Should access to fertility treatment be determined by female body mass index?

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Resource allocation towards fertility treatment has been extensively debated in countries where fertility treatment is publicly-funded. Medical, social and ethical aspects have been evaluated prior to allocation of resources. Analysis of cost-effectiveness, risks and benefits and poor success rates have led to calls of restricting fertility treatment to obese women. In this debate article, we critically appraise the evidence underlying this issue and highlight the problems with such a policy. Poor success rate of treatment is unsubstantiated as there is insufficient evidence to link high body mass index (BMI) to reduction in live birth. Obstetric complications have a linear relationship with BMI but are significantly influenced by maternal age. The same is true for miscarriage rates which are influenced by the confounding factors of polycystic ovary syndrome and age. Studies have shown that the direct costs per live birth are no greater for overweight and obese women. With changing demographics over half the reproductive-age population is overweight or obese. Restricting fertility treatment on the grounds of BMI would cause stigmatization and lead to inequity, feelings of injustice and social tension as affluent women manage to bypass these draconian restrictions. Time lost and poor success of conventional weight loss strategies would jeopardize the chances of conception for many women.

Key words: body mass index / fertility treatment / IVF

Introduction

Obesity is a rapidly growing worldwide phenomenon. The World Health Organization (WHO) estimates that 1.6 billion people worldwide are overweight [body mass index (BMI) between 25 and 30 kg/m²] and 400 million are obese (BMI > 30 kg/m²; http://www.who.int/mediacentre/factsheets/fs311/en/index.html). Rates of obesity in the developing world have tripled in the last two decades (Hossain et al., 2007). In the USA and UK more than half of all women are either overweight or obese (Ogden et al., 2006; Balen and Anderson, 2007), and many are of reproductive age (Balen and Anderson, 2007).

Concerns about poor clinical outcomes, increased health risks and higher costs have led to calls to restrict access to fertility treatment including assisted conception in women with increased BMI (Farquhar and Gillett, 2006; Gillett et al., 2006; Balen and Anderson, 2007), although there is no agreed limit beyond which treatment should be withheld. In the UK most Assisted Reproduction units impose BMI cut-offs, varying from 30 to 35 kg/m² (Zachariah et al., 2006).

A recent article in this journal (Vahratian and Smith, 2009) discussed the influence of female BMI on access to fertility services and observed that obese women were most likely to seek medical help for infertility, but least likely to receive it. These authors also considered medical, social and ethical issues involved in decisions on resource allocation for fertility treatment. In this debate we critically examine the evidence supporting calls for restricting access to fertility treatment in women with high BMI, and argue that such a policy is difficult to define, defend and implement.

Arguments for restricting fertility treatment to women with high BMI

A number of arguments have been used to justify a policy of excluding women with high BMI from fertility treatment. In the section below, we critically analyse each of them and evaluate the strength of the evidence base underpinning them.

Poor success rates of fertility treatment in overweight and obese women

Obesity contributes to ovulatory problems and compromises ovarian response to ovulation induction agents such as clomifene (Polson et al., 1989) and gonadotrophins (Hamilton-Fairley et al., 1992; Nyboe Andersen et al., 2008). Most studies which have shown a negative
association between obesity and success rates following ovulation induction have reported on intermediate outcomes such increased drug doses or episodes of ovulation, rather than more definitive end-points such as pregnancy and live birth. In a study by Balen et al. (2006) in women with BMI 19–35 kg/m², higher BMI was associated with increased gonadotrophin requirements but not with reduced pregnancy rates, confirming a clear discrepancy between surrogate and substantive outcomes. There is limited information in the literature on outcomes in women with BMI >35 kg/m².

High BMI has been shown to be associated with lower success rates following assisted reproduction (Fedorcsak, 2000), including the need for prolonged ovarian stimulation and high doses of gonadotrophins (Fedorcsak et al., 2004). However, not all studies in this field have demonstrated a higher risk of negative outcomes such as cycle cancellation, fewer oocytes or embryos or low pregnancy rates in obese women (Lewis et al., 1990; Lashen et al., 1999; Dechaud et al., 2006). A large retrospective study on 1293 women undergoing IVF (Dokras et al., 2006) failed to confirm an association between BMI and rates of clinical pregnancy or live birth.

A systematic review on the effect of overweight and obesity in women undergoing assisted reproductive techniques concluded that there was insufficient evidence to link high BMI with reduced live birth rates (Maheshwari et al., 2007). Compared with women with BMI >30 kg/m², the odds of pregnancy in women with BMI <30 kg/m² were 1.16 [95% confidence interval (CI) 0.95, 1.43] (Maheshwari et al., 2007). In women, with BMI <25 kg/m², the odds of pregnancy per woman were 1.24 (95% CI: 1.02, 1.50) and per cycle, 0.99 (95% CI: 0.88, 1.12) in comparison with women with BMI ≥ 25 kg/m². This meta-analysis, based on aggregated observational data, was unable to adjust for age confounders such as age, duration of infertility and previous pregnancy. Given the uncertainty surrounding the interpretation of these results, it is difficult to conclude that there is a causal relationship between obesity and live birth rates following IVF and identify a threshold BMI above which success rates are so low (or complication rates are so high) that treatment should be withheld. The debate is further enlivened by results from a recent study showing that obese patients (BMI >30 kg/m²) who respond normally to ovarian stimulation have conception rates which are no lower than those with a BMI < 30 kg/m² (Orvieto et al., 2009).

**Obstetric and perinatal complications**

Those who wish to restrict fertility treatment on grounds of high BMI quote data suggesting increased rates of miscarriage in overweight and obese women following spontaneous conception (Hamilton-Fairley et al., 1992), ovulation induction and IVF (Wang et al., 2002) as well as oocyte donation (Bellver et al., 2003). A recent meta-analysis by Metwally et al. (2008) suggested an increased risk of miscarriage in women with a BMI of ≥ 25 kg/m² [odds ratio (OR) 1.67, 95% CI, 1.25–2.25]. Although the odds of miscarriage in overweight and obese women are higher following ovulation induction (OR, 5.11; 95% CI, 1.76–14.83), these values were not replicated in women who underwent IVF/ICSI (OR, 1.52, 95% CI, 0.88–2.61). A sensitivity analysis based on exclusion of studies where age was likely to be a confounding factor showed that the odds of miscarriage after IVF/ICSI (OR, 1.41; 95% CI, 0.96–2.06), or ovulation induction (OR, 3.93; 95% CI, 0.88–17.61) were not statistically significant (Metwally et al., 2008).

Age apart, miscarriage rates are also significantly influenced by the presence of polycystic ovary syndrome (PCOS) (Homburg, 2006; Boomsma et al., 2008) which often co-exists with obesity. Results showing an association between high BMI and miscarriage thus need to be adjusted for the presence of this condition, which is common in anovulatory obese women.

Obesity is associated with obstetric complications. The linear relationship between BMI and the risk of pre-eclampsia, gestational diabetes, induction of labour and Caesarean section is suggestive of a dose-dependent effect (Bhattacharya et al., 2007). However, while morbidly obese women face a higher risk of perinatal complications, absolute risks in women who are overweight or obese class I (BMI <35 kg/m²) are low (Callaway et al., 2006; Abenhaim et al., 2007; Bhattacharya et al., 2007) and do not justify the cut-off values currently recommended in the UK, Hong Kong and New Zealand to restrict access to IVF.

Maternal obesity has been claimed to be associated with an increased risk of structural anomalies (Watkins et al., 2003; Cedergren, 2004; Nelson and Fleming, 2007). According to Callaway et al. (2006), the adjusted ORs (95% CI) for congenital anomalies were 1.25 (0.85–1.87) for BMI 25.01–30 kg/m², 1.58 (1.02–2.46) for BMI 30.01–40 kg/m² and 3.41 (1.67–6.94) for BMI >40 kg/m² when compared with women with normal weight. Although of concern, this data needs to be interpreted in the context of risks in other clinical situations such as diabetes in women with normal BMI. Correa et al. (2008) examined the association of all birth defects in normoglycaemic women, pre-gestational diabetics and gestational diabetics in various BMI categories. Adjusted ORs for birth defects in pre-gestational diabetics with normal BMI were 3.50 (CI 1.68–7.30). In contrast, adjusted odds for birth defects were 1.07 (CI 0.98–1.18) in overweight and 1.16 (CI 1.04–1.29) in obese (BMI >30 kg/m²) non-diabetic women.

In utero factors can result in small for gestational age fetuses who are at higher risk of long-term adverse outcomes such as cardiac disease (Barker et al., 1989; Barker, 1999). Although maternal obesity has been suspected of being responsible for adult disease in the offspring, the precise mechanism for such programming defects has yet to be conclusively proven (Freeman, 2009).

Any assessment of perinatal risks need to acknowledge the overwhelming negative effect of maternal age. Estimated rates of all clinically significant cytogenetic abnormalities rise from 2.6 per 1000 at age 30, to 53.7 per 1000 at age 45 (Hook, 1981). In a large population based retrospective cohort study of perinatal outcomes in primiparous women, maternal age was an independent risk factor for adverse pregnancy outcomes with adjusted ORs of 1.51 for very preterm birth (CI 1.04–2.19), 1.69 for very low birthweight (CI 1.47–1.94) and 1.68 (CI 1.06–2.65) for perinatal death (Delbaere et al., 2007). Diabetes and hypertension are more common in older women and have the potential to further compromise pregnancy outcomes (van Katwijk and Peeters, 1998). Thus, although obesity is a major cause of increased feto-maternal risk in pregnancy, any decision to defer pregnancy on grounds of obesity must consider the time needed to achieve weight loss and the negative consequences of increased age on the chances of achieving a pregnancy. No pregnancy is risk free (Waldenstrom et al., 1997) and the upper limit of BMI compatible with an acceptable risk profile in pregnancy is still to be determined.
Direct costs of fertility treatment in overweight and obese

It has been argued that providing fertility treatment to overweight and obese women is not cost effective due to poor chances of success, higher risks of pregnancy loss and perinatal complications (Gillet et al., 2006). Yet, the literature on the costs of fertility treatment, antenatal and peripartum care in obese women is sparse. A recent study failed to show any significant differences in costs per live birth following ART in overweight and obese women compared with women with normal BMI (Maheshwari et al., 2009). The mean (95% CI) costs per live birth in women in the BMI groups 18.5–24.9, 25–29.9 and 30–34.9 and >35 kg/m² were £16 497 (£15 374–£17 817), £18 575 (£16 648–£21 081), £18 805 (£15 397–£23 554) and £20 282 (£15 288–£28 424), respectively (Maheshwari et al., 2009). Although these figures might suggest a trend towards an increase in mean costs with increasing BMI, the overlapping CIs around the mean costs in each BMI group argue against such a conclusion.

The argument that public money should be put to the best possible use is consistent with utilitarian principles. These are in conflict with deontological notions which reject the sublimation of the moral right of an individual for the common good (Homer, 2003). Adherence to rigid BMI cut-off values in denying access to fertility treatment may represent adoption of utilitarian values at the cost of individual welfare.

Arguments against BMI-linked access to fertility treatment

Changing demographics

Obesity is common, currently over half (56%) of all women in the UK are overweight or obese (Balen and Anderson, 2007). In the USA, 61% women are either overweight or obese; 33% are classed as obese and 6.9% are morbidly obese (Ogden et al., 2006). Although the intention is not to 'normalize' obesity or to stop encouraging women to lose weight, pragmatism dictates that rationing fertility care on the basis of BMI effectively translates to denying treatment to over half the eligible population. This includes women with anovulatory infertility who are most in need of support and treatment.

Difficulty in implementing a weight policy for access to fertility treatment

The National Institute of Clinical Excellence (NICE) guideline in the UK suggests that it is desirable to achieve a BMI of less than 29 kg/m² prior to fertility treatment (http://www.nice.org.uk/nicemedia/pdf/CG011full-guideline.pdf). The British Fertility Society (BFS) guideline recommends that fertility treatment should be deferred until a woman’s BMI is less than 35 kg/m², but goes on to state that a BMI<30 kg/m² is preferable in women under 37 with normal FSH (Balen and Anderson, 2007). In New Zealand, clinical priority access criteria implemented in 2000, restricts women with BMI>32 kg/m² from accessing fertility treatment (http://www.electiveservices.govt.nz/pdfs/gynaecology-infertility.pdf).

The evidence base underlying these recommendations is tenuous and many of these BMI cut-off values are arbitrary and probably based on select experts’ opinion.

Data linking obesity to poor reproductive outcomes tend to be from meta-analyses which are based on aggregated data, are unable to adjust for key confounders such as age and unable to provide reliable data on substantive outcomes such as live birth. The close correlation between age and BMI coupled with the growing trend for women to seek fertility treatment later in life (Maheshwari et al., 2008) means that a strict BMI rule is unrealistic and unenforceable. The BFS stance in the UK which recommends different age related BMI thresholds reflects the need for flexibility and illustrates the difficulty in enforcing these guidelines. Given the uncertainty of the evidence base and lack of consensus around threshold BMI values for increased reproductive risk and decreased effectiveness and cost-effectiveness of fertility treatment, we feel that it is not possible, at the present time, to justify and successfully implement a single BMI cut-off (Zachariah et al., 2006).

There is also some evidence to suggest that a BMI-based approach may be flawed as waist-to-hip ratio is a better predictor of reproductive outcome than BMI (Zaadstra et al., 1993; Wass et al., 1997).

Stigmatization and discrimination

Article 9 of the Charter of Fundamental Rights of the European Union guarantees the right to marry and the right to found a family in accordance to national laws governing the exercise of these rights. BMI restrictions on access to fertility care may be construed as being tantamount to infringing on an individual’s basic fundamental rights (http://www.europarl.europa.eu/charter/pdf/text_en.pdf).

Restricting fertility care on grounds of weight may also cause stigmatization (Heitmann and Tang-Peronard, 2007) which is known to exacerbate obesity-related disease (Muennig, 2008) and cause depression, low self-esteem and poor body image (Puhl et al., 2008). These outcomes are known to be more common in women with infertility, as are depression, anxiety, social isolation, sexual dysfunction all of which can affect overall wellbeing (Fassino et al., 2002; Chen et al., 2004). Singling out obese infertile women by restricting fertility treatment can thus cause profound psychological consequences. The ability of some affluent women with high BMI to bypass restrictions associated with state-funded fertility treatment (Gillett et al., 2006) can lead to a sense of inequity and feelings of injustice and social tension.

Autonomy and perception of risk

In other areas of healthcare, the risk of complications does not prevent overweight and obese women from receiving medical and surgical treatment and BMI cut-offs are the prerogative of the surgeon and the anaesthetist. Post-operative complications (fever: 59 versus 36%, wound complications: 29 versus 4%) following hysterectomy are higher in obese women as is hospital stay >12 days (35 versus 11%) (Pitkin, 1976). This highlights the existing paradox within the present healthcare system and challenges our role as healthcare professionals to provide care without discrimination.

As long as women understand the risks of a proposed treatment, and the overall clinical benefit is deemed to be greater than any attendant risks, we should be cautious in allowing our inherent paternalism to override patient autonomy. The situation is complicated by the sheer numbers of overweight and obese women who now account for more than half the population in many countries.
Poor success associated with interventions for weight loss

Although observational data suggest that weight loss improves reproductive outcome (Clark et al., 1995a,b; Norman et al., 2004), this is difficult to achieve for many women. Conventional strategies such as lifestyle modification, dietary restriction, increasing physical activity and pharmacotherapy produce varied results. Most successful weight loss interventions result in 5–10 kg weight loss per woman. This translates to less than a 2–4 kg/m² reduction (or in more typical results, just over 1 kg/m²) in BMI for a woman of average height (Laredo, 2006). For many of these women, this may be insufficient to allow them to cross an arbitrary BMI threshold.

Lifestyle modification programmes, including specially dietary interventions are associated with poor rates of compliance (Moran et al., 2003) and are perceived to be too slow for women who are competing against their biological clocks (Palomba et al., 2008).

As far as pharmacotherapy for weight loss is concerned, randomized controlled trials have failed to demonstrate a significant effect of metamorfin on weight loss (Lord et al., 2006; Tang et al., 2006). Small prospective studies on the use of orlistat in obese PCOS have suggested that this drug may be useful, but large randomized controlled trials in obese subfertile women are lacking (Panidis et al., 2008).

The impact of most dietary interventions is short lived and weight lost is often regained over time (Wadden, 1993), and only 15% of the subjects maintain weight loss successfully over the long-term (Ayyad and Andersen, 2000). Preventing older women from attempting to try for a family until they have lost a specific amount of weight may cost them valuable time which can seriously damage their chance of conception.

The potential conflict between BMI and age

Data from a recent population based observational study suggest that the average age of women presenting for fertility treatment at present is much higher compared with 20 years ago (Wilkes et al., 2009). We have previously highlighted the effect of age on the chances of successful fertility treatment as well as on the risk of pregnancy complications. Few studies have compared the independent risks of age versus obesity on the outcome of fertility treatment. In women over 36, age, as opposed to BMI, has been shown to exert a stronger negative effect on oocyte number, number of mature and fertilized oocytes, clinical pregnancy and live birth rates (Sneed et al., 2008). This supports the argument that in older women who are moderately overweight and obese, treatment rather than unsuccessful attempts to lose weight should be the priority.

Pre-pregnancy counselling

As fertility clinicians, we have the opportunity to change the prenatal environment by appropriately counselling women about positive lifestyle measures. The overall public health impact of this is likely to be limited as few women of reproductive age need to seek medical advice for infertility. A recent survey found that whereas nearly one in five women experienced infertility, 68.3% of those with primary infertility and 73% with secondary infertility sought medical advice. Eventually ~60% of them conceived (Bhattacharya et al., 2009). Thus, the impact of attempts by fertility specialists to improve the prenatal environment will be limited to 12% of all women of reproductive age i.e. 88% will fall out with this sphere of influence. There are numerous examples which support the thesis that public health messages are not particularly successful in changing health behaviour in at risk individuals (Roberts et al., 1995; Howell et al., 2001). Since 2004 NICE guidelines on infertility have recommended weight loss in overweight and obese women as a prelude to planning a pregnancy or fertility treatment. This message is included in the version of the summary of the guideline targeted at consumers and lay-people, as well as in the more detailed version meant for clinicians. This has not resulted in any noticeable decrease in overweight obese individuals seeking fertility treatment (http://www.nice.org.uk/nicemed/pdf/CG011full-guideline.pdf).

Conclusion

Overweight and obesity is common in women of reproductive age, many of whom are choosing to delay childbearing thus creating a need to balance the detrimental effects of age versus BMI on fertility and perinatal outcomes. Robust data showing an association between BMI and live birth in subfertile women are lacking. Available evidence suggests that age has a stronger negative impact on fertility and pregnancy outcomes. There is insufficient evidence, at present, to deny women fertility treatment on grounds of BMI given the relatively poor success rates of most weight loss regimens and discriminatory nature of such a policy against half the female population of many countries. Weight loss should be encouraged wherever possible and preconception counselling offered. However, the gain associated with weight loss in older women needs to be balanced against much steeper loss in fertility with age. In a populations where over half of all women are overweight, it can be argued that is unfair to insist on their adherence to an outdated measure of normality, and simplistic to exclude them from fertility treatment.

Authors’ Roles

S.P. contributed to conception and design, performed the literature search on which the article is based and wrote the first draft. A.M. provided significant intellectual input in constructing the arguments presented; revised the manuscript and edited the final version. S.B. conceived the original idea for this article, contributed to the design and structure of the article. Revised the first and all subsequent drafts and edited the final version.

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