Fertility treatment in obese women

Koning, A.M.H.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 8

Summary and
General discussion
Overweight and obesity are increasing worldwide. This has major adverse consequences for health in general and fertility in women in particular. With the increasing number of women in reproductive age being obese, there is also an increasing need for fertility treatment. And with more pregnant women being obese, the amount of pregnancy complications will also continue to increase. In the USA, women with a body mass index (BMI) ≥ 35 kg/m² most frequently sought medical attention to become pregnant, but received surgical fertility-related services least frequent. [34] Assisted reproductive technology (ART) is restricted worldwide beyond a certain BMI, ranging from 25 to 40 kg/m². [32] In the Netherlands several fertility centres have a BMI limit, mostly around 30-35 kg/m². [212-214] This restriction is based on different arguments from safety for the woman to risk for the future child.

This thesis studies several aspects of reproductive problems in overweight and obese women. We address the (cost) effectiveness and safety of fertility treatment in overweight and obese women, the effectiveness of lifestyle intervention in obese women who suffer from subfertility, and we discuss ethical issues regarding fertility treatment in obese women.

In chapter 2 we used decision analysis and economic modelling to assess the costs of a live birth after ART in normal weight, overweight and obese women. We found that in our hypothetical cohort of 1,000 anovulatory subfertile obese women live birth was decreased by 15% (from 806 to 687 live births) compared to women with normal weight. For ovulatory women, live birth rate was decreased by 24% (from 698 to 531 live births). In parallel the number of complications increased. Associated costs were also higher: the cost per live birth for anovulatory obese women was 100% higher than for their normal weight counterparts. For ovulatory women, these costs were 70% higher. ART in obese women is less effective and their pregnancies are more costly than in women with normal weight.

In chapter 3 we asked ourselves the question if fertility treatment in overweight and obese women has different complication rates than in women with normal weight and what the effectiveness of fertility treatment is. We performed a systematic review on complications of ART in relation to body weight. We identified 14 studies that reported on the relationship between overweight
and complications during or after ART. None of the individual studies found a positive association between overweight and ART complications. The pooled odds ratios (OR) for overweight versus normal weight for ovarian hyperstimulation syndrome, multiple pregnancy and ectopic pregnancy were 1.0 (95% confidence interval (CI) 0.77 to 1.3), 0.97 (95% CI 0.91 to 1.04) and 0.96 (95% CI 0.54 to 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 to 1.0), 1.01 (95% CI 0.75 to 1.4) and OR 0.94 (95% CI 0.69 to 1.3), respectively. These data show that both in terms of safety and in terms of effectiveness, the impact of overweight and obesity is very limited.

In chapter 4 we evaluated the effectiveness of a six months weight reduction program (WRP) for obese subfertile women in a retrospective cohort study. The mean weight reduction was 4.3 kg in the intervention group and a mean weight gain of 0.5 kg in the control group compared to the baseline values at the start of treatment (p-value <0.001). There were 33 (32%) women in the intervention group versus 25 (25%) women in the control group who lost more than 5% of body weight compared to baseline (crude odds ratio (OR) 1.40 (95% CI 0.73 to 2.7). The ongoing pregnancy rates were 52 (51%) and 41 (41%) (adjusted hazard rate ratio (HRR) 1.9 (95% CI 1.0 to 3.4)) while live birth rates were 48 (47%) and 37 (37%) (adjusted HRR 2.0 (95% CI 1.1 to 3.8) for the intervention group and control group, respectively. In our study there is potential benefit from a WRP in obese subfertile women. In chapter 5 we compared pregnancy outcome in these women. The composite outcome of pregnancy complications was not different between groups: 19 (37%) women in the intervention group and 12 (34%) women in the control group had at least one pregnancy complication (p-value 0.34). We found no relationship between weight loss and pregnancy complications. Our data do not support a positive effect of lifestyle intervention on the occurrence of pregnancy complications. In chapter 6 we reported on the long term follow up of the singleton children from these women. The mean weights and BMI’s in early childhood are not different between the groups.

Chapter 7 discusses the three different arguments used for a BMI limit for access to ART. First, the argument of safety for the woman. Increased risks of pregnancy complications in obese women are evident but these are not
different than in other women with associated disease that are treated with ART and also not disproportional. Second, risks for the future child. There are increased risks of congenital anomalies and premature birth. But if treatment is rejected on grounds of the welfare of the child this can only be considered in exceptional circumstances, such as when there is “great risk of serious harm”. Third, the cost burden of treatment. It appears that this argument is used selectively while other groups with an additional health problem do get reimbursed for their fertility treatment. With the potential gain of lifestyle intervention in obese subfertile women this should be offered. If weight loss is not achieved however, this should not automatically shut the door to treatment for women with weight above a certain BMI. Looking at the risks and costs that are considered acceptable for other fertility patients this would be unjustified.

**Obesity: result of modern society**

Obesity is considered a chronic disease by the World Health Organisation (WHO), this implies that it is incurable. For a long time it’s development was considered as nature and not nurture. The Barker thrifty hypothesis changed this view as it set out a framework for the importance of the early foetal life environment and the programming of our bodies in terms of metabolism and growth. [215] More recently Armitage et al. proposed the ‘developmental overnutrition hypothesis’ [202] This states that high maternal glucose, free fatty acid and amino acid concentrations result in permanent changes in appetite control, neuroendocrine functioning and/or energy metabolism in the developing foetus, thus leading to risk of adiposity. Obviously, today’s society with access to abundant food for the majority of people plays a substantial role in the arising of this disease. With the knowledge that treating obesity is difficult, prevention should be the cornerstone, preferably starting at childhood. Several programs in the Netherlands have been initiated to inform people and give advice on a healthy lifestyle. With commercials on national television and the use of social media several national campaigns have been launched. For example “drink water” to promote drinking of water, “healthy sports club” to advise clubs on healthy alternatives in the cafetaria and “healthy school cafetaria” with advice on recommended healthy food and drinks. Besides these informative measures other directive methods are used by governments to fight obesity.
It has been well established that drinking sugar sweetened beverages leads to weight gain and obesity. [216] To fight obesity consumption of these drinks can be effectively reduced by raising their prices via taxation. This was for instance shown in a recent British modelling study. [217] Also, in the Netherlands it was demonstrated in an experimental environment that sugar sweetened drink purchases were reduced substantially after raising value added tax from 6 to 19%. [218] In the same manner, reduction of alcohol and tobacco consumption by taxation has been very effective. [219;220] Hence, there are excellent reasons to prevent obesity in a similar way. Another method which is advised by different organisations is the labelling of food with a traffic light method. This is a very simple and clear way to see at a glance if the product contains too much sugar, salt or fat. The food industry is trying to prevent the introduction of these forms of legislation and regulation. Their main goal will mostly remain maximising profit. The lobby they use is by some compared to the tobacco industry lobby because it misleads and hides negative data. [221] They pronounce, for example, that there is no unhealthy food but only an unhealthy diet, or claim that obesity is not because of excessive food but because of a lack of physical activity. [222] Children are an important part of their marketing, they are using packaging, television commercials, websites and apps to promote their product, sometimes aggressively. Children are cognitively incapable of appreciating the commercial purpose of television advertising and are particularly vulnerable to its persuasive techniques. [223] The food industry has resisted legislation and adopted self-regulation of children’s marketing. In a systematic review on the effects of self-regulation a heterogeneous set of results is found. Surveys reported in papers in peer-reviewed journals provide ample evidence of continuing high levels of promotion of less healthy food products and high levels of exposure of children to this type of promotion. Significant reductions were absent in many locations except in response to statutory regulation. Industry-sponsored reports however, indicate a remarkable reduction in the promotion of unhealthy products and children’s exposure. [224] Reports from a variety of other authoritative sources show weak or absent reductions, or insufficient evidence of change as a result of self-regulation, but some reduction following statutory regulation.

Treatment of obesity has been proven difficult, with dieting being the most effective intervention in terms of weight loss. There is, however, substantial
dropout in these programs with figures ranging from 10 to 40% in systematic reviews. [225,226] Furthermore, sustaining the lost weight is a challenge. These figures support the idea that a person with obesity is “set” differently in utero than a person with normal weight. Also children born macrosomic are at risk of becoming obese and having metabolic syndrome (dyslipidemia, hypertension, obesity and insulin resistance). [227] A retrospective study showed that children born from obese mothers are twice as likely to be obese at 2 years of age when compared to mothers with normal weight. [228]

In our current western society characterised by an abundance of (unhealthy) food and intensive marketing of a giant food industry, next to a more sedentary life, obesity seems the logic result. One of its negative consequences is subfertility in obese women. Society is responding with preventive measures, the results of these measures seem inadequate thus far in turning the table.

**Obesity: judged by appearance**

Today it is not general policy to treat obese women for subfertility. Besides the increased risks in pregnancy perhaps other factors play a role in denying fertility treatment. The majority of fertility physicians in the USA feels there should be a BMI limit for access to fertility treatment, and that this limit should be lower than the limit they currently apply in their facility. [229] These feelings are perhaps based on, or a result of judgment of obese women.

It has been demonstrated extensively that obese people are judged and discriminated based on their appearance. [230] This even seems to be the case in health care providers for the obese.

An interview based research study of participants at an obesity conference showed that they attribute negative findings significantly more to fat than to thin people. [231] To our knowledge no research has specifically been performed for fertility care providers but it is conceivable that, in line with the above conference study, they also think negatively of obese women in terms of their individual responsibility for not becoming pregnant or responding to treatment. This will probably have a negative impact on whether or how these women are treated. Prejudice concerning weight leads to substandard care in health care. [232]
In other groups of women judgement has played a role in access to fertility treatment, for example in lesbian couples and single women. Opponents of treating these women used different arguments like only treat people who are infertile or that children need a father and normal upbringing. Several studies have shown that these assumptions and prejudices are totally false. [233] The Ethics Committee in the USA proclaimed it therefore unjustified to withhold these women treatment. [234] The Committee's arguments were however foremost arguments in light of the welfare of the future child. The comparison with obesity is therefore weak because the risk for the woman is the argument used most frequently by proponents of a BMI limit. Another reason to deny fertility treatment is age. Seeking treatment for subfertility at an older age is also judged by society and health care providers. Worldwide, different age limits (39–46 years) are used for access to fertility care. Some argue that women should not be treated beyond a certain age [235] while others warn against discriminating women based on their age. [236] The proponents of not treating older women suggest that it is their own fault they don't conceive and therefore should not be treated. In conclusion, health care professionals should be aware of their prejudices and be able to care for their obese patients without being influenced by implicit negative feelings.

Implications of findings in this thesis

Based on current scientific knowledge, obese subfertile women should be offered lifestyle intervention prior to ART with the objective of losing weight and achieving a spontaneous pregnancy. They should be properly informed about their increased risks of pregnancy complications and that this may have distinct consequences for themselves as well as for their offspring.

Clinical implications

Chapter 3 clearly shows overweight and obesity have a negative impact on fertility. This does, however, not result in unsafe situations, be it for the subfertile woman during fertility treatment, or for the woman and her offspring during and after pregnancy. We conclude that when a woman with excess weight suffers from infertility it is of key importance to help her improve her lifestyle and lose weight. There should be attention for the reason the woman
has excess weight and give guidance in improving possible bad habits. Most people with obesity have tried to lose weight but have regained it. Therefore it is important to explain what different approaches are available and offer an extensive follow up plan. This can be done by a dietician or trained nurse.

Lifestyle intervention should be available in fertility clinics and at least six months treatment should be advised. A combination of diet, exercise and cognitive behavior therapy has the best chance of success. About 25% of women will conceive spontaneously during the intervention. After the lifestyle intervention ART should be offered, even when a woman did not lose weight despite effort. When time is an issue in women above 35 years or in case of low ovarian reserve lifestyle intervention and ART can be offered simultaneously. In order to have a good chance of success with the lifestyle intervention we advise not to judge the patient and consider the excess weight as a health issue instead of a choice. If a woman gets pregnant, in our opinion second line pregnancy care or shared care should be offered depending on her BMI.

Fertility treatment of obese women is lengthy, more costly and less successful than that of a woman with normal weight. However, we show in chapter 4 that the success of ART is still good with an only 10% lower live birth rate compared to women with normal weight and therefore certainly worth the effort.

Guidelines
There is to our knowledge no clinical guideline specifically for ART in obese women. The National Institute for Health and Care Excellence (NICE) has a guideline for weight management before, during and after pregnancy. [237] They recommend all health care professionals to discuss the risks of obesity with these women and help them achieving a more healthy weight with lifestyle intervention. Based on the Dutch guideline for diagnostics and treatment of obesity we recommend the following [158]: from a BMI above 30 kg/m² combined lifestyle intervention should be available. In women with a BMI 25–30 kg/m² and a waist circumference above 88 cm the same risk of comorbidities are at hand as for a woman with BMI ≥ 30 kg/m² and they should therefore also be offered combined lifestyle intervention. Women with a BMI ≥ 40 kg/m² have such a significant increased risk of comorbidities such as type 2 diabetes and cardiovascular disease that they should first be screened for these disorders by
a specialist for internal diseases and treated if necessary. A weight reduction of 5% will lead to a decrease in comorbidity risk and is achievable for a subgroup in six months. Also a substantial amount of women will get pregnant during the six months of lifestyle intervention. If they are not pregnant after this time and were not able to lose weight despite their effort, they should nevertheless be treated for their subfertility.

**Future research**

- Although many studies have shown potential benefit of lifestyle intervention in obese subfertile women, the exact mechanism behind this effect remains to be discovered.

In order to determine the positive effects of lifestyle intervention prior to ART, several parameters should be studied in more detail besides weight loss: exercise, waist circumference, insulin resistance, diet, effect of cognitive behavior treatment. Also patient satisfaction and preference should be monitored.

- There is substantial dropout in lifestyle intervention programs with less weight loss as a result. In order to maximize the positive effects of lifestyle intervention we recommend to search for factors associated with dropout.

- A decrease in pregnancy complications is found in women after bariatric surgery with substantial weight loss. The effect of lifestyle intervention prior to pregnancy on pregnancy complications is still unclear. We did not find a difference between the two groups in our retrospective cohort study but this should be studied prospectively.

- Long term follow up of children born after lifestyle intervention is lacking. With the potential gain of preventing childhood obesity this could help achieving financial support from the government for implementation of lifestyle intervention.