University of Groningen

Lifestyle intervention in obese infertile women

van Oers, Anne Maria

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Summary and general discussion

The aim of this thesis was to investigate in-detailed aspects of the effects of a lifestyle intervention preceding infertility treatment when compared to prompt infertility treatment in obese infertile women.

Summary of the results

Chapter 2 described the main results of the LIFEstyle study, a randomised controlled trial in obese infertile women, investigating the effects of a six-month lifestyle intervention preceding infertility treatment (intervention group) compared to immediate infertility treatment (control group). The primary outcome was the vaginal birth of a healthy baby from a singleton pregnancy at 37 weeks or more within 24 months after randomisation. A total of 290 women were randomly assigned to the intervention group and 287 women were assigned to the control group. The mean weight loss after 6 months was 4.4 ± 5.8 kg in 236 non-pregnant women in the intervention group and 1.1 ± 4.3 kg in the 128 women in the control group (P < 0.001). The discontinuation rate in the intervention group was 22%. Within 24 months after randomisation, the frequency of vaginal births of healthy singletons at term was significantly lower in the intervention group than in the control group: 76 (27%) versus 100 (35%) (RR 0.8; 95% CI 0.6-1.0). The rate of live birth rates within 24 months after randomisation followed a similar pattern. After the inclusion of data from pregnancies that were conceived within 24 months after randomisation but where childbirth occurred following that period, between-group differences in the rates of vaginal births of healthy singletons at term (32% versus 39%, RR 0.8, 95% CI 0.7-1.0) or the rates of live births (53% versus 58%, RR 0.9, 95% CI 0.8-1.1) were no longer statistically significant. Overall, significantly more women in the intervention group than in the control group had ongoing pregnancies that resulted from natural conception (26% versus 16%, RR 1.6, 95% CI 1.2-2.2). The frequencies of complications related to pregnancy and labour in women and neonates did not differ significantly between groups.

Chapter 3 described the effects of the lifestyle intervention in the LIFEstyle study in subgroups of obese infertile women. The predefined subgroups of women were based on age, body-mass index, ovulatory status and waist-hip ratio. The effect of the intervention program in the subgroups was studied on healthy live birth rate within 24 months, as well as the rate of overall live births (live births independent of gestational age, mode of delivery and health) and natural conceptions conceived within 24 months. Neither maternal age, ovulatory status nor BMI had an impact on the healthy live birth rate within 24 months, nor did they influence the overall live birth rate within 24 months after randomisation. Waist-hip ratio showed a significant interaction with the effect of lifestyle intervention on the healthy live birth rate (P = 0.05), resulting in a lower healthy live birth rate in women with a WH ratio

8

< 0.8 who participated in the lifestyle intervention. WH ratio had no interaction regarding overall live birth rate nor on natural conception rate. The rate of natural conceptions resulting in an ongoing pregnancy conceived within 24 months in the total randomised population was significantly higher in women who received the lifestyle intervention (OR 1.8, 95%CI 1.2-2.8). This effect remained in women who were < 36 years (aOR 2.2 95% CI 1.4-3.4), women who were anovulatory (aOR 4.2, 95%CI 2.0-8.4), women with a BMI < 35 kg/m^2 (aOR 3.2, 95% CI 1.4-7.2), women who had a BMI ≥ 35.0 kg/m^2 (aOR 1.9, 95% CI 1.1-3.3), and women with a WH ratio ≥ 0.8 (aOR 2.4, 95% CI 1.5-4.0) In anovulatory women, the lifestyle intervention resulted in more natural conceptions compared to ovulatory women (P - value for interaction = 0.02). There was no interaction between other subgroups and the effect of the intervention on the rate of natural conception.

Chapter 4 presents an economic evaluation comparing the lifestyle intervention preceding infertility treatment to prompt infertility treatment using data of the LIFEstyle study. The economic evaluation was conducted as a cost-effectiveness analysis and included various scenarios using different effectiveness measures and subgroups of women to estimate in which scenario lifestyle intervention preceding infertility treatment could be cost-effective. The primary outcome for effectiveness was the vaginal birth of a healthy singleton baby at term within 24 months after randomisation (the healthy live birth rate). The economic evaluation was performed from a hospital perspective and included direct medical costs of the lifestyle intervention, infertility treatments, medication and pregnancy in the intervention and control group. Further exploratory cost-effectiveness analyses included scenarios with overall live birth within 24 months and overall live birth conceived within 24 months as effectiveness measures and scenarios with subgroups, i.e. of ovulatory and anovulatory women, women < 36 years and ≥ 36 years of age and of completers of the lifestyle intervention. Total mean costs per woman in the intervention group within 24 months after randomisation were €4324 (SD €4276) versus €5603 (SD €4632) in the control group (cost difference of -€1278, P < 0.05). Healthy live birth rates were 27% and 35% in the intervention group and the control group, respectively (effect difference of -8.1%, P < 0.05), resulting in an incremental cost-effectiveness ratio of €15 845 per additional percentage increase of the healthy live birth rate. Mean costs per healthy live birth event were €15 932 in the intervention group and €15 912 in the control group. Expanding the effectiveness outcome to all live births conceived within 24 months, irrespective of delivery within or after 24 months, improved cost-effectiveness of the lifestyle intervention. Using this wider definition of effectiveness, the probability that lifestyle intervention preceding infertility treatment was cost-effective in anovulatory women was 40%, in completers of the lifestyle intervention 39%, and in women ≥ 36 years 29%.

Chapter 5 provided an analysis of the effects of a lifestyle intervention on cardiometabolic health and quality of life (QoL) on the short term. Cardiometabolic outcomes included weight, waist- and hip circumference, body-mass index, systolic and diastolic blood pressure, fasting glucose and insulin, homeostatic model assessment for insulin resistance (HOMA-IR), high-sensitivity C-reactive protein (hs-CRP), lipids and a composite score for metabolic syndrome. All outcomes were measured by research nurses at randomisation and at 3 and 6 months after randomisation. Self-reported quality of life was measured at 3, 6 and 12 months. Weight (-3.1 kg 95% CI: -4.0--2.2 kg; P < 0.001), waist circumference (-2.4 cm 95% CI: -3.6--1.1 cm; P < 0.001), hip circumference (-3.0 95% CI: -4.2 --1.9 cm; P < 0.001), BMI (-1.2 kg/m^2 95% CI: -1.5--0.8 kg/m^2; P < 0.001), systolic blood pressure (-2.8 mmHg 95% CI: -5.0--0.7 mmHg; P = 0.01) and HOMA-IR (-0.5 95% CI: -0.8--0.1; P = 0.01) were significantly lower in the intervention group as compared to controls after six months. Hs-CRP and lipids did not differ between groups. The odds ratio for metabolic syndrome in the intervention group was 0.5 (95% CI: 0.3-0.9) compared to controls. Physical QoL scores were higher in the lifestyle intervention group (2.2 95% CI: 0.9 to 3.5; P = 0.001) while mental QoL scores did not differ.

In **Chapter 6** the effects of periconceptional weight loss on maternal and neonatal outcomes were investigated, independent of randomisation arm of the LIFEstyle study. Women were categorised into quartiles according to the magnitude of their periconceptional weight change. In the LIFEstyle study, 321 obese infertile women achieved an ongoing pregnancy which was conceived within 24 months after randomisation. Periconceptional weight change (units of BMI in kg/m2) was available in 244 of these women (76%). Women in the first quartile (Q1) had a periconceptional weight change of < -2.1 kg/m^2, women in the second quartile (Q2) -2.1 to -0.9 kg/m^2, women in the third quartile (Q3) -0.9 to 0.1 kg/m^2 and women in the fourth quartile (Q4) gained ≥ 0.1 kg/m^2. There were no significant differences between women in the quartiles regarding rates of excessive gestational weight gain, gestational diabetes, preterm birth, induction of labour, spontaneous vaginal birth and Caesarean section. Compared to women in Q4, the adjusted odds ratios, aOR, and 95% confidence interval for a hypertensive complication were; 0.6 (0.2-1.4) for women in Q1, 0.3 (0.1-0.8) for women in Q2, 0.4 (0.2-1.0) for women in Q3 and 0.4 (0.2-0.8) for women in Q1 to Q3 combined. In the subgroup analysis investigating only singleton pregnancies, the statistically significant decreased rate of a hypertensive complication remained in women in Q2 (aOR 0.3, 95% CI 0.1-0.7) and Q3 (aOR 0.4, 95% CI 0.2-1.0) and when comparing women in Q1 to Q3 together to women in Q4 (aOR 0.4, 95% CI 0.2-0.8). Furthermore, there was a significantly decreased aOR (95% CI) of preterm birth in women in Q2 (0.2, 0.1-1.0) and when combining women in Q1 to Q3 (0.4, 0.1-1.0) compared to women in Q4.

8

The aim of **Chapter 7** was to identify determinants of successful lifestyle change in 289 obese infertile women in the intervention group of the LIFEstyle study. We operationalised lifestyle change as successful weight loss (reduction of ≥ 5% of the original body weight or achieving a BMI ≤ 29 kg/m^2), weight loss in kilograms, a reduction in energy intake and an increase in the number of steps. In addition, we investigated determinants of completion of the intervention program. Women with higher scores on external eating behaviour had a higher probability of successful weight loss (OR 1.1, 95% CI 1.0 to 1.1). Women with a higher BMI and previous support by a dietician had a lower probability of successful weight loss (OR 0.9, 95% CI 0.8-1.0 and OR 0.5, 95% CI 0.3-1.0, respectively). On average, women who received previous support by a dietician lost 0.9 kg less weight (0.0-1.9kg) compared to women without a history of support. Women with a higher self-efficacy level had a lower mean energy intake relative to women with the lowest self-efficacy level (P < 0.01). There was a trend in women with increased readiness to change towards taking more daily steps (P = 0.05). The readiness to change towards weight loss was associated with completion of the intervention (P = 0.04), with women in the action phase having a higher probability of completing the intervention compared to women in the maintenance phase. We concluded that the most consistent determinants for lifestyle change in obese infertile women were not having had previous dietetic support and readiness to change.

Reflection on the results

Obesity in women of reproductive age is associated with decreased pregnancy chances following natural and treatment dependent cycles, an increased risk of a pregnancy complications, such as gestational diabetes, hypertensive complications and an increased chance of neonatal macrosomia, congenital birth defects, perinatal death, childhood overweight and premature mortality later in life.[1-9]

The LIFEstyle study: results on main outcome parameters
The main results of the LIFEstyle study show that, in obese infertile women, participating in a six-month lifestyle intervention before commencing infertility treatment does not improve the chance of a healthy singleton at term within 24 months. The LIFEstyle intervention did, however, improve the chance of having a natural conception. Since the LIFEstyle study was the first large randomised controlled trial on this topic, it is difficult to put these findings into the context of the existing literature. Two previous RCTs with small sample sizes show that weight loss is feasible in this patient group, whether this influenced reproductive outcomes was unclear.[10,11]

There may be several reasons why, in the LIFEstyle study, the lifestyle intervention did not

improve the chances of a healthy baby from a singleton pregnancy. It is possible that the mean weight loss (-4.4 kg) in women participating in the lifestyle intervention, but who did not conceive during the intervention period, was not sufficient to improve reproductive outcomes, since many women remained obese and only 38% of non-pregnant women achieved a weight loss of ≥ 5% of their original bodyweight. It is also possible that the total duration of the lifestyle intervention (six months) and consequently not being treated during this period was relatively long compared to the total follow-up period of 24 months. The influence of the follow-up period on the results of the trial is illustrated by the converging rates of live births in the intervention and control group including live births ending beyond 24 months of randomisation (53% versus 58% (RR 0.9, 95% CI 0.8 to 1.1). Therefore, a longer time to pregnancy should be anticipated when obese women participate in lifestyle intervention prior to infertility treatment, without compromising live birth rates. Indeed, lifestyle intervention in obese participants takes time. The recommended period of intervention is at least six to nine months.[12] During the design of the LIFEstyle study we estimated that an intervention of more than six months would hamper inclusion of patients in the trial, and hence an intervention with the duration of six months was chosen. Furthermore, a longer follow up of more than 24 months after randomisation was not possible due to restrains of the funding source. The third reason why women participating in the lifestyle intervention group did not have improved chances of a healthy singleton birth in the LIFEstyle study could be the result of the non-completer rate of the lifestyle intervention of 22%. Similar rates of non-completion or drop-out of a lifestyle intervention have been reported.[13] The per-protocol analysis excluding non-completers of the lifestyle intervention showed comparable rates of healthy singleton birth rates at term (31% versus 35%, RR 0.9, 95% CI 0.1 to 1.1) and live births (51% versus 54%, RR 1.0, 95% CI 0.8 to 1.1) within 24 months after randomisation in the intervention compared to the control group. Therefore, the rate of non-completers in the LIFEstyle study, although anticipated, influenced the rate of the healthy singleton births of the intervention arm of the study, negatively. Indeed, women who dropped-out of the lifestyle intervention had a low rate of the primary outcome (12%). Preventing drop-out in lifestyle interventions might lead to better overall results and should be focus of attention in future studies. The LIFEstyle study was a pragmatic trial, in which both the weight loss that was achieved and the number of women who did not complete the intervention illustrate how difficult changing lifestyle is, despite intensive guidance by trained nurses. On the other hand, this first well-powered trial investigating this topic shows that 78% of the obese infertile women could complete the lifestyle intervention, which resulted in comparable healthy live birth rates, more natural conceptions and less need for additional infertility treatment. A RCT, published in August 2017, evaluating a lifestyle intervention in obese women (BMI between 30 and 35 kg/m^2) preceding IVF treatment, women allocated to the lifestyle intervention (n = 160) received a

8

low-calorie liquid diet of 880 kcal/day for 12 weeks, followed by a weight stabilisation phase for 2-5 weeks and IVF treatment.[14] Women in the control group received IVF treatment only (n = 157). Follow-up in both groups was restricted to one IVF treatment cycle. The intervention resulted in significant mean weight loss (-9.4 kg in the intervention group, versus weight gain +1.2 kg in the control group, P < 0.0001), but the number of live births was did not improve after the lifestyle intervention (30% vs. 28%, P = 0.77). The rate of natural conceptions leading to a live birth was significantly higher in women in the intervention group (11% vs. 3%, P = 0.009). Women in this study received a much more intensive dietary modification, using a low calorie liquid formula diet compared to women in the LIFEstyle study and achieved more weight loss. In addition, participating women had a lower median BMI (33 kg/m^2) at baseline. The effects on the birth rates and the presence of more natural conceptions, however, are similar as in our study, although the shorter follow-up period of only one IVF cycle, in this recent RCT limits direct comparison of both studies.

Subgroup analyses of the LIFEstyle study

The subgroup analyses of the LIFEstyle study revealed an influence of body fat distribution on the chance of a healthy singleton baby born at term within 24 months. In women with a waist-hip (WH) ratio < 0.8, the six-month lifestyle intervention resulted in a lower healthy live birth rate compared to women with a WH ratio ≥ 0.8. This might be an incidental finding, as this finding was not reproduced for the other outcome measures such as overall live births. An alternative explanation could be that women with a WH ratio < 0.8, and therefore a non-central fat distribution, do not benefit from weight loss. It is known that intra-abdominal adipose tissue accumulation is related to increased insulin resistance and cardiometabolic risks.[15,16] This is in contrast with subcutaneous fat accumulation, which is mainly present on the hips, which poses little metabolic risks.[16] Women with subcutaneous fat accumulation (and a normal WH ratio) have a lower risk of metabolic imbalances, such as insulin resistance, compared to women with intra-abdominal adipose tissue accumulation and possibly do not benefit from a lifestyle intervention, which is aimed to alleviate metabolic imbalances and by doing so improving conception rates.[17] This finding should be investigated further, as it might implicate that women with a normal WH ratio, and therefore mainly subcutaneous fat accumulation, do not benefit from lifestyle intervention in terms delivery of a healthy singleton at term within 24 months.

The increased chance of a natural conception, as seen in the LIFEstyle study, is present in subgroups of anovulatory women, women of 36 years and younger and women with a WH ratio of > 0.8. Furthermore, relative to ovulatory women, anovulatory women have a significantly increased chance of a natural conception (P = 0.02). The difference in the rate of natural conceptions between the intervention and control group mainly arose after

the six months of lifestyle intervention, since 41 natural pregnancies in the intervention group and 36 natural conceptions in the control group were present at six months after randomisation. The difference between the rate of natural conceptions in the intervention and control group can therefore not directly be explained by the postponing of infertility treatment and as a consequence a longer time to achieve a natural conception in the intervention group during the first six months of the study. The finding that anovulatory women benefit specifically from a lifestyle intervention preceding infertility treatment in terms of natural conception rates is in line with earlier studies. In a Cochrane review in 2011, Moran et al. concluded that lifestyle interventions in women with PCOS result in improvements in body composition, hyperandrogenism and insulin resistance.[18] However, they found insufficient data in the literature for assessing reproductive outcomes, such as ovulation rates and birth rates. Similar findings as in our study have been reported in a post-hoc analysis of two RCTs by Legro et al., comparing ovulation rates and live birth rates in women with PCOS who received immediate ovulation induction with clomiphene citrate (n = 187) versus women who received a sixteen weeks treatment with lifestyle intervention (n = 48) , oral contraceptives (n = 47) or both (n = 48) prior to ovulation induction.[19] Women who received the lifestyle intervention (either alone or combined with an oral contraceptive respectively) had improved ovulation rates (RR 1.4, 95% CI 1.1 to 1.7 and RR 1.4, 95% CI 1.2 to 1.8) and live birth rates (RR 2.5, 95% CI 1.3 to 4.7 and RR 2.5, 95% CI 1.3 to 4.8) compared to women who received immediate ovulation induction. Furthermore, Kuchenbecker et al. showed that, in obese women with PCOS, loss of intra-abdominal fat is associated with resumption of ovulation.[17] Potential mechanisms explaining improved ovulation rates and therefore increased natural pregnancy rates in obese women with PCOS is an improvement of the insulin resistance after weight loss and a subsequent decrease in the hyperandrogenaemia.[17,20] In light of our results and those of previous studies, it is likely that specifically in anovulatory obese infertile women a preconception lifestyle intervention could lead to resumption of ovulatory cycles and as a consequence higher natural conception rates and hence a reduction in the need for infertility treatment.

Economic evaluation of the LIFEstyle study

The economic evaluation of the LIFEstyle study showed that lifestyle intervention preceding infertility treatment is less costly, but not more effective than prompt infertility treatment in terms of vaginal birth rate of a healthy singleton at term within 24 months of follow-up. This basecase scenario was compared to several other scenarios. Using the overall live birth rate of all ongoing pregnancies conceived within 24 months as the outcome, the probability that the lifestyle intervention was cost-effective increased. With the overall live birth rate of all ongoing pregnancies conceived within 24 months as outcome, the probability that lifestyle intervention preceding infertility treatment was cost-effective in

8

anovulatory women, in women who completed the lifestyle intervention program and in women ≥ 36 years old was higher than in the basecase scenario. Costs per birth event were generally lower in the intervention group compared to the control group using the overall live birth rate conceived within 24 months as effectiveness outcome, but not using the primary outcome as effectiveness outcome. Comparing these results to the literature is not possible, since studies on lifestyle intervention preceding infertility treatment in obese infertile women were mainly focused on anovulatory obese women and did not take costs into account.[19,21] We can conclude that the lifestyle intervention is more likely to be cost-effective for longer follow-up times and with live births conceived within 24 months as the effectiveness outcome (instead of the primary outcome, the healthy singleton live birth rate at term within 24 months). This indicates that the follow-up period of lifestyle interventions in obese infertile women is an important factor that mediates cost-effectiveness. This economic evaluation shows that a lifestyle intervention is a relatively inexpensive intervention (mean costs per woman €174) as compared to the additional infertility treatments that are necessary in women in the control group of the LIFEstyle study. The disadvantage of the lifestyle intervention is less healthy live births after exactly 24 months compared to the control group, but when including pregnancies ending beyond 24 months of randomisation there is no difference in the number of (healthy) live births between the intervention group and control group (as stated in paragraph 2.1). In addition, the chance of achieving cost-effectiveness of the lifestyle intervention increases when including pregnancies ending beyond 24 months of randomisation. Therefore, a lifestyle intervention in obese infertile women seems a small price to pay to prevent additional (unnecessary) infertility treatments with on the longer term similar birth rates.

The LIFEstyle study: Cardiometabolic outcomes and quality of life

We showed that a six-month lifestyle intervention prior to infertility treatment leads to better cardiometabolic health in obese infertile women. Participants in the lifestyle intervention group had lower body weight, waist- and hip circumference, blood pressure, fasting glucose and insulin levels, insulin resistance, and a higher physical quality of life (QoL) compared to women who promptly started infertility treatment. These relatively small but consistent effects on cardiometabolic factors resulted in halved odds of metabolic syndrome.

Landmark lifestyle interventions trials have shown similar effects on the presence on type II diabetes and hypertension. The Diabetes Prevention Program (DPP) focussed on overweight adults at risk for the development of type II DM by investigating if a lifestyle intervention or treatment with metformin delayed the onset of type II DM compared to treatment with a placebo. The lifestyle intervention, with the goals of 7% weight loss and at least 150 minutes of physical activity per week, reduced the incidence of diabetes by

58% (95% CI 48 to 66%) and metformin by 31% (95%CI 17 to 43%) as compared to placebo during the average follow-up time of 2.8 years.[22] During the 10 year follow-up, the original lifestyle group lost, then partly regained weight, while the weight loss with metformin was maintained.[23] Diabetes incidence in the ten years after randomisation was reduced by 35% (24-42%) in the lifestyle group and 18% (7-28%) in the metformin group compared to placebo group. Therefore, the authors conclude that prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years. The Look AHEAD trial was a RCT in overweight and obese individuals already diagnosed with type II DM. The authors aimed to investigate if a lifestyle intervention would decrease cardiovascular morbidity and mortality.[24] 5145 patients were randomised to participate in an intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity, or to receive standard diabetes support and education. Weight loss was greater in patients who received the lifestyle intervention compared to patients who standard diabetes support (8.6% vs. 0.7% weight reduction at 1 year; 6.0% vs. 3.5% weight reduction at 9.6 years). Although there was no difference in morbidity and mortality as a consequence of cardiovascular events,[24] there are important health benefits of lifestyle intervention in overweight and obese individuals with type II DM aside from a reduction in CVD outcomes, such as complete or partial remission of diabetes, reduction in sleep apnoea and better mobility.[25] Furthermore it was noted that participants succeeded to maintain their weight loss on the long term.[24,25]

Lifestyle intervention has also been shown to reduce blood pressure in patients with suboptimal blood pressure. In the PREMIER RCT 810 patients with suboptimal blood pressure were randomized to either advice only, an established lifestyle intervention or the established lifestyle intervention plus a DASH (Dietary Approaches to Stop Hypertension) diet.[26] The DASH diet included additional recommendations about fruit, vegetable, low-fat dairy and fat intake. At six months after randomisation there was a significant reduction in systolic blood pressure in participants of the established lifestyle intervention and the intervention including the DASH diet compared to participants who received advice only (3.7 mmHg, P < 0.001 and 4.3 mmHg, P < 0.001 respectively).

The short term effect of the intervention on the composite outcome for metabolic syndrome in our study might be highly clinically relevant, since metabolic syndrome leads to doubled risks of cardiovascular events and a 50% increase in all-cause mortality.[27-29] Halving the odds of metabolic syndrome could potentially greatly diminish the future risk of a cardiovascular event in this obese infertile group. The long-term effects of the lifestyle intervention on i.a. cardiometabolic health will be investigated in the WOMB project (www.womb-project.nl).

8

The lifestyle intervention led to higher physical QoL, but we did not find any effect on mental QoL. It is known that both cardiometabolic and reproductive morbidity reduce physical and mental quality of life and it is therefore important to address quality of life in obese infertile women.[30,31] It is recommended in women with PCOS to address poor emotional wellbeing and mood disorders.[32] Our finding of higher physical QoL is in concordance with previous weight loss trials.[33] In addition, increases in QoL, reduction in depressive symptoms and anxiety disorders have been noted in women with PCOS after weight loss.[34] The lack of effect of the intervention on mental QoL might be explained by the fact that women participating in this trial were infertile and their primary motivation for participating in the LIFEstyle study was to become pregnant and not to lose weight. For this reason, ongoing infertility and the associated mental distress could overshadow the potential positive effect of the intervention on mental QoL.[35,36]

Effects of periconceptional weight loss on maternal and neonatal outcomes during pregnancy; evaluation within the LIFEstyle cohort

Women who achieved modest periconceptional weight loss had a decreased rate (aOR 0.4, 95% CI 0.2 to 0.8) of hypertensive pregnancy complications compared to women who gained weight during the periconceptional period. For women with a singleton pregnancy the rate of preterm birth was significantly decreased in women who lost -2.1 to -0.9 kg/m^2 during the periconceptional period and also for women in the three quartiles with highest periconceptional weight loss compared to women who gained weight. Studies on the effects of lifestyle interventions in order to decrease periconception weight to possibly counteract the adverse effects of overweight are limited. Villamor and Cnattingius examined the association of weight change between a first and second pregnancy and risk of adverse pregnancy outcomes during the second pregnancy in a Swedish cohort of 151 025 women, of which 36 800 women had a BMI ≥ 25 kg/m^2 at the first pregnancy.[37] The authors did not find a significant difference in the rate of gestational hypertension or gestational diabetes in women with a BMI ≥ 25 kg/m^2 who lost > 1 kg/m^2 before the next pregnancy, but there was a lower rate of LGA (aOR 0.8, 95%CI 0.7-1.0). This was also observed by Jain et al., in a cohort study including 10 444 obese women. We did not observe a decreased rate of LGA in obese women who achieved periconceptional weight loss, possibly as a result of relatively low rate of LGA in our study. Our results are in agreement to findings of Mostello et al., who investigated risks of recurrent preeclampsia in a cohort study of 17 773 women whose first pregnancies were complicated by preeclampsia. Within subgroups of women with normal weight, overweight and obesity, they found that women who decreased their BMI between pregnancies were less likely to experience recurrent preeclampsia.[38]

Results of studies investigating the effects of preconception bariatric surgery may serve as an example regarding how the incidence of pregnancy complications can be affected after weight loss. Studies investigating the effects of preconception bariatric surgery show decreased rates of gestational diabetes (OR 0.3, 95% CI 0.2-0.7), hypertensive disorders (OR 0.4, 95% CI 0.2-0.8), foetal macrosomia (OR 0.4, 95% CI 0.2-0.7) and LGA (OR 0.3, 95% CI 0.2-0.4).[39-41] However, there is a higher risk of SGA (OR 2.2, 95% CI 1.3-3.7) and some studies report a shorter duration of gestation.[40,41] Average weight loss that can be achieved by obese women of reproductive age after bariatric surgery is on average minus 8 to 15 kg/m^2.[40] This is a much greater weight loss than that was achieved with lifestyle intervention in our study. Remarkably, the magnitude of effect in reduction of the rate of hypertensive disorders, aOR 0.4, 95% CI 0.2 to 0.8, is comparable to that in our study. One can hypothesize that there might be a gradual decline in the risk of various complications during pregnancy with increasing magnitude of weight loss prior to conception. However, this was not apparent in our analysis, since all tests for linear relations (which indicate a gradual incline or decline) were not statistically significant for the limited weight reduction that was achieved in our study. However, since the LIFEstyle study was not powered on adverse outcomes, it is possible that not enough women with adverse outcomes were present in the analysis to achieve a significant difference. Remarkably, the risk of hypertensive complications already decreased after moderate weight change from -0.9 to 0.1 kg/m^2, it was apparent that especially weight gain was detrimental, with women who gained weight having the highest incidence of multiple adverse outcomes. Possibly risks for LGA and gestational diabetes only tend to decrease after higher percentages of weight loss as illustrated by studies on effects of bariatric surgery. Ultimately, with increasing amounts of weight loss, an increased rate of being small-for-gestational-age is one of the prices paid by the offspring. Further studies, with greater sample sizes, or meta-analysis of individual patient data should be performed to determine what amount of weight loss in obese women balances risks of hypertensive disorders, gestational diabetes, being large-for-gestational-age and small-for-gestational-age.

Determinants of success in participants of the lifestyle intervention

Despite the many factors we assessed as possible determinants of successful lifestyle change in obese infertile women, only few were associated with lifestyle change. Women who had previous support from a dietician had an approximately 50% lower change of successful weight loss, compared to women without prior support. These women, having had counselling by a dietician in history and were unable to change lifestyle could therefore be less susceptible to a repetition of the support offered during our lifestyle intervention program. This is in line with existing literature, showing that fewer previous weight loss attempts and less previous dieting are predictors of successful weight loss.[42]

8

It is recommended that in future lifestyle intervention studies attention should be paid to weight loss history and previous support of a dietician. Possibly, patients with an elaborate weight loss history do not benefit from guidance focused on information and dietetic support, but benefit from either more extensive support or other types of guidance such as psychological help or more intense motivational counselling.

In our study population, neither educational level nor socioeconomic status (SES) was identified as a determinant of lifestyle change. This suggests that the lifestyle intervention program is effective for women of both lower and higher SES. Our findings are in agreement with literature suggesting that high self-regulation skills and high self-efficacy are associated with a reduction in energy intake and increased physical activity.[43] Remarkably, women in the action phase of readiness to change were both more likely to increase their number of steps and to complete the intervention program compared to women in the maintenance phase (which is the highest level of readiness to change). Hypothetically, a ceiling effect may exist for women in the maintenance phase of readiness to change, limiting their ability to improve any further. Furthermore, our results are in line with a review in which readiness to change was found to be positively associated with physical activity.[44] Thus, it is important to assess and possibly influence readiness to change into consultations with health care providers and lifestyle interventions.[45]

Reflection on the ethical considerations regarding lifestyle intervention and infertility treatment in obese infertile women

There has been a global discussion from an ethical and societal perspective whether infertility treatment should be offered to women with obesity.[46-48] Couples faced with infertility and obesity are often prepared to conceive despite risks for the future mother, risks for the future child and the anticipated decreased live birth rates. Several principles have to be kept in mind when reflecting on this topic.

Obesity as a disease, the obesogenic environment and health inequities in modern society

As discussed in Chapter 1 our current society is characterised by an obesogenic way of life. This consists of an environment with an increasing amount of readily available energy-dense processed foods and decreasing necessity and possibilities for physical activity.[49] Furthermore, a social gradient in health status exists (i.e., health is progressively better the higher the socioeconomic status of people and communities) and people with lower socioeconomic status may not have the abilities, health related skills, or possibilities to maintain a healthy lifestyle and a healthy weight.[50] Inequalities in health among groups

with different socioeconomic status present one of the main challenges to public health.[51,52] Obesity should not be simply seen as a conscious and autonomous choice for an "obese lifestyle", as exemplified by the statement of the American Medical Association in 2013 that obesity should be regarded as a chronic disease.[53] Regarding obesity as a disease highlights its consequences on health, lifespan and quality of life of an individual. Furthermore, it opens pathways for research funding and prioritises obesity on the health agendas of governments. In contrast, it may promote a culture of personal irresponsibility and to absolve an individual from taking action.[54]

The importance of addressing social inequities, specifically in antenatal care, has been recognised and now has become a higher priority in governmental policies. By doing so, the health of future mothers and subsequently the health of future generations can be improved. Changes in healthcare policies have been recommended by European and national authorities, as detailed in the following paragraphs. The *Review of Social Determinants of Health and Health Divide*, which was commissioned to support the health policy framework for Europe called "Health 2020", recommends a focus on certain types of behaviour (such as diet) in national and European policies.[50] Furthermore, the *Review* acknowledges that advantages and disadvantages in health accumulate over the course of life. Therefore, it is important that strategies to reduce inequities benefit women of childbearing age and families with young children to support a healthy start in early life.[50]

In the *Annual Report of the Chief Medical Officer* in the United Kingdom of 2014, the first recommendation was that the government should include obesity in its national risk planning, since it can affect the outcomes of pregnancies and therefore the health of any future children.[55] Furthermore, it was recommended that more research should be initiated in the field of preconception care, to improve maternal and child physical and mental health. The Chief Medical Officer also noted that (quote) "At present, planning for a healthy pregnancy by individuals and their supporting healthcare professional is inconsistent, even for those with co-morbidities who would benefit from pre-conceptual counselling and advice. There is also minimal planning for the postnatal period during pregnancy, when women are probably most motivated to make positive decisions for their health and that of their children."[55]

In the Netherlands, a nationwide project "Healthy Pregnancy 4 All" has been funded by the Ministry of Health, Welfare and Sport. The project recognised the divide in maternal and neonatal outcomes in pregnant women with different socioeconomic backgrounds. The programme has been implemented in ten municipalities in the Netherlands, aiming to target communities with a relatively disadvantageous position with regard to perinatal

8

and child health outcomes.[56] Results are expected in the coming years and could possibly teach us whether such an approach could improve maternal health and the health of future children in women with more disadvantageous socioeconomic positions and the related increased prevalence of obesity.

Benefits and risks of infertility treatment in relation to obesity

The primary aim of infertility treatment is to achieve the birth of a healthy child without exposing women and their future offspring to disproportional risks. This puts the professionals dealing with infertility in obese patients and their obese patients to the test, not only with respect to the wish of the future parents, but also with respect to welfare of the future child. The health care professional working in the field of reproductive medicine has to balance these benefits and risks together with the couple. Secondly, in the field of reproductive medicine, caregivers are required to determine if a woman or a couple could reasonably and safely be able to raise a child. Obesity is related with increased risks during pregnancy and impacts the health of the future child, and as with any chronic disease optimising the health status of a woman with obesity could be an important determinant of the health of the offspring.

Likewise, it can be reasonably expected that patients commit and make serious efforts to optimise the success of their (infertility) treatment. The European Society of Human Reproduction and Embryology (ESHRE) Taskforce on ethics and law composed a position paper called '*Lifestyle related factors and access to medical assisted reproduction*' in 2010. The taskforce states that (quote): "Within this patient doctor relationship, the doctor has an obligation to provide medical help. This may include information, counselling, diagnosis, treatment or referral. It is the patient's responsibility to provide healthcare providers with accurate information that is needed to facilitate medical decision-making, to keep their appointments and to contribute to a successful outcome by following prescription and medical advice. This also includes advice on relevant health or lifestyle factors".[57] As presented in this thesis, a lifestyle intervention poses several advantages and disadvantages, which also involve societal decisions (such as the willingness to pay for infertility treatment and lifestyle interventions). The implications for clinical practice will be addressed in the following section.

Implications for clinical practice

The current multidisciplinary guideline for the diagnosis and treatment of infertility in the Netherlands recommends that obese women are informed that obesity causes a longer time-to-pregnancy and that obesity is detrimental for their chances to become pregnant.[58] In addition, it states that healthcare professionals should recommend obese anovulatory

women to try to achieve weight loss. Weight loss prior to infertility treatment in obese women is also advised in the British and American guidelines of reproductive medicine.[59,60] A BMI of ≥ 35 kg/m^2 is commonly advised as a cut-off value to withhold infertility treatment in certain countries.[47] The abovementioned ESHRE position paper stated that (quote) "a serious effort towards achieving weight loss can be expected from an obese woman, since weight reduction is expected to have beneficial results on infertility treatment outcome and health during pregnancy and of the future child".[57]

This thesis showed that indeed some of the risks for obese women (i.e. metabolic syndrome and hypertensive complications during pregnancy) can be lowered when obese women lose weight during the periconception phase. In addition, especially in anovulatory women, the rate of natural conception increases and costs of infertility treatment and pregnancy may decrease. These are strong arguments to advocate weight loss prior to infertility treatment. However, the results in this thesis and the above-mentioned ethical considerations do not support strict BMI cut-off values to withhold infertility treatment when a lifestyle intervention fails. When a woman fails to lose weight, or cannot complete the lifestyle intervention, additional counselling is necessary. When a woman or couple decides to proceed with infertility treatment it should be initiated when the benefit outweighs the risks both for the woman and the future child. In an invited commentary published on the occasion of the publication of chapter 3 of this thesis, one of the leading scientists in reproductive medicine called for a tearing down of the "weight wall" that women with obesity might encounter and to admit all obese infertile patients after counselling of the involved risks of obesity during pregnancy.[61] In addition, the ESHRE position paper stated that infertility treatment can only be withheld when (quote) "high risk of serious harm" is expected, and for obesity this is not always the case.[57]

As "health advocates", we have to acknowledge that counselling alone is not enough when obstetric or perinatal risks are serious and that obese women require optimal treatment before proceeding to infertility treatment. We should agree with and endorse the definition of obesity as a disease and act accordingly; inform, advice and treat or at least optimise this chronic disease in the obese patient. Moreover, we should not leave our obese infertile patients alone struggling with this disease as many of these women do not have the health-related skills, or possibilities to maintain a healthy lifestyle and to achieve a healthy weight.[50] It should be a mutual responsibility, for doctors and patients, to mitigate the disease's consequences. It will take both time and effort for women to change lifestyle, as well as a willingness of healthcare providers in fertility clinics to guide, support and motivate these women. As mentioned, when these efforts fail, infertility treatment can be initiated after appropriate counselling.[46,57]

8

Additional studies on risks and benefits of infertility treatment are necessary in women who are morbidly obese (BMI above 40 kg/m^2), as their complication rates (such as gestational diabetes and hypertensive disorders) during pregnancy are triple to fourfold compared to controls with normal weight.

The duration of a lifestyle intervention, which is recommended to take at least six months, can be perceived as a barrier to women with advanced age who are trying to conceive. Indeed, there is limited evidence that the effect of advancing age on fertility is stronger than the effect of BMI after the age of 36.[62] Unfortunately, the number of women older than 36 years included in the LIFEstyle study was limited and therefore conclusions based on this topic could not be drawn. Further evidence on this topic is necessary to make further recommendations

It seems appropriate that reimbursement of costs of lifestyle interventions should be made by health-insurance companies, since a lifestyle intervention is associated with reduced costs on the long-term and an increase in general health. An even more favourable economic trade-off can be made when a preconceptional lifestyle intervention also decreases costs during pregnancy by lowering the complication rates. Preferably, the short and long-term effects of these lifestyle programs, both for women and their offspring should be evaluated in research programmes.

Furthermore, preventing obesity in children, adolescents and young women, who will be the parents of our future generations, should be a priority in governmental policies. Especially young women should be educated, encouraged and guided to maintain a healthy weight and obesity should preferably be addressed prior to reproductive age. As stated in thesis, intervening in the trans generational cycle of obesity in both fertile and infertile women is important. Therefore, initiatives such as the Healthy Pregnancy 4 All project, which are properly evaluated and aimed at all pregnant women, must be welcomed and supported. Finally, neither doctors, nor lifestyle coaches, nor patients can deflect the pandemic of obesity and its devastating consequences in virtually all health domains, it is beyond their reach. Governments, industries, municipalities, employer organisations, schools, but also health care organizations should take action. In virtually all domains within our society measures can be taken to improve the lifestyle of women, children and men. From legislation for the food industry, to school meals, sporting hours at school, playground and free sporting facilities in cities and villages, safe walking and cycling lanes to planology of new working and living areas, all will add up to an improvement of the chances for a healthy lifestyle and consequently healthier weight of future generations. To break the trans generational burden of this non-communicable disease we as health care workers should put this important health issue on the agenda of the government and those in politics.

Recommendations for future research

1. To strengthen evidence regarding rare pregnancy outcomes, an individual patient data meta-analysis on periconceptional weight loss and risk of maternal and neonatal complications during pregnancy should be performed.
2. Interventions should preferably be shaped according to patient preferences. A discrete choice experiment could investigate which intervention characteristics obese women prefer.
3. Even more important is to know if women want to invest time and effort in losing weight to achieve a higher rate of natural pregnancy and possibly better pregnancy outcomes? This can also be investigated using a discrete-choice experiment.
4. A well powered randomised controlled trial comparing the effects and costs of a lifestyle intervention followed by ovulation induction or immediate ovulation induction in obese women with PCOS is necessary since up to now only underpowered studies with live birth as outcome were published. These data can be used to determine;
   a. What is the ideal percentage of weight reduction to improve natural conception chance?
   b. Does body-fat distribution influence the effects of a lifestyle intervention in this group?
   c. Does age influence the effects of a lifestyle intervention in this group?
5. There is no literature assessing what the best treatment options are for obese class III infertile women. A RCT in infertile women with a BMI ≥ 40 kg/m^2 investigating pregnancy chances after bariatric surgery compared to lifestyle intervention could assess the benefit-risk ratio between these two treatment options both for women and their offspring.
6. Investigate whether more extensive motivational counselling and psychological counselling could increase the readiness to change towards weight loss and if this makes a lifestyle intervention more successful and decreases non-completion rates.
7. Long term reproductive and cardiometabolic effects on the health of the woman and the offspring of a lifestyle intervention prior to infertility treatment in obese infertile women are unknown. The WOMB project will investigate these effects in women who participated in the LIFEstyle study (www.womb-project.nl).

8

References

1. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sorensen TI, Olsen J. Subfecundity in overweight and obese couples. *Hum Reprod*. 2007;22(6):1634-1637.

2. van der Steeg JW, Steures P, Eijkemans MJ, et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. *Hum Reprod*. 2008;23(2):324-328.

3. Legro RS, Barnhart HX, Schlaff WD, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2007;356(6):551-566.

4. Kawwass JF, Kulkarni AD, Hipp HS, Crawford S, Kissin DM, Jamieson DJ. Extremities of body mass index and their association with pregnancy outcomes in women undergoing in vitro fertilization in the united states. *Fertil Steril*. 2016;106(7):1742-1750.

5. Marchi J, Berg M, Dencker A, Olander EK, Begley C. Risks associated with obesity in pregnancy, for the mother and baby: A systematic review of reviews. *Obes Rev*. 2015;16(8):621-638.

6. Weiss JL, Malone FD, Emig D, et al. Obesity, obstetric complications and cesarean delivery rate--a population-based screening study. *Am J Obstet Gynecol*. 2004;190(4):1091-1097.

7. Aune D, Saugstad OD, Henriksen T, Tonstad S. Maternal body mass index and the risk of fetal death, stillbirth, and infant death: A systematic review and meta-analysis. *JAMA*. 2014;311(15):1536-1546.

8. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: A systematic review and meta-analysis. *PLoS One*. 2013;8(4):e61627.

9. Reynolds RM, Allan KM, Raja EA, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: Follow-up of 1 323 275 person years. *BMJ*. 2013;347:f4539.

10. Sim KA, Dezarnaulds GM, Denyer GS, Skilton MR, Caterson ID. Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: A randomized controlled trial. *Clin Obes*. 2014;4(2):61-68.

11. Moran L, Tsagareli V, Norman R, Noakes M. Diet and IVF pilot study: Short-term weight loss improves pregnancy rates in overweight/obese women undertaking IVF. *Aust N Z J Obstet Gynaecol*. 2011;51(5):455-459.

12. Stegenga H, Haines A, Jones K, Wilding J, Guideline Development Group. Identification, assessment, and management of overweight and obesity: Summary of updated NICE guidance. *BMJ*. 2014;349:g6608.

13. Mutsaerts MA, Kuchenbecker WK, Mol BW, Land JA, Hoek A. Dropout is a problem in lifestyle intervention programs for overweight and obese infertile women: A systematic review. *Hum Reprod*. 2013;28(4):979-986.

14. Einarsson,Snorri, Bergh,Christina, Friberg,Britt, et al. Weight reduction intervention for obese infertile women prior to IVF: A randomized controlled trial. *Human Reproduction*. 2017;32(8):1621-1630.

15. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: An update. *Physiol Rev*. 2013;93(1):359-404.

16. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444(7121):881-887.

17. Kuchenbecker WK, Groen H, van Asselt SJ, et al. In women with polycystic ovary syndrome and obesity, loss of intra-abdominal fat is associated with resumption of ovulation. *Hum Reprod*. 2011;26(9):2505-2512.

18. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2011;(7):CD007506. doi(7):CD007506.

19. Legro RS, Dodson WC, Kunselman AR, et al. Benefit of delayed fertility therapy with preconception weight loss over immediate therapy in obese women with PCOS. *J Clin Endocrinol Metab*. 2016;101(7):2658-2666.

20. Balen AH, Morley LC, Misso M, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: An analysis of the evidence to support the development of global WHO guidance. *Hum Reprod Update*. 2016.

21. Sim KA, Partridge SR, Sainsbury A. Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obes Rev*. 2014;15(10):839-850.

22. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.

23. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the diabetes prevention program outcomes study. *Lancet*. 2009;374(9702):1677-1686.

24. Look AHEAD Research Group, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369(2):145-154.

25. Wing RR, Look AHEAD Research Group. Implications of look AHEAD for clinical trials and clinical practice. *Diabetes Obes Metab*. 2014;16(12):1183-1191.

26. Appel LJ, Champagne CM, Harsha DW, et al. Effects of comprehensive lifestyle modification on blood pressure control: Main results of the PREMIER clinical trial. *JAMA*. 2003;289(16):2083-2093.

27. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: An american heart association/national heart, lung, and blood institute scientific statement. *Circulation*. 2005;112(17):2735-2752.

28. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56(14):1113-1132.

29. Cerezo C, Segura J, Praga M, Ruilope LM. Guidelines updates in the treatment of obesity or metabolic syndrome and hypertension. *Curr Hypertens Rep*. 2013;15(3):196-203.

30. Hahn S, Janssen OE, Tan S, et al. Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome. *Eur J Endocrinol*. 2005;153(6):853-860.

31. Han JH, Park HS, Shin CI, et al. Metabolic syndrome and quality of life (QOL) using generalised and obesity-specific QOL scales. *Int J Clin Pract*. 2009;63(5):735-741.

32. Teede HJ, Misso ML, Deeks AA, et al. Assessment and management of polycystic ovary syndrome: Summary of an evidence-based guideline. *Med J Aust*. 2011;195(6):S65-112.

33. Danielsen KK, Sundgot-Borgen J, Maehlum S, Svendsen M. Beyond weight reduction: Improvements in quality of life after an intensive lifestyle intervention in subjects with severe obesity. *Ann Med*. 2014;46(5):273-282.

34. Dokras A, Sarwer DB, Allison KC, et al. Weight loss and lowering androgens predict improvements in health-related quality of life in women with PCOS. *J Clin Endocrinol Metab*. 2016;101(8):2966-2974.

35. Boivin J, Domar AD, Shapiro DB, Wischmann TH, Fauser BC, Verhaak C. Tackling burden in ART: An integrated approach for medical staff. *Hum Reprod*. 2012;27(4):941-950.

36. Gameiro S, Boivin J, Dancet E, et al. ESHRE guideline: Routine psychosocial care in infertility and medically assisted reproduction-a guide for fertility staff. *Hum Reprod*. 2015;30(11):2476-2485.

37. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: A population-based study. *Lancet*. 2006;368(9542):1164-1170.

38. Mostello D, Jen Chang J, Allen J, Luehr L, Shyken J, Leet T. Recurrent preeclampsia: The effect of weight change between pregnancies. *Obstet Gynecol*. 2010;116(3):667-672.

39. Maggard MA, Yermilov I, Li Z, et al. Pregnancy and fertility following bariatric surgery: A systematic review. *JAMA*. 2008;300(19):2286-2296.

40. Yi XY, Li QF, Zhang J, Wang ZH. A meta-analysis of maternal and fetal outcomes of pregnancy after bariatric surgery. *Int J Gynaecol Obstet*. 2015;130(1):3-9.

41. Johansson K, Cnattingius S, Naslund I, et al. Outcomes of pregnancy after bariatric surgery. *N Engl J Med*. 2015;372(9):814-824.

42. Teixeira PJ, Going SB, Sardinha LB, Lohman TG. A review of psychosocial pre-treatment predictors of weight control. *Obes Rev*. 2005;6(1):43-65.

43. Teixeira PJ, Carraca EV, Marques MM, et al. Successful behavior change in obesity interventions in adults: A systematic review of self-regulation mediators. *BMC Med*. 2015;13:84-015-0323-6.

44. Trost SG, Owen N, Bauman AE, Sallis JF, Brown W. Correlates of adults' participation in physical activity: Review and update. *Med Sci Sports Exerc*. 2002;34(12):1996-2001.

45. Stonerock GL, Blumenthal JA. Role of counseling to promote adherence in healthy lifestyle medicine: Strategies to improve exercise adherence and enhance physical activity. *Prog Cardiovasc Dis*. 2017;59(5):455-462.

46. Koning AM, Mol BW, Dondorp WJ. Obesity: Argument for withholding fertility treatment? *Ned Tijdschr Geneeskd*. 2014;158:A7258.

47. Balen AH, Anderson RA, Policy & Practice Committee of the BFS. Impact of obesity on female reproductive health: British fertility society, policy and practice guidelines. *Hum Fertil (Camb)*. 2007;10(4):195-206.

48. Pandey S, Maheshwari A, Bhattacharya S. Should access to fertility treatment be determined by female body mass index? *Hum Reprod*. 2010;25(4):815-820.

8

49. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: Shaped by global drivers and local envi-ronments. *Lancet*. 2011;378(9793):804-814.

50.   Marmot M, Allen J, Bell R, Bloomer E, Goldblatt P, Consortium for the European Review of Social Deter-minants of Health and the Health Divide. WHO european review of social determinants of health and the health divide. *Lancet*. 2012;380(9846):1011-1029.

51. Mackenbach JP, Stirbu I, Roskam AJ, et al. Socioeconomic inequalities in health in 22 european countries. *N Engl J Med*. 2008;358(23):2468-2481.

52. Marmot M. Social determinants of health inequalities. *Lancet*. 2005;365(9464):1099-1104.

53. THE COUNCIL ON SCIENCE AND PUBLIC HEALTH. Is obesity A disease? (resolution 115-A-12). . 2013;CSAPH Report 3-A-13.

54. Stoner L, Cornwall J. Did the american medical association make the correct decision classifying obesity as a disease? *Australas Med J*. 2014;7(11):462-464.

55. Department of Health. Annual report of the chief medical officer, 2014 the health of the 51%: Women 2015.

56. Waelput AJM, Sijpkens MK, Lagendijk J, et al. Geographical differences in perinatal health and child welfare in the netherlands: Rationale for the healthy pregnancy 4 all-2 program. *BMC Pregnancy Childbirth*. 2017;17(1):254-017-1425-2.

57. ESHRE Task Force on Ethics and Law, Dondorp,W., de Wert G, Pennings G, et al. Lifestyle-related factors and access to medically assisted reproduction. *Hum Reprod*. 2010;25(3):578-583.

58. Dutch Society of Obstetrics and Gynaecology (NVOG). Guidelines subfertility. 2015.

59. National Collaborating Centre for Women's and Children's Health (UK). . 2013.

60. Practice Committee of the American Society for Reproductive Medicine. Obesity and reproduction: A com-mittee opinion. *Fertil Steril*. 2015;104(5):1116-1126.

61. Legro RS. Mr. fertility authority, tear down that weight wall! *Hum Reprod*. 2016;31(12):2662-2664.

62. Sneed ML, Uhler ML, Grotjan HE, Rapisarda JJ, Lederer KJ, Beltsos AN. Body mass index: Impact on IVF suc-cess appears age-related. *Hum Reprod*. 2008;23(8):1835-1839.

8