we were not able to differentiate further between obesity classes because of lacking data. As mentioned earlier, several clinics throughout the world use upper limits for BMI for ART with scarce evidence on morbid obese women as a consequence. One might expect more complications or lower outcome results in obesity class III than in class I (WHO definition obesity class I BMI 30–35 kg/m² and class III BMI > 40 kg/m²) (Luke et al., 2011). However, in view of the lack of evidence on the outcomes of ART in severe obesity and in view of the little impact that we found from mild obesity, it remains difficult to define a threshold.

We found an OR of 0.90 for the association between overweight and life birth, indicating a 10% reduction in the success rates of IVF in overweight women. The absolute effect of such an association obviously depends on the absolute live birth rates after IVF. When, for example, the probability of live birth is 30% in a normal weight woman, then the success rates of an overweight woman drop to 27.8%. In other words, when we treat 46 normal weight women with IVF, there is one additional pregnancy when compared with when we treat 46 overweight women with the same treatment.

Another drawback is that most articles are retrospective observational cohort studies with the disadvantage of observation bias and confounding. This bias could be overcome with prospective studies where covariate data can be collected extensively and in sufficient detail to more accurately evaluate confounding and effect modification. Moreover, the studies applied different cut-off points to define overweight and obesity, as well as different definitions of outcome and the population of women differed between studies. Because of these differences, we were not able to pool all studies in our analysis, e.g. half of the studies on live birth rate with ≈60 000 women could not be used in our analysis (Witternem et al., 2000; Lintsen et al., 2005; Thum et al., 2007; Matalliotakis et al., 2008; Bellver et al., 2010; Luke et al., 2011) hypothetically changing our conclusion. For argument sake, we therefore performed the analysis including the results of Luke et al., comprising 45 000 ET, to establish the possible impact on our pooled OR. The OR for live birth rate remained within the same margins with OR 0.86 (CI 0.83–0.89) for overweight and OR 0.85 (CI 0.81–0.9) for obese women, now also showing a significant lower live birth rate for obese women.

We expected to find a difference in complication rates in controlled ovarian hyperstimulation due to difficulty monitoring follicles with ultrasound in overweight or obese women. Therefore, we searched literature specifically for this association but we did not identify any study reporting on this subject. As OHSS is found more often in women with PCOS (Tummon et al., 2005), we presumed that there might be a difference between normal and overweight women. However, no literature was found on the subject.

Our results on the effectiveness of ART concur with those of Maheshwari et al. (2007). Since publication of that review, 14 relevant additional studies were published on the subject. We found a moderate negative effect of obesity on ART outcome. Women with a BMI of 25 kg/m² or higher achieve reasonable, but slightly lower live birth rates when compared with normal weight women. The fact that the pooled OR for overweight women is significant, but the pooled OR of obese women lacks statistical significance is probably due to the smaller group of obese women when compared with overweight women, as point estimates for both groups were from the same magnitude. A large study on subfertile women undergoing ART with autologous and donor oocytes subclassifying between several obesity classes did show significant lower live birth rates in increasing obesity classes with autologous oocytes (Luke et al., 2011). However, they compared obesity classes to normal weight women, whereas we tried to find a cut-off value and compare, for example, BMI > 30 kg/m² with BMI < 30 kg/m².
Table II  Incidence of positive outcomes after ART in overweight and obese versus normal weight women in the studies analysed.

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>ART</th>
<th>n</th>
<th>Outcome</th>
<th>Per</th>
<th>% women BMI &gt; 25</th>
<th>OR (95% CI) BMI &gt; 25</th>
<th>% women BMI &lt; 25</th>
<th>OR (95% CI) BMI &lt; 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luke et al. (2011)</td>
<td>Cohort</td>
<td>IVF</td>
<td>451</td>
<td>Live birth</td>
<td>ET</td>
<td>34</td>
<td>0.9 (0.8 to 0.9)</td>
<td>32</td>
<td>0.9 (0.8 to 0.9)</td>
</tr>
<tr>
<td>Hill et al. (2011)b</td>
<td>Cohort</td>
<td>IVF</td>
<td>117</td>
<td>Live birth</td>
<td>Woman</td>
<td>44</td>
<td>1.6 (0.8 to 3.4)</td>
<td>33</td>
<td>0.8 (0.3 to 2.1)</td>
</tr>
<tr>
<td>Sathya et al. (2010)</td>
<td>Cohort</td>
<td>IVF</td>
<td>308</td>
<td>cp</td>
<td>Woman</td>
<td>41</td>
<td>0.9 (0.6 to 1.5)</td>
<td>33</td>
<td>0.6 (0.4 to 1.1)</td>
</tr>
<tr>
<td>Farhi et al. (2010)</td>
<td>Cohort</td>
<td>IVF</td>
<td>233</td>
<td>Live birth</td>
<td>Woman</td>
<td>41</td>
<td>1.1 (0.6 to 2.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kilic et al. (2010)</td>
<td>C-S</td>
<td>IVF</td>
<td>1970</td>
<td>cp</td>
<td>Woman</td>
<td>47</td>
<td>1.1 (0.9 to 1.3)</td>
<td>50</td>
<td>1.3 (1.1 to 1.5)</td>
</tr>
<tr>
<td>Zhang et al. (2010)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>2628</td>
<td>Live birth</td>
<td>Woman</td>
<td>24</td>
<td>0.9 (0.7 to 1.1)</td>
<td>26</td>
<td>1.0 (0.4 to 2.4)</td>
</tr>
<tr>
<td>Bellver et al. (2010)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>6500</td>
<td>Cycle</td>
<td>28</td>
<td>0.9 (0.8 to 1.0)</td>
<td>24</td>
<td>0.7 (0.6 to 0.9)</td>
<td></td>
</tr>
<tr>
<td>Maheshwari et al. (2009a)</td>
<td>C-S</td>
<td>IVF</td>
<td>1756</td>
<td>Live birth</td>
<td>Woman</td>
<td>23</td>
<td>0.9 (0.7 to 1.1)</td>
<td>22</td>
<td>0.9 (0.6 to 1.2)</td>
</tr>
<tr>
<td>Orvieto et al. (2009a)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>516</td>
<td>cp</td>
<td>Cycle</td>
<td>NA</td>
<td>NA</td>
<td>20</td>
<td>0.6 (0.3 to 1.2)</td>
</tr>
<tr>
<td>Matalliotakis et al. (2008)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>278</td>
<td>Live birth</td>
<td>Woman</td>
<td>47</td>
<td>1.0 (0.6 to 1.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sneed et al. (2008)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>1273</td>
<td>Live birth</td>
<td>Woman</td>
<td>21</td>
<td>0.8 (0.6 to 1.1)</td>
<td>22</td>
<td>0.9 (0.7 to 1.2)</td>
</tr>
<tr>
<td>Esinler et al. (2008)</td>
<td>Cohort</td>
<td>ICSI</td>
<td>775</td>
<td>cp</td>
<td>ET</td>
<td>46</td>
<td>1.1 (0.8 to 1.4)</td>
<td>48</td>
<td>1.2 (0.8 to 1.6)</td>
</tr>
<tr>
<td>Martinuzzi et al. (2008)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>417</td>
<td>op</td>
<td>Woman</td>
<td>45</td>
<td>0.9 (0.6 to 1.4)</td>
<td>42</td>
<td>0.8 (0.5 to 1.5)</td>
</tr>
<tr>
<td>Thum et al. (2007)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>8145</td>
<td>Live birth</td>
<td>Woman</td>
<td>26</td>
<td>0.9 (0.8 to 1.0)</td>
<td>24</td>
<td>0.8 (0.6 to 1.0)</td>
</tr>
<tr>
<td>Dokras et al. (2006)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>1291</td>
<td>Delivery Woman</td>
<td>42</td>
<td>1.0 (0.8 to 1.3)</td>
<td>41</td>
<td>0.9 (0.7 to 1.2)</td>
<td></td>
</tr>
<tr>
<td>Ku et al. (2006)</td>
<td>Cohort</td>
<td>ICSI</td>
<td>223</td>
<td>cp</td>
<td>Woman</td>
<td>11</td>
<td>0.3 (0.1 to 1.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dechaud et al. (2006)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>789</td>
<td>op</td>
<td>Cycle</td>
<td>13</td>
<td>0.8 (0.4 to 1.3)</td>
<td>13</td>
<td>0.7 (0.3 to 1.8)</td>
</tr>
<tr>
<td>Styne-Gross et al. (2005)</td>
<td>Cohort</td>
<td>IVF donor oocyte</td>
<td>536</td>
<td>op</td>
<td>Woman</td>
<td>74</td>
<td>1.1 (0.7 to 1.7)</td>
<td>74</td>
<td>1.1 (0.6 to 1.9)</td>
</tr>
<tr>
<td>Lintsen et al. (2005)</td>
<td>Cohort</td>
<td>IVF</td>
<td>8105</td>
<td>Cycle</td>
<td>14</td>
<td>0.9 (0.8 to 1.1)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Van Swieten et al. (2005)b</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>162</td>
<td>cp</td>
<td>Woman</td>
<td>33</td>
<td>0.6 (0.3 to 1.1)</td>
<td>41</td>
<td>1.0 (0.5 to 2.3)</td>
</tr>
<tr>
<td>Spandorfer et al. (2004)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>828</td>
<td>cp</td>
<td>Cycle</td>
<td>56</td>
<td>1.0 (0.7 to 1.5)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fedorcsak et al. (2004)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>2660</td>
<td>Live birth</td>
<td>Woman</td>
<td>19</td>
<td>0.9 (0.7 to 1.1)</td>
<td>18</td>
<td>0.8 (0.6 to 1.1)</td>
</tr>
<tr>
<td>Loveland et al. (2001)</td>
<td>Cohort</td>
<td>IVF</td>
<td>139</td>
<td>op</td>
<td>Cycle</td>
<td>25</td>
<td>0.3 (0.2 to 0.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Salha et al. (2001)b</td>
<td>CC</td>
<td>IVF</td>
<td>100</td>
<td>cp</td>
<td>Woman</td>
<td>26</td>
<td>0.6 (0.2 to 1.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wang et al. (2000)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>3586</td>
<td>Fecundity Cycle</td>
<td>40</td>
<td>0.8 (0.7 to 0.9)</td>
<td>37</td>
<td>0.7 (0.6 to 0.9)</td>
<td></td>
</tr>
<tr>
<td>Wittern et al. (2000)</td>
<td>Cohort</td>
<td>IVF/ICSI</td>
<td>325</td>
<td>Delivery</td>
<td>Cycle</td>
<td>14</td>
<td>0.8 (0.4 to 1.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lashen et al. (1999)b</td>
<td>CC</td>
<td>IVF</td>
<td>228</td>
<td>cp</td>
<td>Woman</td>
<td>24</td>
<td>1.2 (0.6 to 2.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

C-S, cross-sectional; CC, case–control; cp, clinical pregnancy; op, ongoing pregnancy; ET, embryo transfer; NA, not available.

*Comparisons were as stated except where indicated BMI > 24, BMI > 26, BMI > 31, BMI > 27, BMI > 28 versus BMI 20–25.

bProspective trial others were retrospective.
In the debate whether overweight or obese women should be denied access to ART, it is of interest to compare the effect of BMI with that of female age on ART outcome, as this is a well-accepted criterion to deny or allow ART (Templeton et al., 1996). In view of the decreasing success rates of ART in older women, most countries have an upper limit for age with respect to access to ART programmes. In the Netherlands, national guidelines recommend not offering ART to women older than 41 years because of poor pregnancy chances; but in clinical practice, this threshold has moved to an age of 43.

Figure 7 shows live birth rates following IVF in relation to female age for women with a BMI of <25 and >25 kg/m², which decrease from 26% for younger women to 10% for women aged 40 (Maheshwari et al., 2009b). When we consider an effect of overweight and obesity as pooled OR 0.9, the profound effect of age is much stronger when compared with the moderate effect of overweight on the live birth rate following IVF. This combined OR 0.9 should be viewed in the light of the earlier mentioned remarks on the level of evidence of the included studies.

Although high BMI is associated with obstetric and perinatal complications, the BMI thresholds now applied in some countries are not justified by empirical evidence. Since weight loss programmes have shown limited success, thus indicating how difficult it is to lose weight, certainly in older patients, the gain in outcome variables must be balanced against the detrimental effect of older age (Sneed et al., 2008). Indeed, to delay attempts to conceive to the age of 40 is probably more detrimental and perhaps more changeable than the decision to gain weight.
In the Netherlands, at present, a multicentre randomized controlled trial is in process which compares lifestyle intervention prior to conventional fertility care (including ART) with direct conventional fertility care in women with a BMI of $\geq 29$ kg/m$^2$ (Mutsaerts et al., 2010). If this study shows better results in the treatment group, this would provide scientific evidence for recommending lifestyle intervention before fertility treatment is started.

Apart from the slightly negative effect of BMI $\geq 25$ kg/m$^2$ on ART outcome, there is a substantial risk of pregnancy complications in overweight and obese women, such as hypertension, gestational diabetes, macrosomia and an increased risk of Caesarean section and perinatal death (Garbaciak et al., 1985; Edwards et al., 1996; Weiss et al., 2004). Moreover, the general health risk in terms of increased prevalence of, for example, cardiovascular disease and type 2 diabetes of overweight is well described (Visscher and Seidell, 2001). In our opinion, overweight women should be informed about these overall health risks, obstetric risks and slightly lower success rates of ART when seeking fertility care.

In conclusion, there is a lack of studies reporting on complications following ART. In the published literature, we did not find more complications in subfertile overweight and obese women when compared with subfertile normal weight women. We found slightly lower success rates in these overweight women following ART. Therefore, we feel there is no evidence for excluding women above a certain BMI threshold from ART but counselling on the increased obstetrical risks is mandatory. Furthermore, following the recommendations of the SIG Safety and Quality of the ESHRE, an international complication registration system for ART should be implemented to increase safety of women undergoing ART.

**Authors’ roles**

A.M.H.K. contributed to the study design, conception, data acquisition, analysis and writing of the manuscript. M.A.Q.M. performed statistical analyses, contributed to data acquisition, revising and approval of the final draft. W.K.H.K. and F.J.B. took part in revising and approval of the final draft. J.A.L. contributed to the design, conception, drafting, revising and approval of the final draft. B.W.M. and A.H. contributed to the design, conception, drafting, revising and approval of the final draft. W.K.H.K. and F.J.B. took part in revising and approval of the final draft.

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**Conflict of interest**

None declared.

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