Lifestyle interventions for obese women before and during pregnancy: The effect on pregnancy outcomes
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Summary and general discussion
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Summary
The prevalence of overweight women (body mass index >25kg/m\(^2\)) in The Netherlands is increasing sharply in line with the increase observed in populations worldwide; 37% in 2012 in the Netherlands and 35% in 2008 worldwide\(^1\). In addition to the long-term health risks of being overweight, overweight women of reproductive age are more commonly faced with reproductive disorders including fertility rate, and pregnancy complications. Due to the increased risk of miscarriage chances of a live birth are decreased. In addition, pregnancy outcomes are compromised by obesity-related complications of pregnancy.

The aim of this thesis was to assess effects of weight-reduction interventions before, and lifestyle interventions during pregnancy on gestational weight gain and pregnancy related outcomes. Furthermore, we aimed to estimate direct and indirect costs to society associated with obesity and weight gain in pregnancy, expressed as monetary costs and sick leave.

Chapter 1 gives an outline and describes the objective of this thesis.

Chapter 2 describes an insight into effects of being overweight on fertility and pregnancy complications. Overweight or obesity in women of reproductive age negatively affects the probability of pregnancy approximately three times. The outcome of pregnancy is more often adversely affected by obesity including an increased risk of gestational diabetes, hypertensive disorders and macrosomia. In addition, delivery is more often complicated by increased induction of labour, shoulder dystocia, birth trauma, and lower Apgar scores in women who are overweight. The rate of caesarean section in women who are overweight is three times higher compared to normal weight women. We hypothesise that weight reduction increases the chance on pregnancy and reduces the risk on pregnancy-related complications.

Chapter 3 describes the result of a meta-analysis to check whether treatment of overweight or obese women of reproductive age (<40 years) with insulin sensitising agents contribute to weight reduction. Fourteen randomised controlled trials (RCTs) (649 women), unintentionally all but two on women with polycystic ovary syndrome only, were included in the analysis. Treatment with metformin showed a statistically significant decrease in BMI compared with placebo (weighted mean difference, -0.68; 95% CI -1.13 to -0.24). We found a (minimal) greater effect with high-dose metformin (>1500 mg/day) and longer duration of therapy (>8 weeks).

We concluded that a structured lifestyle modification programme to achieve weight loss should still be the first line treatment in obese women with or without polycystic ovary syndrome. Although we found a statistical decrease of body mass index (BMI) in women treated with
high dose metformin, data used for this analysis were of limited quality due to heterogeneity and lack of intention to treat analysis in most trials. Therefore results should be interpreted with caution. Adequately powered RCTs are required to confirm the findings of this review and to assess whether the addition of high-dose metformin therapy to a structured lifestyle modification programme contributes to increased weight loss.

Chapter 4 describes the result of a meta-analysis confirming the association between gestational weight gain and pregnancy complications. Twenty-three RCTs (4,990 women) were included in this analysis. Increased gestational weight gain (GWG) was associated with an increased risk of pre-eclampsia (0.2% per gained kg), gestational diabetes (0.3% per gained kg), and induction of labour (1.5% per gained kg), albeit that these results were not statistically significant. Reduction in GWG due to lifestyle interventions in pregnancy had some effects on lowering the incidence of pre-eclampsia, gestational diabetes and induction of labour. We speculate that the beneficial effect of lifestyle interventions on pregnancy outcomes is due to an effect (at least partly) independent of the reduction of gestational weight gain.

Chapter 5 evaluates the relationship of objectively measured physical activity (PA) and sedentary behaviour with GWG and birth weight. In total 113 women were included for this analysis. We found no association between physical activity and sedentary behaviour with gestational weight gain or birth weight in a combined analysis of two prospective studies. Early in pregnancy, 32% of women spent ≥30 minutes/day in at least moderate PA versus 12% in late pregnancy. The small percentage of women meeting the recommended levels of PA indicates the necessity to inform and support pregnant women to maintain regular PA, as there seems to be no adverse effect on birth weight and as maintaining physical activity increases overall health.

Chapter 6 evaluates the budget impact of decreasing the risk of pregnancy complications through lifestyle interventions in a hypothetical cohort of 100,000 pregnant women who are overweight or obese. The costs for maternal complications in our cohort in the lifestyle intervention group were €580 million compared to €602 million in the usual care group, indicating a reduction of 3.5% in health care costs by lifestyle intervention. This implicates that lifestyle intervention may have a substantial impact on budget.

Chapter 7 describes the relationship between BMI and sick leave before, and during pregnancy and one year postpartum. A total of 490 employed pregnant women with the intention to return to work after maternity leave participated in this study. The risk of pre-pregnancy sick leave (within one year before pregnancy) was significantly higher in obese women compared to normal weight women (OR 2.8, CI 1.4 to 5.8, p=0.006). The
risk of sick leave during pregnancy was significantly higher in overweight women compared to normal weight women (OR 2.0, CI 1.2 to 3.3, p=0.01). In the year postpartum no significant statistical differences were found.

This analysis showed an increased risk for pre-pregnancy sick leave and sick leave during pregnancy for obese and overweight women, respectively, indicating that interventions for weight loss or maintenance before or during pregnancy may be effective in reducing sick leave. Furthermore, from a societal perspective, sick leave should be included in cost-effectiveness studies of interventions for weight reduction in pregnancy.

Chapter 8 presents the protocol for an individual patient data (IPD) meta-analysis to evaluate the differential effects of diet and physical activity based interventions on maternal and foetal outcomes according to their (i) body mass index, (ii) age, (iii) ethnicity, (iv) parity, and (v) underlying medical conditions. The international Weight Management in Pregnancy (i-WIP) IPD Collaboration was established for this IPD meta-analysis. Already thirty-seven collaborators have joined the network providing access to anonymised individual data of 9,391 women.

Chapter 9 explains the need for international collaboration in research and describes the mission of Global Obstetrics Network (GONet), its objectives, structure and function, current collaborators and plans for the future.

Already some research networks have been established. GONet was formed to link the different types of networks in order to improve ongoing and future trials. Its goal is to provide a forum for international interaction and collaboration among groups that perform clinical trials and observational studies in maternal foetal medicine and obstetrics. It is expected that this will lead to better studies and more efficient use of resources. Moreover larger international trials can be conducted, with more diversity in socio-economic status and ethnicity, increasing its applicability for clinical use.

General Discussion

In this thesis, we assessed the maternal and foetal complications in pregnant women who are overweight or obese and options for weight reduction (lifestyle/medical intervention) in this population.

The effectiveness of insulin sensitising drugs on weight loss was examined, with the aim to increase pregnancy rate of women of reproductive age with obesity and infertility. Our meta-analysis of 14 RCT showed that treating women of reproductive age, with polycystic ovary syndrome who are overweight or obese, with metformin results in a significant decrease in BMI. However, considering the limitations of this review, this conclusion should be interpreted with caution.

The NIH stated that in view of the low success rate in achieving weight loss and even lower success rate for maintaining this weight loss, drug therapy for obesity in conjunction with the continuation of lifestyle
changes is advised according to obesity guidelines. Based on our results we cannot endorse this recommendation.

Due to the limited societal awareness most obese women are not counselled by a health care provider prior to pregnancy. This implies that options for initiating interventions in the pre-pregnancy period are limited, and not used as an opportunity for optimising pregnancy outcomes. Because of this limitation, we explored the possibilities during pregnancy to decrease the chances of maternal and foetal complications due to maternal obesity. A previous meta-analysis showed that reducing GWG in overweight and obese women potentially reduces maternal and foetal complications. However, the association between changes in GWG due to these interventions and the actual reduction in complications including hypertensive disorders, gestational diabetes and preterm birth, is unknown. Therefore, we were interested in the causal role of GWG in this process.

We have shown that reduction in GWG due to lifestyle interventions in pregnancy had statistically non-significant effects on lowering the incidence of pre-eclampsia, gestational diabetes and induction of labour. Possibly, the beneficial effect of lifestyle interventions on pregnancy outcomes is due to an effect independent of the reduction of gestational weight gain e.g. it could be that lifestyle interventions, such as a healthy diet or physical activity, do not (or not only) lead to decreased weight gain per se, but change metabolism and overall health, resulting in better pregnancy outcomes.

Many trials have been performed assessing the effect of interventions based on diet and physical activity in order to optimise GWG with varied effects on clinical outcomes, but sedentary behaviour has not been studied. Although an association between sedentary behaviour and weight (gain) has been described in non-pregnant women, it is unknown whether the amount of time spent sedentarily in pregnancy influences gestational weight gain or birth weight.

We measured daily physical activity and sedentary behaviour objectively in pregnant women with an accelerometer. No association was found between the time spent in physical activity or the time spent in sedentary behaviour with gestational weight gain or birth weight. The small percentage of women (12%) meeting the recommended levels of physical activity set by the ACOG (30 minutes or more of physical activity per day of at least moderate intensity on most days of the week) indicates the need to inform and support pregnant women to maintain regular physical activity, as there seems to be no adverse effect on birth weight and maintaining physical activity increases overall health. Instead of aiming for 30 minutes of physical activity per day, a solution might be more frequent short-term intervals e.g. 3x10 minutes daily. However, this needs to be investigated by a RCT.

Costs to society associated with obesity and gestational weight gain can potentially be reduced; less weight gain during pregnancy may result in a decrease in monetary costs and reduced sick leave. These issues were also addressed in this thesis. A budget impact analysis was performed to
assess the effect of lifestyle interventions on maternal pregnancy outcomes. Using the results of a recent meta-analysis estimating the effect of lifestyle interventions on pregnancy outcomes, we concluded that implementing a lifestyle intervention not only has a positive effect on maternal health, but also leads to a substantial decrease in health care costs. Moreover, the relationship between body mass index and sick leave was evaluated. The risk of pre-pregnancy sick leave was higher in obese women (≥30 kg/m²), and during pregnancy it was higher in overweight women (>25-30 kg/m²) compared to normal weight women. In the postpartum period no differences in sick leave were found between women in different BMI categories.

For society this means that implementing lifestyle interventions in normal antenatal care in overweight or obese women may reduce sick leave and monetary costs associated with pregnancy complications, and thereby, the economic burden of maternal obesity.

Most meta-analyses, including the ones presented in this thesis, are based on aggregated average outcomes per study and heterogeneity within and between studies, thereby limiting the statistical precision of the meta-analysis. Since women in the antenatal period are highly motivated to make changes that may improve their pregnancy outcomes, it forms a good opportunity to implement lifestyle interventions. It would be unfortunate if firm recommendations cannot be made because of such methodological restrictions.

An individual patient data meta-analysis would overcome heterogeneity within and between studies, we therefore are planning an IPD meta-analysis to evaluate the differential effects of diet and physical activity based interventions on maternal and foetal outcomes. Over three years ago, the Global Obstetrics Network (GONet) has been established. GONet is a group of international investigators collaborating in research in maternal foetal medicine and obstetrics, emphasising the importance of a global network in research, resulting in better studies and more efficient use of resources. GONet’s knowledge and network will amongst others contribute to aforementioned IPD meta-analysis.

Safety
Interventions in the period prior and during pregnancy need to be safe for both mother and unborn child and can only be implemented if proven safe for both short and long-term outcomes. Therefore, many treatment options are not possible during pregnancy but should be re-directed pre-conceptionally.

If metformin treatment does contribute to weight loss, treatment of women of reproductive age with obesity and infertility could improve the chances of conception. Data on the safety of metformin use in the first trimester are re-assuring. There seems to be no increase in congenital abnormalities. The trial of Stridsklev et al. investigated the effect of metformin during pregnancy by measuring the mid-pregnancy pulsatility index, which is one of the markers to predict adverse pregnancy
outcomes, including pre-eclampsia and intrauterine growth restriction.\textsuperscript{14-15} They found that metformin use from the first trimester of pregnancy to delivery did not affect the uterine blood flow. Two other trials reported less maternal weight gain and smaller infant birth weight in women using metformin (gestational age at inclusion between 11-33 weeks) with gestational diabetes, although these trials were not powered to detect a significant difference for these outcomes.\textsuperscript{16,17} Also, effects of metformin use in pregnancy on offspring in the long-term are unknown.\textsuperscript{18}

Data on adverse effects of physical activity during pregnancy are reassuring; recent trials did not show an increased risk for preterm delivery\textsuperscript{19} or foetal growth restrictions.\textsuperscript{20,21} Furthermore, a randomised controlled trial evaluating the effect of regular aerobic exercise on endothelium-dependent vasodilation showed that the exercise group in pregnancy had a statistically greater flow-mediated dilatation and normalised flow-mediated dilatation than controls.\textsuperscript{22} Given findings that endothelial dysfunction is associated with pre-eclampsia,\textsuperscript{23} improvements in flow-mediated dilatation induced by exercise may reduce risks for pre-eclampsia. Downs et al.\textsuperscript{24} state that epidemiologic studies have observed a protective effect of PA in early pregnancy on pre-eclampsia,\textsuperscript{25,26} while others have found no association.\textsuperscript{21,27,28} However, no adverse effects of physical activity on pre-eclampsia are described.

Two randomised trials evaluating physical activity did not show an increase in staining of amniotic fluid, uterine atony, or chorioamnionitis. There were no significant maternal or foetal adverse effects such as cord abnormalities, threatened miscarriage, abnormal foetal heart rate pattern, maternal sepsis, or chorioamnionitis observed with physical activity during pregnancy.\textsuperscript{29,30} In line with these findings, in our trial (chapter 5) evaluating the effect of physical activity on GWG and birth weight, we found no adverse effect on birth weight.

Internationally, several countries have made positive recommendations regarding physical activity during pregnancy, encouraging physical activity for pregnant women without obstetric/medical complications. The review of Downs et al.\textsuperscript{24} provides a summary of the literature on physical activity and pregnancy and the current recommendations internationally. These recommendations are relatively consistent with each other, encouraging all women without contraindications to participate in aerobic and strength-conditioning physical activity as part of a healthy lifestyle.\textsuperscript{31-34} These recommendations are based on several prospective and retrospective studies.\textsuperscript{35-37}
Methodological considerations

All meta-analyses are based on aggregated data, which limits statistical precision. This also applies to this meta-analysis. Moreover, there is heterogeneity within and between the studies due to the aggregated data: meta-analyses are susceptible to heterogeneity in definitions of outcome measures, population characteristics, interventions and duration of interventions.

Figure 1. Example of funnel plots showing publication bias

Top: A funnel plot of hypothetical studies. The plot is asymmetrical, suggesting that studies in which negative or non-significant results are found were not published, hence suggesting publication bias.

Bottom: A funnel plot of hypothetical studies. The plot is symmetrical, suggesting that both positive and negative studies were published, hence suggesting absence of publication bias.
Another common problem in meta-analyses is the lack of uniformity in how interventions are performed and outcomes are measured. Other limitations of meta-analyses are publication bias (‘positive’ studies are more likely to be published, figure 1), search bias and selection bias. Even by trying to minimise these limitations (i.e. by including several databases in our search, reducing selection bias by clearly defined criteria, and having studies scored by two researchers independently), some bias will remain.

In chapter 5 physical activity and sedentary behaviour was measured objectively by using an accelerometer. This uniaxial device measures and records vertical acceleration, and therefore does not optimally record movements such as cycling, a common activity of pregnant women in the Netherlands. Furthermore, it has been shown that accelerometers might be less valid in pregnancy, mostly because of slower walking speeds of the women. This may have resulted in an underestimation of the amount of physical activity. However, objective measurement of physical activity is to be preferred over using self-reported physical activity since most questionnaires show poor validity in pregnancy.

Recommendations for Future Research
For future research an individual patient data meta-analysis is recommended, as statistical resolution can be enhanced by using individual instead of aggregated average data, and as more homogenous sub groups (e.g. allocated by BMI) and larger sample size within these groups can be established. This approach should provide adequate power in order to generate valid, reliable answers and to populate the model for decision analytic modelling for health economic evaluation.

Another recommendation would be to enhance standardisation and thereby homogeneity in definitions. Frequently, different definitions and end-points are used, complicating the comparison of trials through normal meta-analysis. The use of end-point definitions, standardising common definitions, defining variables, baseline characteristics, and end-point measurements, consistently will facilitate and enhance the quality of meta-analyses.

Costs to society associated with obesity and gestational weight gain can potentially be reduced; less weight gain during pregnancy may result in lower monetary costs and reduced sick leave on short term outcomes.

In chapter 6 the impact of lifestyle interventions on budget was assessed, using the effect of lifestyle interventions on pregnancy complications determined in the review by Thangaratinam et al. It showed that implementation of a lifestyle intervention programme reduced the health care cost of obese pregnant women. However, due to the restrictions of a meta-analysis as stated above, the effects of lifestyle interventions on pregnancy complications were not all statistically significant.

In order to assess the effect of lifestyle interventions on health care costs properly, the effect of lifestyle interventions on pregnancy complications needs to be determined, for example by IPD meta-analysis, this in turn can be used for a cost-effectiveness analysis of lifestyle interventions in
overweight or obese pregnant women.

Regarding sick leave, we found an increased risk for pre-pregnancy sick leave and sick leave during pregnancy for obese and overweight women, respectively, indicating that interventions for weight loss or maintenance before or during pregnancy may be effective in reducing sick leave. The reason for sick leave in obese women is probably multifactorial; Obesity is known to increase the chance on adverse health outcomes.\textsuperscript{41} Studies have also found an association between increased BMI and higher incidence of depression amongst women.\textsuperscript{42,43} These adverse effects may contribute to the amount of sick leave in women who are overweight or obese. Weight loss may have a positive effect on these adverse outcomes, resulting in a decreased amount of sick leave. Furthermore, sick leave should be included in cost-effectiveness studies of interventions for weight reduction in pregnancy.

**Recommendation for Clinical Practice**

Obesity is the consequence of genetic, behavioural, environmental, physiological, social, and cultural factors that result in energy imbalance and promote excessive fat deposition. The relative contribution of each of these factors has been studied extensively, and although genes play an important role in the regulation of body weight, the World Health Organization Consultation on Obesity\textsuperscript{44} concluded that behavioural and environmental factors (i.e., sedentary lifestyles combined with excess energy intake) are primarily responsible for the dramatic increase in obesity during the past two decades.\textsuperscript{41}

In pregnant women who are overweight or obese, reduction in GWG due to lifestyle interventions in pregnancy had statistically non-significant effects on lowering the incidence of pregnancy complications. Lifestyle interventions in obese pregnant women have shown to reduce adverse maternal outcomes of pregnancy. This indicates the beneficial effect of lifestyle interventions on pregnancy outcomes, and is probably due to an effect independent of the reduction of GWG.

It could be that lifestyle interventions, such as a healthy diet, do not (or not only) lead to decreased weight gain per se, but change metabolism and overall health, resulting in better pregnancy outcomes. The same theory could be used for physical activity interventions, leading to a change in body composition (with more muscle and less fat), without reducing GWG as muscle tissue weighs more than fat. Active women may thus experience less pregnancy complications and in the long-term both women and their children will benefit.

This thesis indicates the need to inform and support pregnant women to maintain regular physical activity, as many women do not meet the recommendations for sufficient physical activity, and there seems to be no adverse effect on birth weight. Maintaining physical activity increases overall health and reduces the incidence of pre-eclampsia, gestational diabetes and induction of labour. Furthermore, we found an increased risk for pre-pregnancy sick leave and sick leave during pregnancy for obese
and overweight women, respectively, indicating that interventions for weight loss or maintenance before or during pregnancy may be effective in reducing sick leave.

In the antenatal period, women are regularly in contact with health care workers, both by midwives and gynaecologists. We suggest that advice on lifestyle is implemented by both.

As some overweight or obese women are undergoing assisted reproduction, lifestyle advice is given more easily to this group of patients. However, the majority of the obese or overweight population is harder to reach for lifestyle advice in the period before pregnancy. A campaign conducted by the government in collaboration with general practitioners may be the best route to implement lifestyle advice.
References

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