Lifestyle interventions for obese women before and during pregnancy: The effect on pregnancy outcomes

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Citation for published version (APA):
Background

The increasing prevalence of obesity worldwide has forced the World Health Organization (WHO) to regard this as one of the priorities for reducing the ‘Global burden of disease’.\(^1\)

In addition to long-term health consequences, the rising prevalence of obesity in women worldwide has implications for their reproductive outcome, and affects their chances of pregnancy. Also, the result of pregnancy may be adversely affected by obesity.

Obesity is associated with menstrual disorders and anovulation\(^2\)-\(^4\) but fertility is also decreased in women with regular menstrual cycles who are overweight.\(^5\)-\(^6\) Furthermore, women, who are overweight or obese while undergoing assisted reproduction, have lower pregnancy rates and higher miscarriage rates.\(^7\)-\(^9\) During pregnancy, obesity leads to a significant increase in pregnancy complications\(^10\)-\(^11\) and difficulties during labour.\(^12\) Infants are at greater risk of congenital abnormalities\(^13\)-\(^14\) and intrauterine demise\(^15\)-\(^16\) contributing to an increase in perinatal morbidity and mortality.

Not only pre-pregnancy obesity is related to adverse outcomes. Also excessive weight gain during pregnancy is associated with an increased risk of obstetrical, maternal and foetal complications, postpartum maternal weight retention, and also with an increased risk of obesity in the offspring.\(^17\)-\(^28\)

Excessive gestational weight gain and the associated postpartum weight retention contribute to the prevalence of women who are overweight or obese and increase the long-term risk of body weight-associated diseases, which impose a great pressure on health care.\(^28\)-\(^31\)

The Institute of Medicine (IOM) guidance in the US provides recommended weight gain ranges in pregnancy for normal, overweight and obese women based on observational data.\(^32\) In the absence of validation of these recommendations in large interventional trials, the benefits of adhering to these weight gain guidelines during pregnancy are unclear. The economic evaluation commissioned by NICE acknowledged this limitation and considered that the assumed effects of weight changes on pregnancy outcomes were subject to strong assumptions.\(^33\) Currently, the National Institute for Health and Clinical Excellence in the United Kingdom\(^34\) does not recommend specific weight gain targets in pregnancy in the absence of robust data validated in interventional trials. Therefore, there is a clear need for establishing the relationship between gestational weight gain and pregnancy outcomes from randomised intervention trials.
Results of Recent Trials

Pre-pregnancy Interventions
Norman et al.\textsuperscript{35} showed in their review that reducing the pre-pregnancy weight in overweight or obese women with infertility increases the chances of both spontaneous conception and conception after ovulation induction and assisted reproduction. Weight loss achieved by a lifestyle programme – a combination of diet and physical activity – leads to an increase in spontaneous pregnancies and pregnancies after fertility treatment.\textsuperscript{36} An RCT of Hoeger et al.\textsuperscript{37} showed that in obese women with polycystic ovary syndrome (PCOS), not the type of treatment (metformin versus lifestyle programme versus placebo), but the amount of weight reduction was the most important factor for the resumption of ovulation. These trials show that weight loss in infertile obese women should be considered as the first treatment.

In view of the low success rate of lifestyle interventions 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 could be an asset in the treatment of women with infertility.

Although insulin sensitising drugs are not considered anti-obesity drugs, evidence indicates that metformin therapy might contribute to weight loss.\textsuperscript{38,39} If metformin treatment does contribute to weight loss, treatment of women of reproductive age with obesity and infertility could improve the chances of conception.

According to a randomised controlled trial (RCT), the combination of a lifestyle modification programme with drug therapy achieves more weight loss than a lifestyle programme alone.\textsuperscript{40}

Interventions during Pregnancy
Many trials have been conducted evaluating the effect of different lifestyle interventions on gestational weight gain (GWG) and adverse pregnancy outcomes, which were recently reviewed and combined in a meta-analysis.\textsuperscript{41}

Dietary and lifestyle interventions in pregnancy have been shown to significantly reduce gestational weight gain, and lead to reduced risk of pregnancy complications such as pre-eclampsia, gestational diabetes mellitus, gestational hypertension and preterm delivery without any reported adverse effects.\textsuperscript{42} In a subgroup analysis, a stronger effect was observed in obese and overweight women. Dietary interventions seem to be more effective than physical activity.\textsuperscript{42} However, it must be noted that the compliance with the interventions was either not assessed or insufficient in some trials. Furthermore, the relationship between GWG and pregnancy complications was not investigated.

Impact on Society
Worldwide working women of childbearing age are a vital part of the working population. Given the association between obesity and
pregnancy complications and obesity and sick leave in general, one might expect that obese pregnant women would have an increased risk for sick leave. However, to date, the relationship between body mass index and sick leave in pregnant women has not been investigated.

Pre-pregnancy maternal obesity, and excessive weight gain in pregnancy impose an increasing pressure on health care resources, due to increase chance of pregnancy complications.

A reduction of the number of maternal and neonatal complications, for instance by decreasing GWG, might result in a decrease in health care cost during and after pregnancy. Previous meta-analysis already reported positive effects of lifestyle interventions in pregnancy on maternal and neonatal health. A reduction of the number of maternal and neonatal complications, might result in a decrease in health care cost during pregnancy.

Little is known about the effect of GWG and pregnancy complications. Also the budget impact of lifestyle intervention is not yet clear. The potential economic consequences of providing a lifestyle intervention for overweight and obese women in pregnancy could be helpful to stimulate policymakers to advocate implementation of lifestyle interventions in pregnancy.

**Aim of the Thesis**

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

**Outline of this Thesis**

Obesity is associated with a decreased fertility and an increased rate of complications during pregnancy. *Chapter 2* shows an overview of the possible effects of obesity on fertility and pregnancy complications in women of reproductive age. In *chapter 3* of this thesis we assessed the effects of insulin sensitising drugs on weight loss compared to diet or a lifestyle programme in overweight and obese women of reproductive age.

Lifestyle interventions in obese pregnant women reduce adverse maternal outcomes of pregnancy. However, the association between differences in gestational weight gain due to interventions and the actual reduction in complications is unknown. In *chapter 4*, the association between gestational weight gain and pregnancy complications was assessed.

The relationship between sedentary behaviour and weight (gain) has been found in women and adolescent girls outside of pregnancy.
During pregnancy, women in the United States spent more than half of the monitored day in sedentary behaviour. However, whether the amount of time spent sedentary influences gestational weight gain or birth weight is currently unknown.

In chapter 5, the relationship of physical activity and sedentary behaviour in pregnancy with gestational weight gain and birth weight was determined.

Being overweight or obese during pregnancy and excessive weight gain increase the chance of complications, including among others maternal death, miscarriage, pre-eclampsia, gestational diabetes mellitus, postpartum haemorrhage. This imposes a great pressure on health care. In chapter 6 we evaluated the budget impact of decreasing the risk of pregnancy complications through lifestyle interventions.

In many cost-effectiveness analyses of interventions in pregnancy, only short term effects on health care consumption and associated costs were evaluated. However, sick leave associated with obesity and/or pregnancy complications might have a great impact on costs for society. To date, the relationship between body mass index and sick leave of pregnant women has not been investigated. In chapter 7 we assessed the relationship between BMI and sick leave before, and during pregnancy and one year postpartum.

Most meta-analyses are based on aggregated average outcomes per study, thereby limiting the statistical precision of the meta-analysis. Also, due to the aggregated data there is heterogeneity within and between the studies. An individual patient data (IPD) meta-analysis would overcome this problem. This approach provides adequate power to generate valid, reliable answers and to create models for decision analytic modelling for health economic evaluation.

We therefore plan an IPD meta-analysis to evaluate the differential effects of diet and physical activity based interventions on maternal and foetal outcomes. Chapter 8 describes the protocol for this IPD meta-analysis, which is conducted in international collaboration.

IPD meta-analyses and large clinical studies provide information and insight that are used to develop clinical guidelines. Many researchers have therefore initiated multicentre studies. In some situations, the activities of these groups have led to networks, through which multiple trials have been executed over a longer period of time. The Global Obstetrics Network (GONet) was formed to link the different types of networks. The expectation is that this will lead to better studies and more efficient use of resources. Chapter 9 explains the need of international collaboration and the mission, goals and structure of GONet.
References

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