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human reproduction update

Economic consequences of overweight and obesity in infertility: a framework for evaluating the costs and outcomes of fertility care

A.M.H. Koning[1], W.K.H. Kuchenbecker[2], H. Groen[3], A. Hoek[4], J.A. Land[4], K.S. Khan[5], and B.W.J. Mol[6,7]

[1]Department of Obstetrics and Gynaecology, Meander Medical Centre, Ringweg Randenbroek 110, 3816 CP Amersfoort, The Netherlands [2]Department of Obstetrics and Gynaecology, Isala Clinics, Dr van Heesweg 2, 8000 GK Zwolle, The Netherlands [3]Department of Epidemiology, University Medical Centre Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands [4]Department of Obstetrics and Gynaecology, University Medical Centre Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands [5]Department of Obstetrics and Gynaecology, University of Birmingham, Birmingham Women's Hospital, Birmingham B15 2TG, UK [6]Academic Medical Centre, Meibergdreef 15, 1100 DD Amsterdam, The Netherlands

[7]Correspondence address. Tel: +31-20-5663693; E-mail: b.w.mol@amc.uva.nl

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BACKGROUND: Overweight and obesity are an epidemic in Western society, and have a strong impact on fertility. We studied the consequences of overweight and obesity with respect to fecundity, costs of fertility treatment and pregnancy outcome in subfertile women.

METHODS: We searched the literature for systematic reviews and large studies reporting on the effect of weight on both fecundity and pregnancy outcome in subfertile women. We collected data on costs of treatment with ovulation induction, intrauterine insemination and *in vitro* fertilization, as well as costs of pregnancy complications. We calculated, for ovulatory and anovulatory women separately, the number of expected pregnancies, complications and costs in a hypothetical cohort of 1000 normal weight, overweight and obese women each.

RESULTS: In our hypothetical cohort of 1000 women, compared with women with normal weight, live birth was decreased by 14 and 15% (from 806 live births to 692 and 687 live births) in overweight and obese anovulatory women, respectively, for ovulatory women it was decreased by 22 and 24% (from 698 live births to 546 and 531 live births), respectively. These outcomes were associated with an increase in the number of complications and associated costs leading to cost per live birth in anovulatory overweight and obese women were 54 and 100% higher than their normal weight counterparts, for ovulatory women they were 44 and 70% higher, respectively.

CONCLUSIONS: Overweight and obese subfertile women have a reduced probability of successful fertility treatment and their pregnancies are associated with more complications and higher costs.

Key words: infertility / body mass / assisted reproduction / cost / effectiveness

Introduction

The prevalence of overweight and obesity varies in populations and is estimated to range from 5% in some developing countries to >30% in developed countries (James *et al.*, 2004). The World Health Organization defines overweight as a body mass index (BMI) $\geq$ 25 kg/m^2, and obesity as a BMI $\geq$ 30 kg/m^2 (World Health Organisation, 2000). Considering the trends in childhood obesity, a significant increase in

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obesity related subfertility can be anticipated in the future (Schokker *et al*., 2007). Nowadays, the rate of obesity in women of child bearing age is 12% in Western Europe and 25% in North America (Butler, 2004; Linné, 2004; Haslam and James 2005; Watson, 2005).

The strongest obesity related effect on fertility is anovulation. Polycystic ovarian syndrome (PCOS), the most noted cause of anovulation, is furthermore exacerbated by increased insulin resistance and hyperinsulinemia associated with overweight and obesity (Pasquali *et al*., 2007). In 65% of patients with PCOS, obesity therefore contributes to anovulation (Pasquali *et al*., 2003). On the other hand, even obese women with an ovulatory cycle have a lower chance of spontaneous conception (Jensen *et al*., 1999; Van der Steeg *et al*., 2007).

In cases of chronic anovulation, ovulation induction (OI) with clomiphene citrate in overweight and obese women results in lower ovulation rates (Imani *et al*., 1998) and lower cumulative live birth rates for women with a BMI $> 30\ kg/m^2$ (Legro *et al*., 2007). McClure *et al*. (1992) showed that in overweight women ovulation rates are lower due to higher cancellation rates, but if OI is successful no difference is found in pregnancy rates in different weight categories. Mulders *et al*. (2003) also found obesity to be associated with higher cancellation rates and substantially higher miscarriage rates leading to a lower live birth rate per started cycle. This decreased success rate is however not found in all studies (Balen *et al*., 2006).

The literature on the impact of body weight on the effectiveness of intrauterine insemination (IUI) is just as for OI, inconsistent. Koloszar *et al*. showed a negative impact of increasing body weight on the success rates of IUI, but Wang *et al*. (2004) could not confirm this finding.

Furthermore, several retrospective studies have shown a negative impact of overweight and obesity in women on the outcome of *in vitro* fertilization (IVF) (Lashen *et al*., 1999; Wang *et al*., 2000; Koloszar *et al*., 2002; Fedorcsak *et al*., 2004). The ongoing pregnancy rate and live birth rate is however consistently decreased especially due to an increased miscarriage rate in women with obesity (Wang *et al*., 2002; Lintsen *et al*., 2005; Maheshwari *et al*., 2007).

Apart from these obesity related fertility problems, there is indisputable evidence that 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 (Cedergren, 2004; Linné, 2004; Sebire *et al*., 2001). Pregnancy complications associated with obesity are hypertensive disorders, gestational diabetes, prolonged duration of labour, increased need of operative delivery, macrosomia, shoulder dystocia and increased blood loss (Garbaciak *et al*., 1985; Edwards *et al*., 1996; Weiss *et al*., 2004). Obesity is furthermore associated with an increased risk of adverse pregnancy outcomes such as unexplained stillbirth (Cnattingius *et al*., 1998; Linné, 2004; Kristensen *et al*., 2005) and neonatal admissions (Usha Kiran *et al*., 2005).

In view of the issues stated above, it is likely that overweight and obesity have a negative impact on the outcome as well as the costs of fertility treatment. The aim of this article is to conceptualize the impact of overweight and obesity on fertility treatment and the resultant pregnancies, in terms of effectiveness, costs and cost-effectiveness.

Methods

We developed a framework within which the consequences of fertility treatment and outcomes of resultant pregnancy can be evaluated simultaneously for subfertile women in different body weight categories. We performed systematic reviews to obtain information on outcomes and costs to generate cost-effectiveness estimates for inclusion in decision analytic models. To do so, we searched the literature for evidence on the effect of obesity on spontaneous pregnancy chances, success of assisted reproduction technologies (ART), as well as pregnancy outcome.

We used the following electronic databases: PubMed, Embase, DARE and the Cochrane Library to initially search for systematic reviews on each of the subjects. In absence of reviews, we identified large, reliable studies.

To identify studies that reported on the association between obesity and spontaneous pregnancy chances we combined the key words ('obesity', 'overweight' or 'BMI') and ('pregnancy' or 'fertility'). By adding the key words ('ART', 'IUI') and ('OI') we looked for studies reporting on the effect of obesity on these treatments. To identify studies reporting on the association between obesity and pregnancy outcome, we used the key words: ('obesity', 'overweight' or 'BMI') and ('pregnancy outcome').

We included studies reporting on maternal morbidity as well as pregnancy outcome. The reported odds ratios (ORs) in the reviews were used, or if not available, calculated by using a 2×2 table cross classifying BMI and one of the aforementioned outcomes. These ORs were used as input for calculating the additional impact of overweight and obesity on both fecundity as well as pregnancy.

The economic analysis was performed from a hospital perspective. Costs of fertility treatments were obtained from a series of Dutch studies, which reported on the costs of OI, IUI and costs of IVF (Goverde *et al*., 2000; Eijkemans *et al*., 2005). Furthermore, we looked for studies reporting on costs of pregnancy in overweight women and costs of pregnancy complications in these women. To do so, we performed a search of several major journals in obstetrics and gynaecology for economic evaluations. We looked for studies that reported on the costs of each of the complications miscarriage, pre-eclampsia, gestational diabetes and Caesarean delivery. We assumed no difference in multiple pregnancy rates between different weight categories (Esinler *et al*., 2008).

Next, we assessed the impact of overweight and obesity on the costs and effects of fertility treatments. To achieve this, we distinguished between the case of ovulatory women and the case of anovulatory women. For each of these situations, we considered women with normal weight, overweight and obese women. According to the WHO normal weight is defined as a BMI between 20 and 25 kg/m^2, overweight as a BMI between 25 and 30 kg/m^2 and obesity as a BMI over 30 kg/m^2. Because of differences in definitions of overweight and obesity in some studies we used in our review, we could not use the very strict BMI cut off points proposed by the WHO for our different weight groups.

We then constructed a theoretical model, simulating the situation where women were treated for their subfertility. For each of the six categories, i.e. anovulatory women with normal weight, anovulatory overweight women and anovulatory obese women and ovulatory women with normal weight, ovulatory overweight women and ovulatory obese women, we calculated the expected pregnancy rates, the expected number of fertility treatments and the expected number of pregnancy complications for a hypothetical group of 1000 women. We performed multiple sensitivity analyses on the following variables success rate of IVF (range 40–60%), success rate of OI (range 70–90%) and IUI (range 30–50%). With these figures we calculated and then plotted in two figures different success rates of ART against the costs per live birth in anovulatory and ovulatory women in different weight categories.

Results

Literature identified

The search for studies on the association between spontaneous pregnancy chances in overweight women revealed two reviews by Jensen

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et al. (1999) and Gesink Law et al. (2007) as well as the study of Van der Steeg et al. (2007). The results of these studies are shown in Table I. Both reviews as well as the study of Van der Steeg et al. showed that overweight women take longer to conceive than normal weight women. The reviews were retrospective studies in a cohort of women not seeking medical help for any subfertility, whereas Van der Steeg et al. studied women in fertility clinics. On the basis of these results, we assumed that among obese ovulatory women spontaneous pregnancy chances were 90% of those in normal weight or overweight women. Moreover, we assumed that spontaneous pregnancy chances prior to and in between ART cycles was 10% in all groups.

From the literature no unequivocal conclusion could be drawn about the influence of obesity on IUI. Whereas Wang et al. (2004) reported an increased probability of success of IUI in women with a BMI > 30 kg/m^2, Koloszar et al. reported exactly the opposite, i.e. a decrease of success of IUI with increasing BMI. In view of these conflicting results on IUI, for purpose of this review we considered no effect of BMI on IUI.

Maheshwari et al. (2007) published a systematic review of the literature from 1960 until 2006 on the outcome of IVF for overweight and obese women. They reported an OR for pregnancy after IVF of 0.71 (CI 95% 0.62–0.81) for women with a BMI > 25 kg/m^2 compared with women with a BMI between 20 and 25 kg/m^2, and for women with a BMI > 30 kg/m^2 even 0.68 (CI 95% 0.55–0.83) (Table I). We applied these ORs in our model. Maheshwari et al. (2007) also found that overweight women require more total units of gonadotrophins during hyperstimulation for IVF, but these additional costs were not considered in the present analysis.

We found one meta-analysis and three studies that reported on the impact of BMI on the effectiveness of OI in anovulatory women (Table II) (Imani et al., 2002; Al-Azemi et al., 2004; Mulders et al., 2003; Balen et al., 2006). The study of Al-Azemi et al. showed a negative impact of obesity on live birth rate after OI with clomiphene citrate. The meta-analysis of Mulders et al. did not show a significant impact of BMI on the fecundity after OI with gonadotrophins. However, they found higher cancellation rates per cycle (OR 1.9) and higher miscarriage rates in the obese group (OR 3.1), thus leading to lower ongoing pregnancy rates per started cycle.

Balen et al. studied anovulatory women with a BMI up to 35 kg/m^2 and also did not find a significant difference in pregnancy rates after OI with gonadotrophins in overweight and obese women compared with women of normal weight (Balen et al., 2006). Imani et al. found among anovulatory women a hazard ratio of 0.92 for obese versus lean women for ovulation after OI with clomiphene citrate, but they also did not find a difference in live birth chances between the weight groups (Imani et al., 2002). We therefore assumed in our analysis that there is no influence of BMI on pregnancy rates after OI in anovulatory women.

Table III shows the additional risk of obstetric complications due to overweight and obesity. We applied meta-analyses conducted by Chu et al. (2007a, b, c) and Cnossen et al. (2007). These studies report that there is an additional risk of stillbirth, Caesarean delivery, pre-eclampsia and gestational diabetes with increasing BMI. Fedorcsak et al. (2004) studied the impact of overweight in women undergoing IVF treatment, and found an increased risk of miscarriage.

Table I Spontaneous fecundity and pregnancy chances after reproductive treatment in different weight categories

Author	Study period	Study population	Data collection	Outcome measure	Results
Spontaneous pregnancy					
Gesink Law	1959–1965	First planned pregnancy	Retrospective	Chance conceiving per cycle	OR 0.92 (CI 95% 0.84–1.01) for BMI 25–29.9 OR 0.82 (CI 95% 0.75–0.92) for BMI > 30 OR 0.66 (CI 95% 0.49–0.89) for primipari with BMI > 30
Jensen	1972–1987	First planned pregnancy	Retrospective	Chance conceiving per cycle	OR 0.77 (CI 95% 0.70–0.84) for BMI > 25
V/d Steeg	2002–2004	Subfertile ovulatory	Prospective	Time to pregnancy < 12 months	HR 0.95 (CI 0.91–0.99) per extra kg/m^2 from a BMI > 29
Intrauterine insemination					
Wang	1990–2000	Infertile couples undergoing IUI treatment	Retrospective	Chance conceiving per cycle	OR 1.5 (95% CI 1.1–1.9)* for BMI > 30
Koloszar	1992–1998	Infertile ovulatory	Prospective	Pregnancy	OR 0.66 (95% CI 0.49–0.88)* for BMI 25–27 OR 0.42 (95% CI 0.25–0.73)* for BMI 28–36
In vitro fertilization					
Maheshwari	1966–2006	Infertile women undergoing IVF	Systematic review	Pregnancy	OR 0.71 (CI 95% 0.62–0.81) for BMI > 25 OR 0.68 (CI 95% 0.55–0.83) for BMI > 30

IUI, intrauterine insemination; IVF, *in vitro* fertilization; OR, odds ratio; HR, hazard ratio; *, calculated OR.

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Table II Odds ratio's of pregnancy chances of overweight and obese anovulatory women following OI

Author	Study period	Study population	Study design	Outcome measure	Results
Azemi	Not reported	Infertile women undergoing CC–OI	Retrospective cohort study	Live birth	OR 0.74* (0.39–1.4) for BMI 25–29 OR 0.15* (0.07–0.30) for BMI >30
Mulders	1986–2002	Infertile women undergoing gonadotrophin-OI	Meta analysis	Pregnancy Cancellation rate Miscarriage rate	OR 1.22 (CI 95% 0.77–1.93) obese versus lean women OR 1.86 (CI 95% 1.13–3.06) OR 3.05 (CI 95% 1.45–6.44)
Balen	2002–2003	After three cycles CC failed OI –> gonadotrophins	Prospective cohort study	Pregnancy	OR 1.3* (0.71–2.2) for BMI >25 OR 0.99* (0.48–2.0) for BMI > 30
Imani	1993–1995	Infertile women undergoing CC–OI	Prospective cohort study	Ovulation live birth	OR 0.92 (0.88–0.96) obese versus normal weight OR 1.00 (0.97 to 1.04)

CC, clomiphene citrate; OI, ovulation induction; BMI, body mass index; *, calculated OR.

Table III Odds ratios of maternal and fetal complications in overweight and obese women

Author	Study period	Study population	Study design	Outcome measure	Results
Fedorcsak	1996–2002	IVF/ICSI	Retrospective cohort	Abortion < 6wks	OR 2.0* (CI 95% 1.1–3.7) for BMI > 25
Chu (b)	1980–2005	Birth registries, clinical medical records etc.	Meta analysis	Stillbirth	OR 1.5 (CI 95% 1.1–1.9) for overweight women OR 2.1 (CI 95% 1.6–2.7) for obese women
Cnossen	1980–2006	Cohort (prospective and retrospective)	Meta analysis	Pre-eclampsia	LRs (95% CI) 1.7 (0.3–11.9) for BMI ≥ 25 and 0.73 (0.22–2.45) for BMI < 25 (OR 2.3) LRs 2.7 (1.0–7.3) for BMI ≥ 35 and 0.86 (0.68 to –1.07) for BMI < 35 (OR 3.7)
Chu (c)	1980–2005	Cohort (prospective and retrospective)	Meta analysis	Cesarean delivery	OR 1.5 (CI 95% 1.3–1.6) for overweight women OR 2.1 (CI 95% 1.9–2.3) for obese women OR 2.9 (CI 95% 2.3–3.8) for severely obese women
Chu (a)	1980–2006	Cohort (prospective and retrospective)	Meta analysis	Gestational diabetes	OR 2.1 (95%CI 1.8–4.2) for overweight women OR 3.6 (CI 95% 3.1–4.2) for obese women OR 8.6 (CI 95% 5.1–16) for severely obese

BMI, body mass index; OR, odds ratio; LR, likelihood ratio; *, calculated OR.

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Table IV Costs of pregnancy complications and ART per pregnancy

Study	Complication/treatment	Costs per pregnancy (€)
Chen *et al.* (2001)	Cesarean delivery	3350*
Barton *et al.* (2006)	Hypertensive disorder	8250*
Moss *et al.* (2007)	Gestational diabetes mellitus	345*
Graziosi *et al.* (2005)	Miscarriage	683
Goverde *et al.* (2000)	IVF	1700*
Eijkemans *et al.* (2005)	OI	250
Goverde *et al.* (2000)	IUI	450*

*Calculated from US and AUS dollars and Dutch guilders.

Table IV presents expected costs of fertility treatment and pregnancy complications. We used several studies on costs of pregnancy complications and calculated the costs presented in euro's using the current exchange rates (Chen *et al.*, 2001; Graziosi *et al.*, 2005; Barton *et al.*, 2006; Moss *et al.*, 2007). Furthermore, we used studies on costs in the Netherlands for OI, IUI and IVF treatment (Goverde *et al.*, 2000; Eijkemans *et al.*, 2005).

Expected outcome and costs

Table V shows the result when the model was applied on a hypothetical cohort of 1000 anovulatory women. Our model represents costs until birth, including the costs of delivery. In 1000 normal weight anovulatory women, treatment with three cycles of OI and, if needed, followed by one or two cycles of IVF, would result in 900 pregnancies. Figure 1A shows that costs per live birth are higher for overweight and obese anovulatory women with different success rates of OI and IVF and these differences in costs are roughly constant over a large range of success rates.

Of these pregnancies 90 are expected to end in miscarriage and 810 women will have an ongoing pregnancy. The expected number of pregnancies complicated by pre-eclampsia, gestational diabetes and Caesarean delivery, will be 81, 41 and 81, respectively, whereas four women will suffer stillbirth. Overall, 806 women are expected to deliver a child, for a total cost of €2430 per woman, resulting in a cost of €3016 per live birth.

From Table V, it can also be seen that in overweight anovulatory women the effectiveness of treatment decreases, resulting in a

Table V Hypothetical cohort of 1000 anovulatory women in different weight categories

	Normal weight	Overweight[1]	Obese[2]
Cohort	1000	1000	1000
Impact of overweight on OI (OR)	1	1	1
Pregnant after three cycles OI (baseline rate 80%)	800	800	800
Number of women undergoing IVF	200	200	200
Impact of weight on effectiveness IVF (OR)	1	0.71	0.68
Pregnant after two cycles IVF (baseline rate 50%)	100	71	68
Expected number of pregnancies	900	871	868
Impact of weight on miscarriage (OR)	1	2	2
Expected number of miscarriages (baseline rate 10%)	90	174	174
Number of women without ongoing pregnancy	190	303	306
Number of women with ongoing pregnancy	810	697	694
Impact of weight on pre-eclampsia (OR)	1	2.3	3.7
10% pregnancies complicated by pre-eclampsia	81	160	257
Impact of weight on gestational diabetes (OR)	1	2.1	3.6
5% pregnancies complicated by gestational diabetes	41	73	125
Impact of weight on Caesarean deliveries (OR)	1	1.5	2.1
10% pregnancies Caesarean delivery	81	105	146
Impact of weight on stillbirth (OR)	1	1.5	2.1
0.5% pregnancies stillbirth	4	5	7
Total women with live birth	806	692	687
Total costs complications (€)	1000	1788	2724
Total expected cost (*€1000)	2430	3218	4154
Cost per live birth (€)	3016	4653	6045
Cost per pregnancy (€)	3001	4618	5982

[1]Applied BMI (kg/m^2) threshold differed from study to study (range 25–27).
[2]Applied BMI (kg/m^2) threshold differed from study to study (range 29–35).

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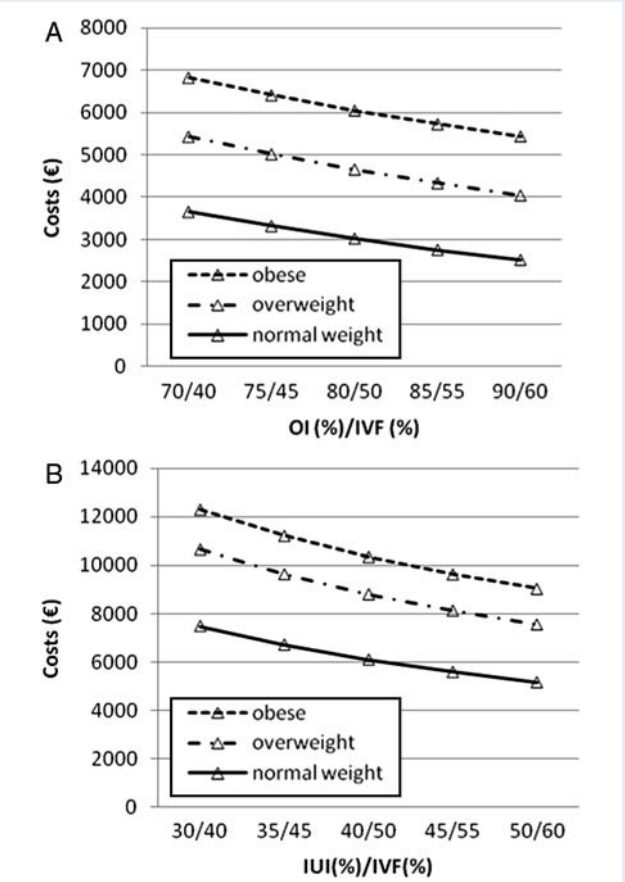

Figure 1 (**A**) Sensitivity analyses showing the effect of variation of success rates of OI and IVF on costs per live birth in anovulatory women. (**B**) Sensitivity analyses showing the effect of variations of success rates of IUI and IVF on costs per live birth in ovulatory women.

decrease of the number of pregnancies and live births, an increase in costs and a relative increase of the number of complications. This results in a decrease in the number of live births of 114 (14%), and an expected increase in costs of almost €800 (32%) per patient. For obese anovulatory women, these figures are slightly worse, as the number of live births decrease to 119 (15%), and the expected increase in cost of approximately €1700 (71%) per patient as compared with normal weight women.

Table VI shows the results for a theoretical cohort of 1000 ovulatory women. In 1000 normal weight ovulatory women, treatment consisted of three cycles of IUI and if this was unsuccessful one or two cycles of IVF, added with 10% spontaneous pregnancies that occur on waiting lists or in between cycles, would result in 780 pregnancies. Figure 1B show that over a large range of different success rates of IUI and IVF the costs per live birth are higher for overweight and obese ovulatory women.

Of these pregnancies 78 are expected to suffer a miscarriage and 702 women will have an ongoing pregnancy. The expected number of pregnancies complicated by pre-eclampsia, gestational diabetes and Caesarean delivery, will be 70, 35 and 70, respectively, whereas four women will suffer stillbirth. Overall, 698 women are expected to deliver a child, for a total cost of €4258 per woman, resulting in a cost per live birth €6096.

Similarly as for anovulatory women, it can be shown that in overweight ovulatory women the effectiveness of treatment decreases, resulting in a decrease of the number of pregnancies and live births, an increase in costs and a relative increase of the number of complications. This results in a decrease in the number of live births of 153 (22%), with the expected increase in costs of €543 (13%), resulting in a cost per live birth of €8800. For obese ovulatory women, these figures are worse with a decrease in live births of 167 (24%), with the expected increase in costs of almost €1250 (29%), resulting in a cost per live birth of €10 355.

Discussion

Overweight and obesity are an increasing problem in Western society. In this review, we collected data on the impact of overweight and obesity on fertility care. We found that both in ovulatory and in anovulatory subfertile women overweight and obesity resulted in a decreased fecundity and in an increase in the number of pregnancy complications and associated costs. However, there is no proven cause and effect between overweight and subfertility. It remains possible that excessive weight and subfertility are both symptoms of an unknown pathology.

Our results roughly suggest that overweight leads to an additional cost of €1500 per pregnancy and 100 fewer pregnancies per 1000 anovulatory women undergoing fertility treatment, where this is €2500 and 150 pregnancies, respectively, for anovulatory women.

The validity of our findings depends on the robustness of our methodology. We put forward a framework that can be used to encourage development of more advanced models for generating cost-effectiveness information through robust economic evaluation. In our review of the literature, we found different and occasionally conflicting results on the impact of overweight and obesity on the effect of fertility treatment. When this was the case, we chose to consider no effect of overweight. Furthermore the success rate of IVF decreases with increasing BMI (Maheshwari *et al*., 2007), thus overweight and obese women will have to undergo more cycles compared with normal weight women.

As a consequence, our findings may be an underestimation of the impact of overweight and obesity. Since the purpose of this review was not to give exact figures on costs but to show a trend in costs and cost-effectiveness, we feel this possible inaccuracy does not undermine the overall conclusion.

From our analysis several issues rise. First, as a higher BMI is associated with more pregnancy complications, there is the question as to whether women should lose weight before fertility treatment is started. A recent retrospective analysis by Maheshwari *et al*. (2009) concludes that cost of IVF is not different for several weight categories but because of obstetric complications associated with higher BMI women with overweight should be advised to lose weight prior to IVF. Our analysis concurs with this conclusion and gives indicative results that merit consideration in counselling patients and guiding evidence-based discussions on current practice and policy.

Weight loss may be achieved by lifestyle modification interventions, incorporating multiple approaches (diet, exercise, behaviour). Interventions of this kind are advised as a key component for the

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Table VI Hypothetical cohort of 1000 ovulatory women in different weight categories

	Normal weight	Overweight[1]	Obese[2]
Cohort	1000	1000	1000
Impact of overweight on spontaneous pregnancies (OR)	1	1	0.9
Spontaneous pregnancies (baseline rate 10%)	100	100	90
Number of women undergoing IUI	900	900	910
Treatment effect of IUI (OR)	0.4	0.4	0.4
Pregnant after three cycles IUI (baseline rate 40%)	360	360	364
Number of women undergoing IVF	640	640	636
Impact of overweight on effectiveness IVF	1	0.71	0.68
Pregnant after two cycles IVF (baseline rate 50%)	320	227	216
Expected number of pregnancies	780	687	670
Impact of weight on miscarriage (OR)	1	2	2
Expected number of miscarriages (baseline rate 10%)	78	137	134
Number of women without ongoing pregnancy	298	450	464
Number of women with ongoing pregnancy	702	550	536
Impact of weight on pre-eclampsia (OR)	1	2.3	3.7
10% pregnancies complicated by pre-eclampsia	70	126	198
Impact of weight on gestational diabetes (OR)	1	2.1	3.6
5% pregnancies complicated by gestational diabetes	35	58	97
Impact of weight on Caesarean deliveries (OR)	1	1.5	2.1
10% pregnancies Caesarean delivery	70	82	113
Impact of weight on stillbirth (OR)	1	1.5	2.1
0.5% pregnancies stillbirth	4	4	6
Total women with live birth	698	546	531
Total costs complications (€)	867	1410	2103
Total expected cost (* €1000)	4258	4801	5494
Cost per live birth (€)	6096	8800	10 355
Cost per pregnancy (€)	6066	8734	10 246

[1]Applied BMI (kg/m^2) threshold differed from study to study (range 25–27).
[2]Applied BMI (kg/m^2) threshold differed from study to study (range 29–35).

improvement of reproductive function in overweight women, specifically with PCOS (Kiddy *et al*., 1992; Clark *et al*., 1995, 1998; Huber-Buchholz, 1999; Hoeger *et al*., 2004; Norman *et al.*, 2004; Balen *et al*., 2006; Tang *et al*., 2006), although the evidence of its effectiveness as demonstrated in clinical studies is limited. The cost-effectiveness of losing weight has never been assessed in large groups of subfertile women with respect to increasing treatment success for weight-related subfertility, prevention of complications during pregnancy and improvement of perinatal outcome. Until this has been demonstrated we do not think it should be obligatory for overweight subfertile women to undergo a lifestyle intervention programme before starting fertility treatment but in counselling patients there should be attention for possible pregnancy complications with increasing BMI. It is clear that losing weight takes great effort and we feel that overweight should be considered a disease rather than an amenable condition.

Second, apart from the unproven effectiveness of lifestyle interventions in overweight subfertile women, there is the question as to whether there should be upper limits for BMI above which couples should not be treated. Some authors have suggested limits for BMI for women undergoing fertility treatment, both with the arguments of patient safety concerns, as well as a lack of effectiveness of treatment of obese women (Gillett *et al*., 2006; Zachariah *et al*., 2006; Maheshwari *et al*., 2007). However, we feel that from the perspective of effectiveness of treatment, our data show that there is no reason to withhold treatment. Although effectiveness rates decrease with increasing BMI, the same appears true for women undergoing assisted reproduction over the age of 40, which is a well accepted practice in many countries. Age is however a predictable and amenable factor considering the fact that many couples delay conception to for example pursue career opportunities. In our opinion, studies on weight loss interventions should show a clear increase of effectiveness of fertility treatment and a clear decrease in pregnancy related complications, before BMI thresholds can be implemented. In conclusion, in ovulatory and anovulatory subfertile women overweight and obesity is associated with a decrease in the number of pregnancies, a sharp increase in the number of complications with an additional rise of associated costs per pregnancy. There is not enough evidence

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however to prove that losing weight will improve the outcome of fertility treatment and decrease complications in pregnancies, and therefore strict BMI thresholds cannot be recommended yet. However, overweight and obese subfertile women should be counselled that overweight is a risk factor in pregnancy and is associated with several complications in both mothers and their children.

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