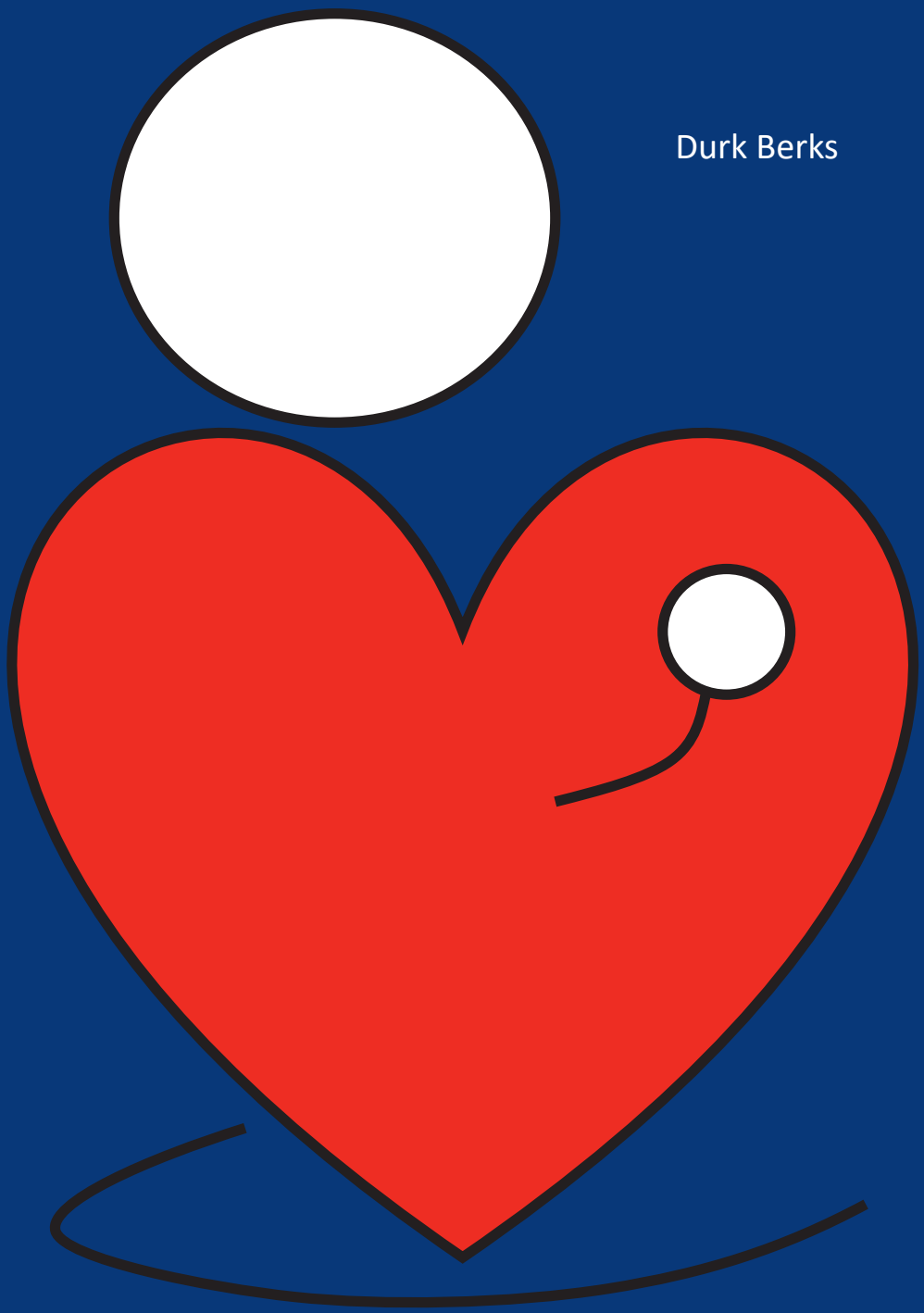
Pro-active Management of Women's Health after Cardiometabolic Complicated Pregnancies

Durk Berks



PRO-ACTIVE MANAGEMENT OF WOMEN'S HEALTH AFTER CARDIOMETABOLIC COMPLICATED PREGNANCIES

Durk Berks

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Co-promotor:	Dr. J.J. Duvekot

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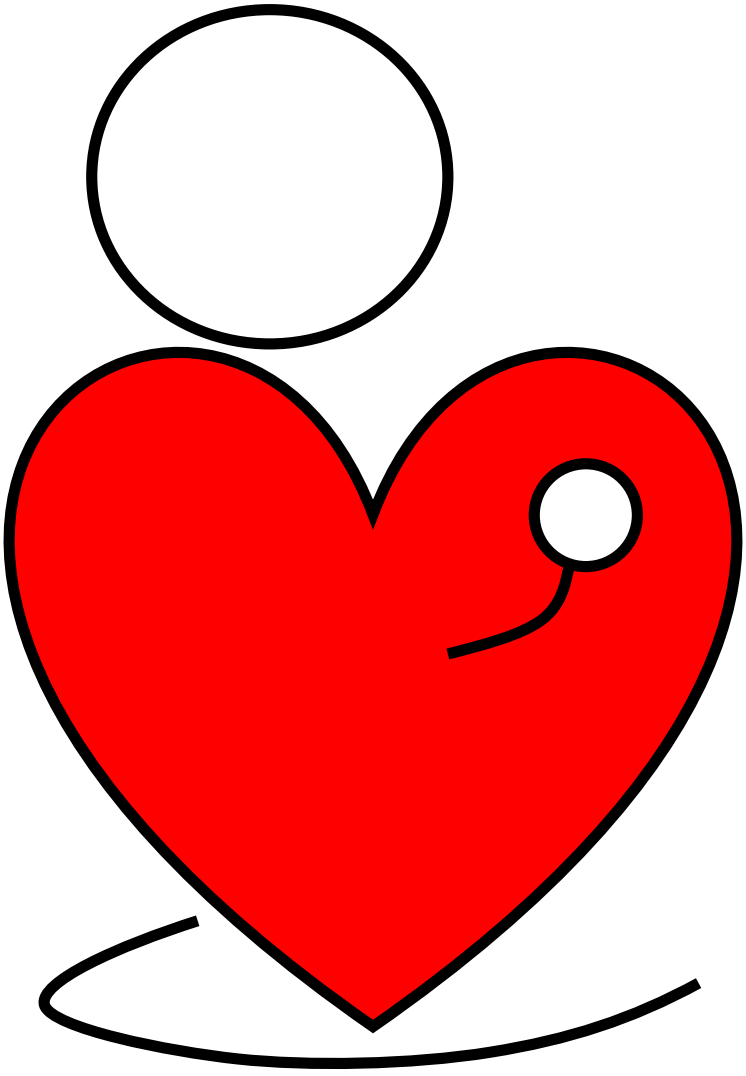
We can't solve problems by using the same kind of thinking we used when we created them – Albert Einstein

Part One

Introduction



During pregnancy, the maternal body needs to adapt to a fast growing, highly active, new organ: the placenta. To meet its demands, it reversibly presses the maternal body to its metabolic and cardiovascular limits. Women with a good cardiometabolic health will have no problem to handle this pressure. If, however cardiometabolic health is already compromised and fetal demands cannot be met, it will push women beyond their limits into a state of physical 'overdrive', leading to cardiometabolic complicated pregnancy (figure 1). Well known phenotypes of cardiovascular complicated pregnancies are preeclampsia and fetal growth restriction. An example of metabolic complicated pregnancy is gestational diabetes mellitus.

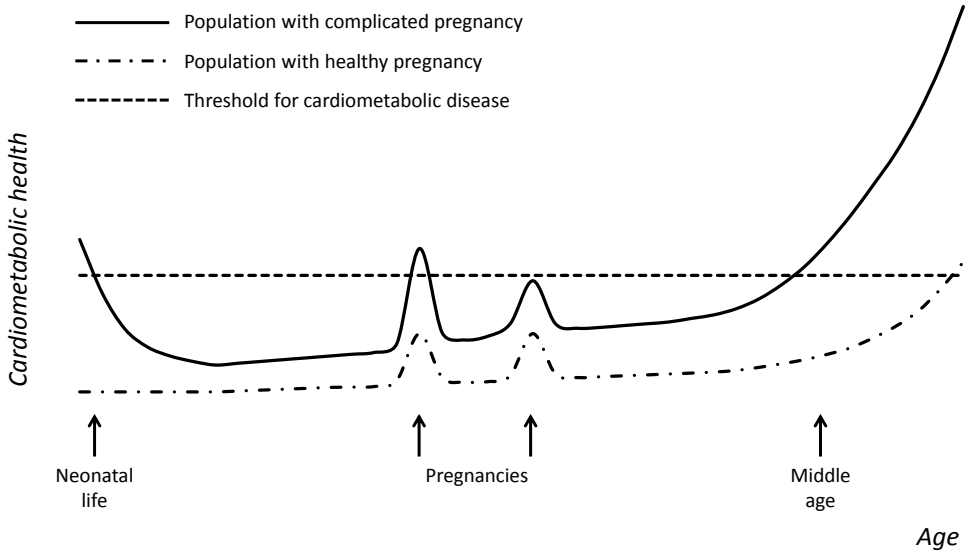
In 2002 Sattar and Greer were the first to postulate the hypothesis that pregnancy is a stress-test for cardiometabolic health[1] (figure 1.1). If complicated pregnancy occurs, it flags for decreased cardiometabolic health. These women are at increased risk for future cardiometabolic disease. It is unclear whether having had the complicated pregnancy contributes to the increased risk.

Cardiovascular complications of pregnancy

Cardiovascular complications of pregnancy are gestational hypertension, preeclampsia, eclampsia, placental abruption, and fetal growth restriction. For gestational hypertension, preeclampsia and fetal growth restriction an increased risk for future cardiovascular disease has been shown[2 3].

Preeclampsia complicates 2-8% of pregnancies[4]. It is characterized by hypertension and proteinuria above the 20th week of gestation[5]. Preeclampsia can occur as different phenotypes. Common phenotypes are early (<34 weeks of gestation) or late (>=34 weeks of gestation) onset, with or without HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) and with or

Figure 1.1. Risk factors for cardiometabolic disease are identifiable during excursions into the cardiometabolic syndrome of pregnancy (adapted from Sattar and Greer, 2002[1])

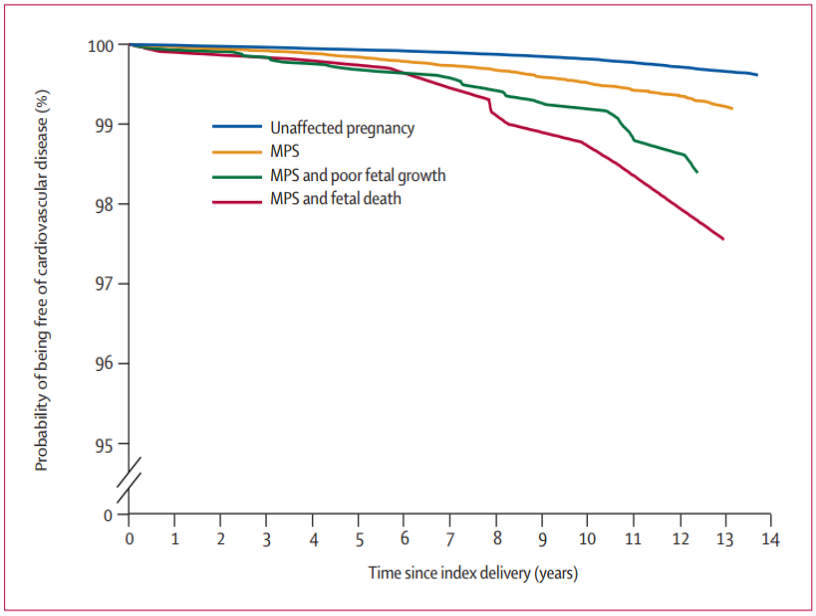


without fetal growth restriction. Clinically preeclampsia is differentiated in severe (severe hypertension, fetal growth restriction, HELLP syndrome, early onset) and mild (mild hypertension, appropriate fetal growth, no HELLP syndrome, late onset) preeclampsia.

Already in 1976 Chelsey observed an increased mortality in former eclamptic women[6]. More recent studies show a 2-fold increased risk for future cardiovascular disease up to 30 years after preeclampsia[2 3 7-16]. More severe preeclampsia is associated with an even higher risk. If preeclampsia is combined with fetal growth restriction, the increase is 4-fold[10]. When fetal growth restriction is accompanied with premature birth, the risk is increased 16-fold[10]. As shown by Ray et al, this increased risk for cardiovascular disease is already observed the first decade after the pregnancy[3] (figure 1.2).

Previous studies show a decreased cardiovascular health in formerly preeclamptic women[17-27]. They have higher blood pressure[25 28-31], higher

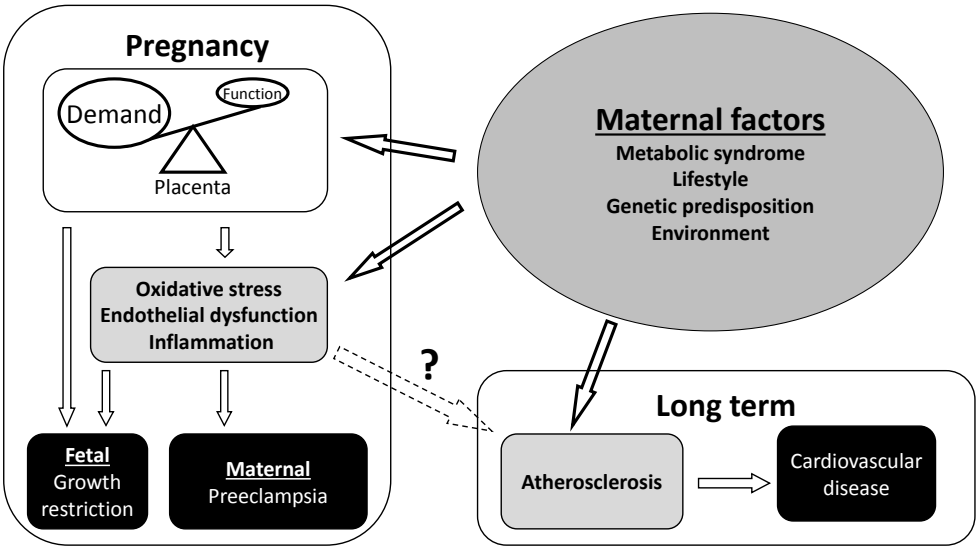
Figure 1.2. Risk of cardiovascular disease associated with a maternal placental syndrome (MPS, composite of preeclampsia, gestational hypertension, placental abruption or placental infarction) or an affected fetus or both[3]



cholesterol level[21 31], higher BMI[31 32] and tend to be more insulin resistant[25 33] compared to women after an uncomplicated pregnancy. However, due to their relative young age traditional risk prediction models[34-40] cannot identify these women as high-risk the first years after their pregnancy[41]. Extrapolated to an older age however, these women are clearly high-risk for cardiovascular events[41].

Risk factors for cardiovascular disease also increase the risk of preeclampsia[18 42], suggesting a 'common soil' for preeclampsia, fetal growth restriction and cardiovascular disease (figure 1.3). Since studies focus on women after their pregnancy, it remains unclear whether the preeclampsia itself (irreversibly) affects cardiovascular health and whether different aspects of preeclampsia (severity, duration of the disease) have different effects on cardiovascular health.

Figure 1.3. 'Common soil' theory of the origin of preeclampsia, fetal growth restriction and cardiovascular disease

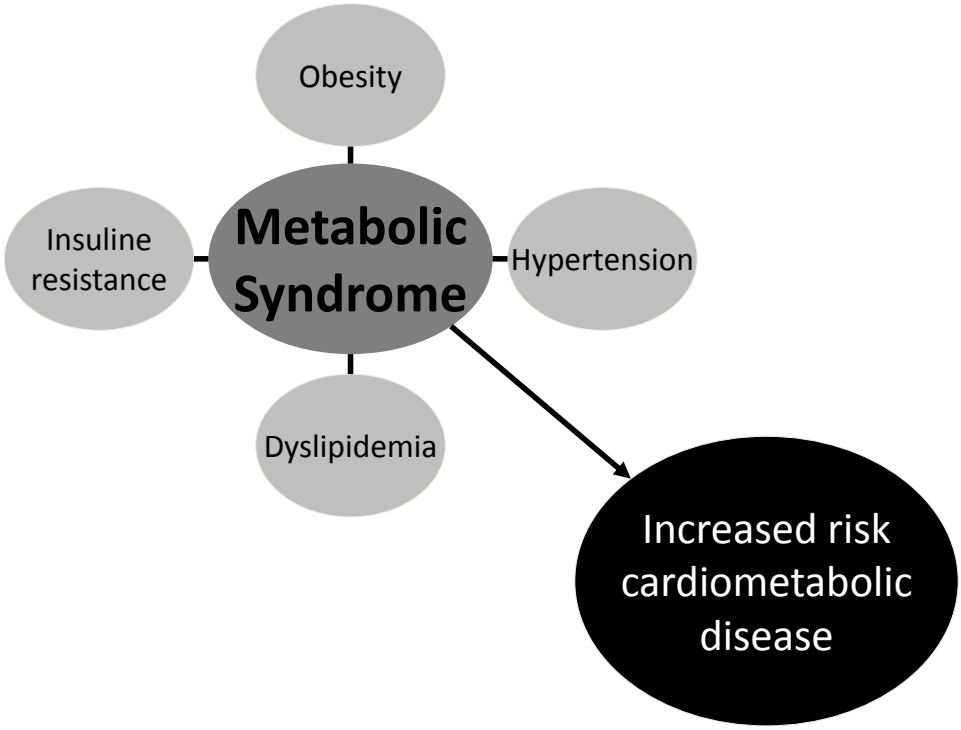


Metabolic complications of pregnancy

Gestational diabetes mellitus complicates 8-10% of all pregnancies. Women with a pregnancy complicated by gestational diabetes mellitus, are at increased risk for future type 2 diabetes mellitus. The 5 to 15-years risk for diabetes is 33%-60%[43-48], compared to 2-3% after uncomplicated pregnancy. The more severe gestational diabetes mellitus (early onset <24 weeks of gestation, need for insulin), the higher the risk of future diabetes mellitus[43]. Also, BMI in case of gestational diabetes mellitus is independently positively associated with the risk of future diabetes mellitus[43 44 46 47].

Women with a history of gestational diabetes mellitus have a worse metabolic health compared to women with an uncomplicated pregnancy[49]. Fasting glucose levels are higher, as is BMI, lipid levels and blood pressure.

Figure 1.4. The metabolic syndrome



Studies show no increased risk for cardiovascular disease[13 15]. However, since diabetes mellitus is a risk factor for cardiovascular disease, the follow-up of the cohort studies might have been too short to identify this increased risk.

Currently the pre-pregnancy metabolic health of women with a subsequent first episode of gestational diabetes mellitus has not been studied. Whether gestational diabetes mellitus itself adds to the risk of future diabetes mellitus is unclear.

Metabolic syndrome

Women with a history of preeclampsia, fetal growth restriction or gestational diabetes mellitus show increased risk factors for future cardiometabolic health: higher blood pressure, higher BMI, higher fasting

glucose levels and higher cholesterol-levels. These symptoms are likely to co-occur as the metabolic syndrome (figure 1.4). The metabolic syndrome is defined as the presence of three or more of the following traits[50 51]:

- Abdominal obesity (waist circumference in men ≥ 102 cm, in women ≥ 88 cm)
- Elevated serum triglycerides (≥1.7 mmol/l) or drug treatment
- Low high-density lipoprotein (HDL) cholesterol (in men <1.0 mmol/l, in women <1.3 mmol/l) or drug treatment
- Blood pressure ≥ 130/85 or drug treatment
- Elevated fasting plasma glucose (≥ 5.6 mmol/l) or drug treatment

The metabolic syndrome is not the only explanatory link between a complicated pregnancy and future cardiometabolic risk. Other risk factors like genetic predisposition and maybe the complicated pregnancy itself contribute to the increased future risk (figure 3).

Opportunities to reduce risk of future disease

Whether complicated pregnancy is a marker or a risk factor for future cardiometabolic disease does not alter the fact that the complicated pregnancy uniquely identifies these women at a young age as high risk for future disease. Since in the major part of these women classic risk factors like hypertension or hypercholesterolemia are not manifested jet, primary lifestyle intervention can help to postpone or even prevent future cardiometabolic disease. As shown by the INTERHEART study, lifestyle factors have a cumulative population attributive risk for cardiovascular disease in women of 65%[52] indicating the possible gain of lifestyle intervention.

Smoking cessation reduces the risk for cardiovascular disease with 47% within 10 years, with the greatest effect in the first year after cessation[53].

Consuming less unsaturated fat can lower cardiovascular risk with 40-50%[54]. Physical activity lowers cardiovascular risk with 52% if the time spent walking is more than 2 hours per week, compared to a sedentary lifestyle[55]. Physical activity also decreases weight and blood pressure. Lowering of BMI reduces the risk of myocardial infarction with 7% per 1 Kg/m^2[56]. Small changes in blood pressure can have tremendous effects on cardiometabolic risk. If diastolic blood pressure is 2 mmHg lower, the risk for future myocardial infarction is decreased by 6%. If lowered 5-6 mmHg, the decrease can be 25%. For cerebrovascular accidents, the decrease is 15% and 40% respectively[57]. Weight reduction and reduced fat intake, increased fiber intake and physical activity can reduce the risk of diabetes mellitus with 50%[58 59].

In applying primary lifestyle intervention, it is difficult to reach and motivate the eligible people to change their lifestyle. Participation and compliancy are generally low, while dropout rates are as high as 31%, even with short-term benefits of lifestyle intervention[60].

In contrast to other people that are eligible for primary lifestyle intervention, women after complicated pregnancy have been confronted with a -sometime life threatening- disease during pregnancy. Next to the fact that pregnancy itself is a motivator for lifestyle changes[61 62], experiencing disease during pregnancy might be an additional strong motivator to comply with primary lifestyle intervention, opening a window of opportunity to guide these women to a healthier future[63-70]. The use of web-based interventions can increase compliance and effectiveness of primary lifestyle intervention programs[65 71-78]. However, whether lifestyle intervention after complicated pregnancy is feasible and effective still needs to be addressed.

Aims and outline of the thesis

The general aim of this thesis is to develop and evaluate a postpartum program appraising cardiovascular health and offering lifestyle intervention after complicated pregnancy to reduce future cardiovascular risk.

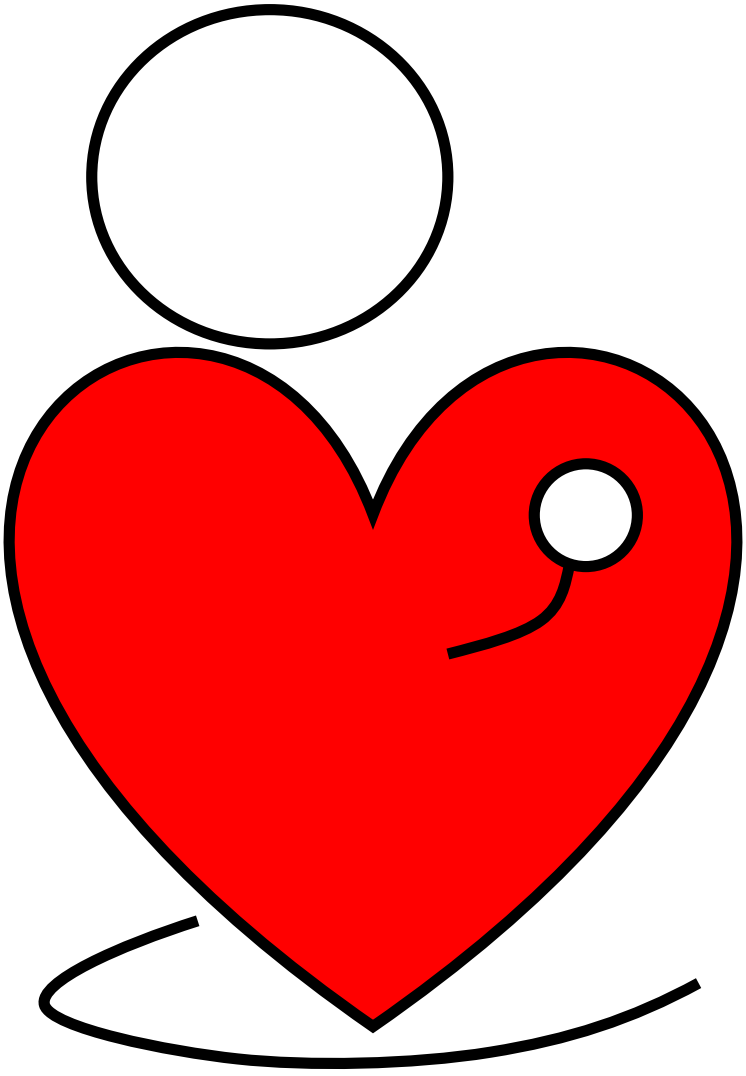
Part 2 describes research in developing postpartum appraisal of cardiovascular health. To identify when to appraise postpartum cardiovascular health, a historic prospective cohort was used to study recovery after a complicated pregnancy. The results are presented in chapter 4.1. Chapter 4.2 presents a case series, showing associations between thrombophilia -being an unchangeable risk factor for future cardiovascular disease- and different phenotypes of preeclampsia.

Part 3 discusses the development and evaluation of the lifestyle intervention program of the Postpartum Rotterdam Appraisal of Cardiovascular Health and Tailored Intervention (Pro-Active) study. First, chapters 5.1 and 5.2 present literature-based studies on what is already known about post-partum lifestyle intervention and what estimated effect it might have on cardiometabolic risk. Second, chapters 5.3 and 5.4 show the results of focus group studies on the preferences, motivators and barriers in women with a formerly complicated pregnancy with regard to a postpartum lifestyle intervention program. Finally, chapter 5.5 displays the results of the Pro-Active-study. In this chapter the feasibility and effect of a postpartum lifestyle intervention program after complicated pregnancy are described.

Chapter 6 presents a general discussion and focusses on future clinical and scientific implications.

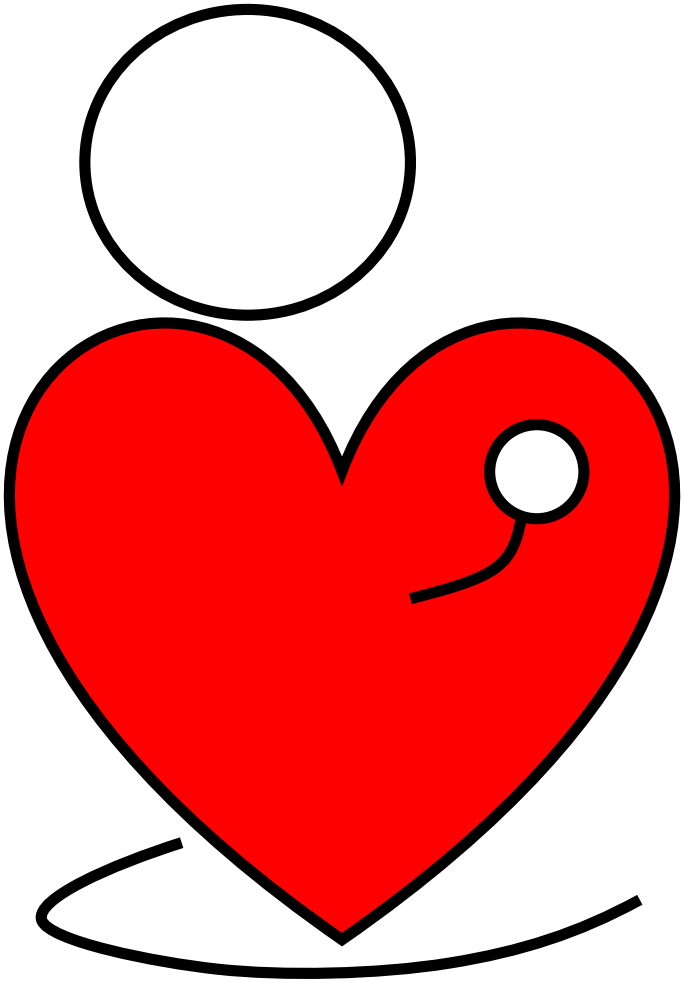
Part Two

Postpartum appraisal of cardiovascular health



Chapter 2.1

Resolution of hypertension and proteinuria after preeclampsia: a 2-year follow-up study



Obstetrics & Gynecology
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ABSTRACT

Objective (1) To estimate the time required for hypertension and proteinuria to resolve after preeclampsia. (2) How this time to resolution correlate with the levels of blood pressure and proteinuria during preeclampsia and the prolongation of pregnancy after the development of preeclampsia.

Methods This is a historical prospective cohort study of 205 preeclamptic women, who were admitted between 1990 and 1992 at the Erasmus University Medical Center in Rotterdam, the Netherlands. Data were collected at 1.5, three, six, 12, 18 and 24 months after delivery. Hypertension was defined as a blood pressure ≥ 140/90 mmHg or use of antihypertensive drugs. Proteinuria was defined as ≥ 0.3 gram/day. Resolution of hypertension and proteinuria were analyzed with Turnbull's extension to the Kaplan-Meier procedure. Correlations were calculated with an accelerated failure time model.

Results At three months postpartum 39% still had hypertension, falling to 18% at two years postpartum. Resolution time increased with higher systolic ($p<0.001$) and diastolic blood pressure during preeclampsia ($p=0.044$), as well as a longer time interval between diagnosis and delivery ($p=0.001$). At three months postpartum 14% still had proteinuria, falling to 2% at two years postpartum. Resolution time increased with higher levels of proteinuria during preeclampsia ($p<0.001$). Gestational age at onset of preeclampsia was not correlated with resolution time of hypertension and proteinuria.

Conclusion Following a preeclampsia, it can take up to two years for hypertension and proteinuria to resolve. Therefore, we suggest that further invasive diagnostic tests for underlying renal disease may be postponed until two years postpartum.

INTRODUCTION

Preeclampsia complicates about 5% of all pregnancies[79]. The associated hypertension and proteinuria usually resolve after delivery. But recent studies show that preeclampsia is associated with an increased risk for remote cardiovascular disease[80] and end stage renal disease[81]. More knowledge on postpartum resolution of hypertension and proteinuria will help to properly identify chronic hypertension and proteinuria. This can help justify further invasive diagnostic tests for underlying disease.

The time required for resolution however is not clear. International guidelines state that hypertension should resolve within three months after a preeclamptic pregnancy[82] [83]. Otherwise, chronic hypertension is present. Previous publications indeed show rapid postpartum fall of the blood pressure[84-87]. However, they were not designed to estimate resolution after three months postpartum, having a follow-up period of seven days or excluding patients with persistent hypertension at three months postpartum. If data of resolution of hypertension beyond three months postpartum was available, women with chronic hypertension could be better identified. For proteinuria, no statement exists when postpartum persistence should be considered chronic. Previous publications suggest a high risk of renal injury if proteinuria is persistent after six or 12 weeks postpartum. However, publications are case reports[88] or consist of retrospectively collected data on renal biopsies[89] [90]. If prospectively collected data of postpartum resolution of proteinuria was available, women with persistent proteinuria could also be better identified. In our own experience, hypertension and proteinuria could resolve beyond three months after a preeclamptic pregnancy.

In this historical prospective cohort study, we address the following

questions. (1) How long can it take for hypertension and proteinuria to resolve after a preeclamptic pregnancy and (2) how do prolongation of pregnancy after the development of preeclampsia and the levels of blood pressure and proteinuria during preeclampsia correlate with postpartum time to resolution and to what extent?

METHODS

This historical prospective cohort study was carried out on preeclamptic women who were admitted to the Department of Obstetrics and Gynecology of the Erasmus University Medical Center and delivered between January 1, 1990 and December 31, 1992. Preeclampsia was defined as the occurrence after 20 weeks' gestation of a blood pressure of 140/90 mmHg or more and proteinuria of 0.3 g/day or more. The HELLP syndrome was defined as the simultaneous occurrence of a platelet count of < 100 x 10^9/l, serum aspartate aminotransferase (ASAT) and serum alanine aminotransferase (ALAT) concentrations > 30 U/l (2 S.D. above the mean in our hospital). Women with a record of chronic hypertension or kidney disease prior to pregnancy or before 20th week of gestation were excluded. Severity of the disease was retrospectively defined according to ACOG-criteria[83].

During the study period, a consultant of internal and obstetric medicine used a protocol for the follow-up. All women who were admitted with preeclampsia were offered visits at 1.5, three, six, 12, 18 and 24 months after delivery. If a woman did not present for the check-up, she was sent a reminder once. However, not every woman attended every visit. The hospital files were searched to collect data on blood pressure, use of anti-hypertensive drugs, urinary protein excretion and serum-creatinine levels at every attended visit.

Hypertension was defined as the use of anti-hypertensive drugs or a blood pressure ≥ 140/90 mmHg. Proteinuria was defined as ≥ 0.3 grams/day urinary protein loss. For both conditions separately the first visit of measured resolution was identified. Because resolution obviously occurred somewhere between visits, actual time of resolution was analyzed as interval censored. If no visit of resolution could be identified and follow-up data was incomplete, women were considered lost-to-follow-up. Turnbull's extension of the Kaplan-Meier procedure to interval-censored data[91] was then used to calculate resolution-curves with 95% confidence bands (SAS 9.1.3, SAS Institute Inc., Cary, NC, USA). The women that were lost-to-follow-up were right-censored in the analysis under the assumption of independent censoring from the time of resolution. This means that after the last known visit, the proportion of right-censored women who showed resolution was equal to the proportion of women with complete follow-up who showed resolution at a specific time.

Hospital files were searched to collect clinical features of preeclampsia. They included maximal systolic and diastolic blood pressure during admission, maximal level of proteinuria during admission, gestational age at onset of preeclampsia and the time interval between diagnosis and delivery. To analyze the correlation between these covariates and the rate of resolution, we used an accelerated failure time (AFT) model with flexible error distribution allowing for interval censoring as described elsewhere[92] (smoothSurv 0.3-12 R 2.7.1, Komarek). This model is not restricted to assume a specific distribution for the error like Gaussian or extreme value distribution, but allows a smooth error distribution resulting from the penalized normal mixture.

This study was approved by the Institutional Research Board of the Erasmus University Medical Center (trail number MEC-2009-169).

RESULTS

A total of 242 women were admitted with preeclampsia during the study period. Of these women 37 were excluded: 30 women had been diagnosed with hypertension before pregnancy, two had been diagnosed with proteinuria before pregnancy and five women had been diagnosed with both. A total of 205 women were included for analysis. Whilst for 116 women complete blood pressure data was available, complete proteinuria data was available for 121 women. General characteristics are summarized in Table 2.1.1.

Hypertension

For 116 women, complete blood pressure data was available: for 112 women resolution of hypertension was identified, four women still had (known) hypertension two years postpartum. The remaining 89 women were lost to follow-up before normalization of blood pressure. Table 2.1.2 shows the comparison between these two groups, showing the latter group having had worse clinical features of preeclampsia.

Figure 2.1.1 shows the resolution curve for hypertension with 95% confidence

Table 2.1.1. General characteristics of study population (n=205)

Age (years)	28 (16-45)
Gestational age at diagnosis (weeks)	31 (21-42)
Gestational age at delivery (weeks)	34 (22-42)
Prolongation of preeclampsia (days)	8 (0-62)
Maximal systolic blood pressure during preeclampsia (mmHg)	170 (140-280)
Maximal diastolic blood pressure during preeclampsia (mmHg)	110 (90-170)
Maximal level of proteinuria during preeclampsia (g/24h)	4.2 (0.3-31.4)
Maximal level of creatinine during preeclampsia (mmol/l)	82 (45-626)
Nulliparous	69.8% (143)
Severe preeclampsia	89.3% (183)
HELLP	32.2% (66)
Eclampsia	5.4% (11)

Table 2.1.2. Characteristics of women with full follow-up data and lost-to-follow-up with regard to blood pressure measurements

	Complete Data n=116	**Lost-to-follow-up n=89**	**p-value**
Gestational age at diagnosis (weeks)	32 (21-42)	31 (25-41)	0.02
Prolongation of preeclampsia (days)	6 (0-60)	14 (0-62)	0.01
Maximal systolic blood pressure during preeclampsia (mmHg)	170 (130-226)	180 (130-280)	0.001
Maximal diastolic blood pressure during preeclampsia (mmHg)	110 (90-145)	115 (90-170)	0.02
Maximal level of proteinuria during preeclampsia (gr/24h)	4.0 (0.3-25.3)	5.4 (0.3-31.4)	0.09
Maximal level of creatinine during preeclampsia (mmol/l)	82 (45-626)	84 (52-394)	0.19

Values are presented as median(range) and compared using Mann-Whitney tests.

interval. At discharge after delivery 78% still had hypertension. At six weeks postpartum in 54%, and at three months postpartum in 39% of the women hypertension was still present. Finally, at two years postpartum 18% had persistent hypertension. No difference was observed in normalization between primiparous and multiparous women. In the AFT-model, both a higher maximal systolic blood pressure and higher maximal diastolic blood pressure during preeclampsia increased resolution time (resp. $p<0.001$ and $p=0.044$). Also, longer time interval between diagnosis and delivery increased resolution time ($p=0.001$). Figures 2.1.2, 2.1.3 and 2.1.4 show the effect of these variables on the resolution curve. The baseline in each figure is defined as maximal systolic blood pressure of 140 mmHg, maximal diastolic blood pressure of 90 mmHg and time interval between diagnosis and delivery of 0 days. The curves show the effect on the rate of resolution of hypertension when the specific variable changes, leaving the other variables at baseline. The coefficients for the corresponding AFT-model are presented in table 2.1.3. Resolution time of hypertension was not significantly correlated with the maximum level of proteinuria and gestational age at onset of preeclampsia.

Figure 2.1.1. Resolution of hypertension after preeclampsia (0 weeks = delivery)

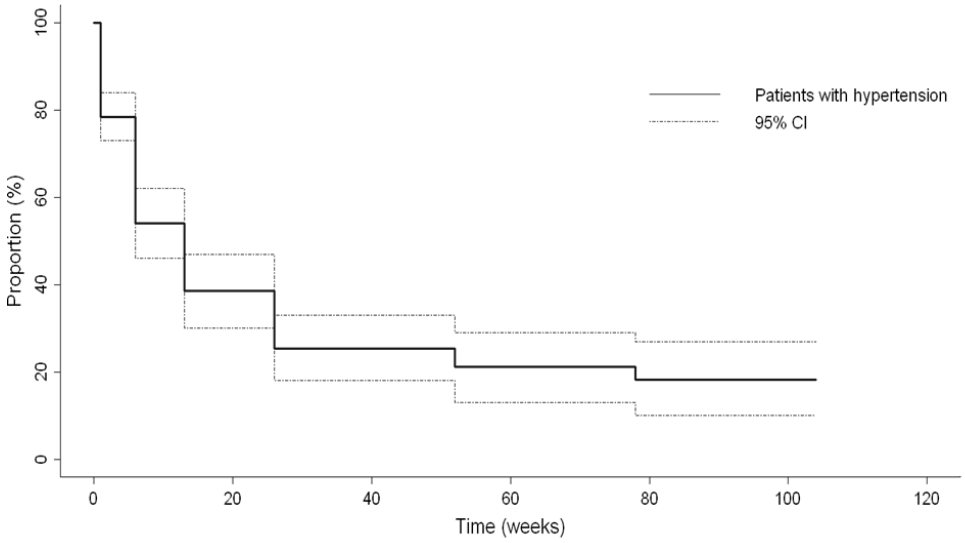


Figure 2.1.2. Accelerated failure time model of resolution of hypertension for different levels of maximal systolic blood pressure during pregnancy

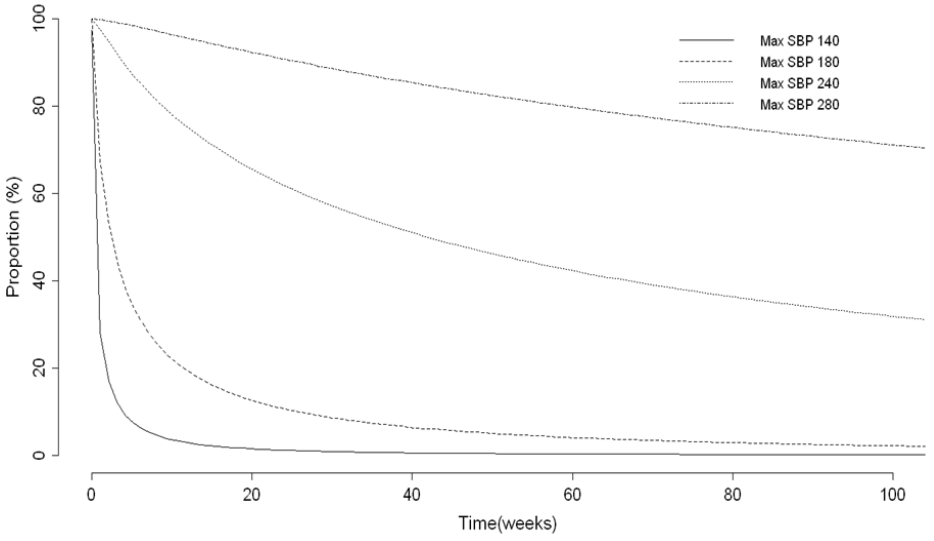


Figure 2.1.3. Accelerated failure time model of resolution of hypertension for different levels of maximal diastolic blood pressure during pregnancy

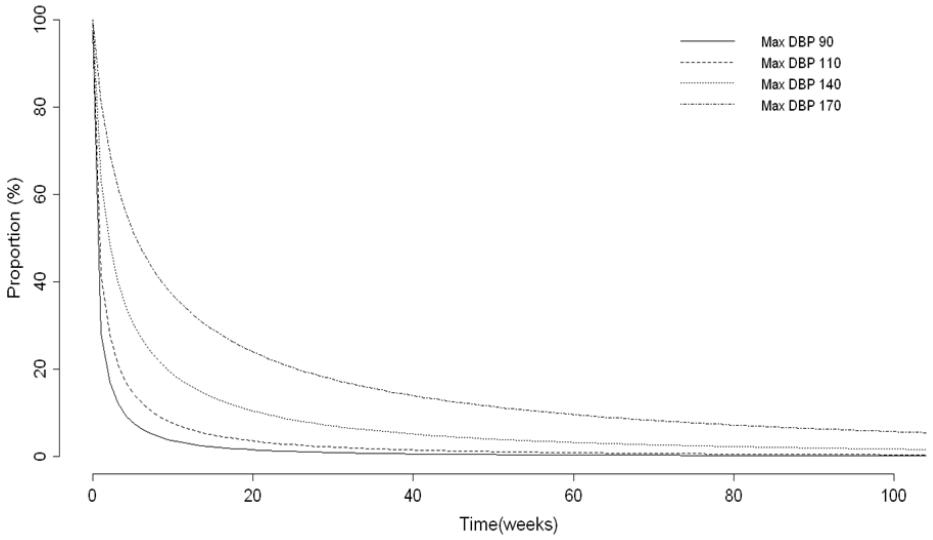


Figure 2.1.4. Accelerated failure time model of resolution of hypertension for different time intervals between diagnosis and delivery

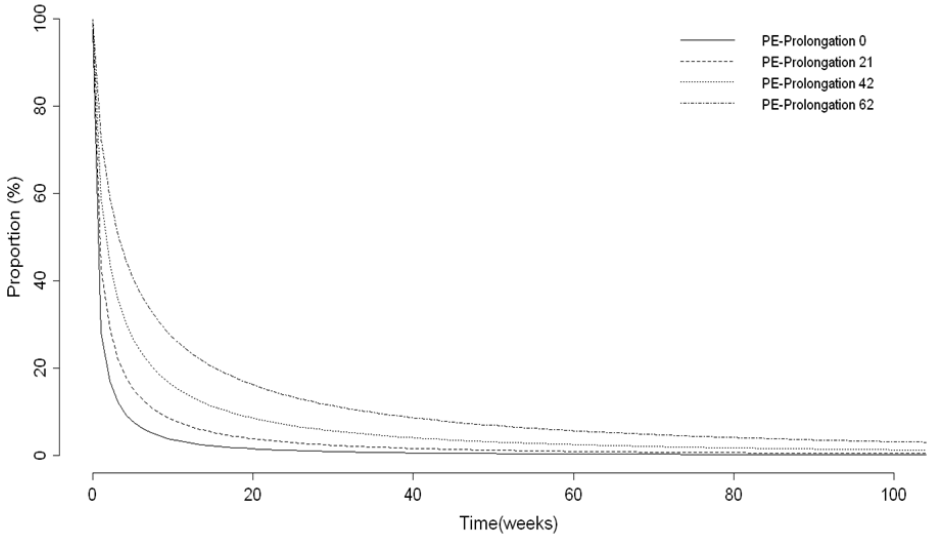


Table 2.1.3. Coefficients of the AFT-model

	Coefficient	(95%-CI)	p-value
Resolution of hypertension			
Constant	-10.76	(-14.21- -7.16)	
Maximum systolic blood pressure (mmHg)	0.05	(0.03-0.07)	<0.001
Maximum diastolic blood pressure (mmHg)	0.03	(0.00-0.07)	0.044
Prolongation of preeclampsia (days)	0.04	(0.01-0.06)	0.001
Resolution of proteinuria			
Constant	-0.53	(-0.95-0.10)	
Maximum level of proteinuria (gr/24h)	0.15	(0.11-0.19)	<0.001

Values are presented as median(range) and compared using Mann-Whitney tests.

Proteinuria

For 121 women complete proteinuria data was available: for all those women resolution of proteinuria was identified. The remaining 84 women were lost to follow-up before resolution of proteinuria. Table 2.1.4 shows the comparison between these two groups, showing the latter group having had higher levels of maximal proteinuria during preeclampsia.

Figure 2.1.5 shows the resolution curve for proteinuria with 95% confidence interval. At discharge after delivery 65% of women still had proteinuria. At six weeks postpartum in 21%, and at three months postpartum in 14% of women proteinuria was present. Finally, at two years postpartum 2% had persistent proteinuria. No difference was observed in normalization between primiparous and multiparous women. In the AFT-model, higher maximum level of proteinuria during preeclampsia increased resolution time ($p<0.001$). Figure 2.1.6 shows the effect on the rate of resolution of proteinuria when this variable changes. The coefficients for the corresponding AFT-model are presented in table 2.1.3. Resolution time of proteinuria was not significantly correlated with the maximal systolic and diastolic blood pressure during preeclampsia, gestational age at onset of preeclampsia and time interval between diagnosis and delivery.

Table 2.1.4. Characteristics of women with full follow-up data and lost-to-follow-up with regard to proteinuria measurements

	Complete Data n=121	**Lost-to-follow-up n=84**	**p-value**
Gestational age at diagnosis (weeks)	31 (21-42)	31 (25-41)	0.46
Prolongation of preeclampsia (days)	5 (0-62)	11 (0-50)	0.11
Maximal systolic blood pressure during preeclampsia (mmHg)	170 (130-250)	170 (130-280)	0.73
Maximal diastolic blood pressure during preeclampsia (mmHg)	110 (90-170)	110 (90-160)	0.80
Maximal level of proteinuria during preeclampsia (gr/24h)	3.1 (0.3-27.2)	6.9 (0.3-31.4)	0.001
Maximal level of creatinine during preeclampsia (mmol/l)	82 (45-394)	83 (45-626)	0.72

Values are presented as median(range) and compared using Mann-Whitney tests.

DISCUSSION

Our results show that hypertension and proteinuria can resolve during the first two years following a preeclamptic pregnancy. Of all women that had hypertension at 3 months postpartum, 50% resolved within two years postpartum. So these women could not have had true chronic hypertension and would have been misclassified by current definition. Furthermore, a surprisingly 14% still had proteinuria at three months postpartum. Of these women, 85% resolved within two years postpartum. Clinical features that were associated with a longer time to resolution were higher maximal blood pressure and higher maximal level of proteinuria during pregnancy and a longer time interval between diagnosis and delivery.

Previous longitudinal studies of resolution of hypertension are limited in follow-up time and mainly focus on the differences of resolution between the types of hypertensive disorder in pregnancy[84-87]. The longest previous longitudinal study on resolution of hypertension had a follow-up time of 50 days

Figure 2.1.5. Resolution of proteinuria after preeclampsia (0 weeks = delivery)

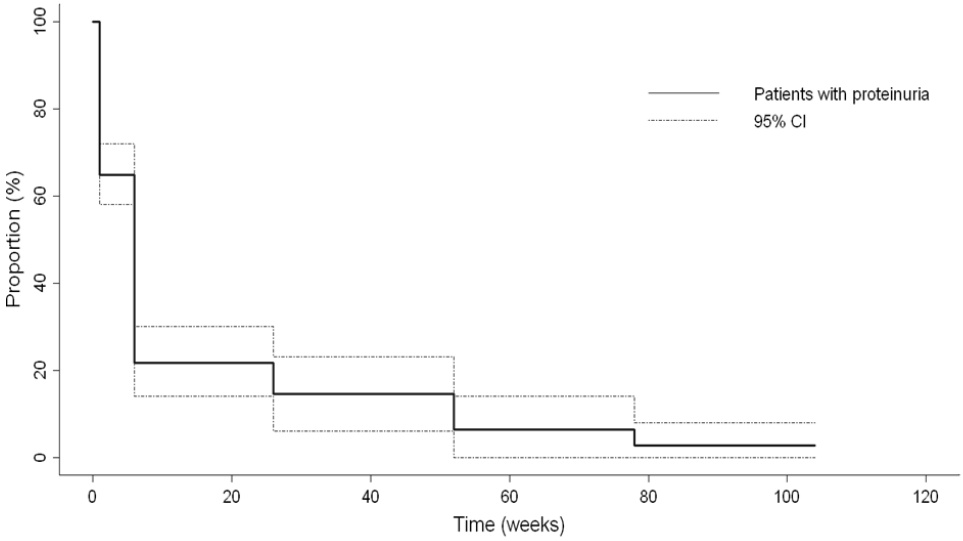
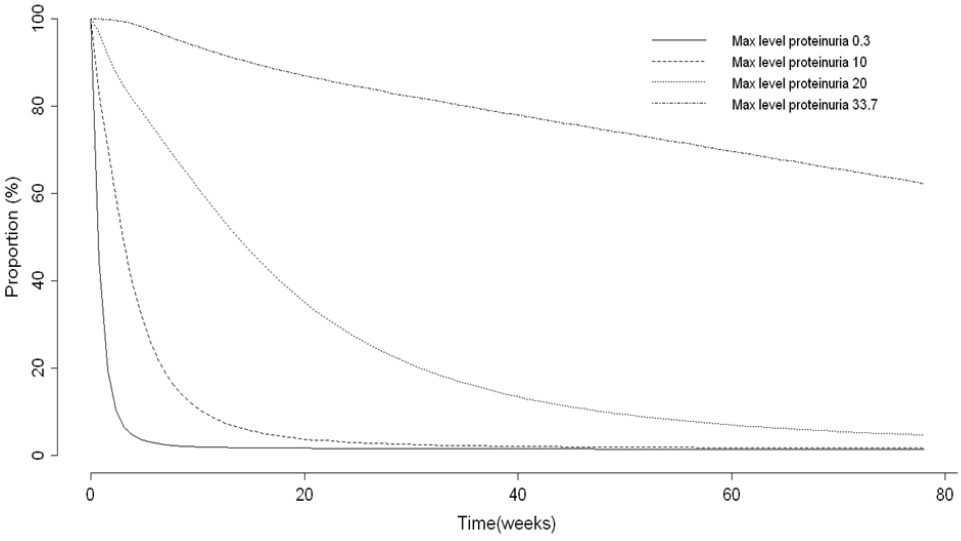


Figure 2.1.6. Accelerated failure time model of resolution of proteinuria for different maximal levels of proteinuria during pregnancy



after delivery[84]. However, women with persistent hypertension at 50 days postpartum were excluded for analysis, thereby precluding any estimate of later resolution. Suzuki et al[87] describe a postpartum observational study of 52 women with gestational hypertension. Of the 52 women, 9 (17%) still had hypertension two years postpartum. However, the rate of resolution between delivery and two years postpartum was not analyzed.

We found an incidence of proteinuria of 14% at three months postpartum. This is higher than in previous studies. In 1992 Chua and Redman describe a longitudinal study on the resolution of proteinuria after preeclampsia[93]. They showed persistent proteinuria in 2% at three months postpartum. However, proteinuria was defined as ≥ 0.5 gram protein a day. That might explain the difference with our findings.

Other studies have looked at renal lesions after preeclampsia[89 90]. Two types of renal lesions, characteristic for preeclampsia, can be discriminated: Those that disappear within days after delivery (glomerular deposits of various hemostatic factors) and those that resolve gradually until as long as 18 months after delivery (endothelial swelling and subendothelial enlargement). The latter supports our conclusion that proteinuria at three months postpartum does not imply chronic disease, but might still be a transient effect of endothelial damage during preeclampsia. Moreover, this finding suggests that a renal biopsy for prolonged proteinuria within two years postpartum may be postponed, since the majority of lesions will disappear.

Sometimes, resolution of proteinuria might be explained by a fall in glomerular filtration rate, or a decrease in blood pressure. Unfortunately, serum-creatinine levels were not routinely measured during follow-up, since all but five women had normal serum-creatinine levels within three months postpartum. So, we think it to be very unlikely that a fall in glomerular filtration rate would

have contributed to resolution of proteinuria. At every postpartum visit, blood pressure levels were comparable between women with and without proteinuria. So it is unlikely that the level of blood pressure has interfered with the resolution of blood pressure.

This study of resolution of hypertension and proteinuria could well reflect endothelial recovery after preeclampsia, as previously suggested[84]. Endothelial dysfunction plays a central role in the pathogenesis of preeclampsia and might account for most of the pathological changes[94 95]. Our findings suggest that the level of endothelial cell injury during preeclampsia, reflected by highest blood pressure and level of proteinuria, is correlated with the time to postpartum recovery. Whether prolonged resolution is reassuring, remains unclear. It might very well reflect worse subclinical cardiovascular health. This should be aim for further research. If true, it can help to identify women at risk for future cardiovascular disease.

Moreover, our findings also suggest that the duration of exposure to endothelial cell injury, as reflected by diagnose-to-delivery interval, is correlated with the time to postpartum resolution of hypertension. We are the first to describe this association. It suggests that preeclampsia itself affects remote cardiovascular health. This implies that temporizing treatment may increase remote cardiovascular risk. Whether this is true should be part of further study.

The main limitation of this study is the number of women lost-to-follow up. With regard to the Turnbull's analysis, they are considered right-censored. This means that after the last known visit, they were expected to behave like the women with complete follow-up. Since the women lost-to-follow-up had more severe clinical features of preeclampsia, our method probably resulted in a best-case scenario. However, within the AFT-model the clinical features of preeclampsia have been adjusted for. These clinical features could be related to

the probability of censoring. Therefore, given the clinical features the censoring mechanism could have been independent from the time of resolution. In this case, as the resolution curves obtained from the AFT models are conditional on the clinical features, they would provide valid estimate of survival probability for the group with a given value of clinical features[92].

The second limitation of this study is that the follow-up period is two years. Hereby we preclude any estimate of later resolution. However, we believe it is unlikely that resolution would occur beyond two years postpartum. Because we found an incidence of hypertension of 18% at two years postpartum. This is comparable with other studies that showed similar proportions of women with hypertension until seven years after preeclampsia[18 24 87 96].

The third limitation of this study is that, due to the fact that our hospital is a referral center, a large proportion of women have had severe preeclampsia (89%). This may limit the ability to generalize our findings to women with mild preeclampsia.

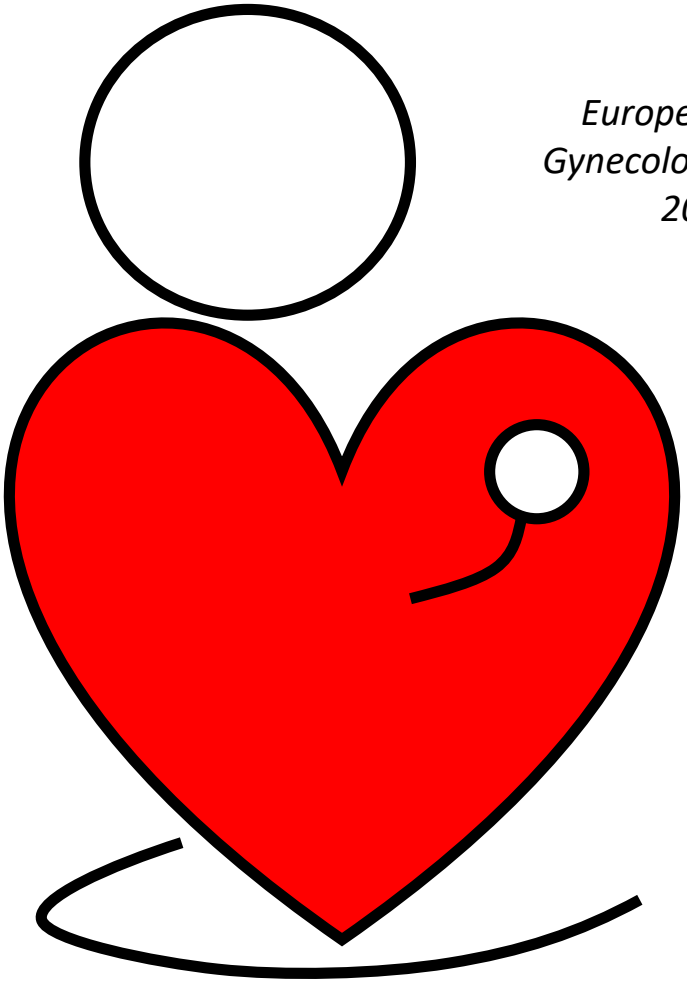
The period of recruitment of this study was 1990 to 1992 for two reasons. First, the data of this cohort had already been processed to minimize missing data. However, proper analysis had never been conducted. Recent development of the accelerated failure time model[92] made it possible to analyze the dataset as presented and quantify the effect of blood pressure, proteinuria and temporizing treatment of preeclampsia on postpartum resolution. Second, temporizing treatment was more common during the study-period, compared to current practice. This allowed a better analysis of effect of temporizing treatment on postpartum recovery, than if we had used more recent data.

Since women with a preeclamptic pregnancy are at risk for cardiovascular disease and end stage renal disease, proper follow-up after delivery is necessary. However, this is not always the case: In 2004 Samwiil et al reported that of 257

former preeclamptic women, at six weeks postpartum 6% had not had their blood pressure measured and 68% had not had their urine tested for proteinuria[97]. Hypertension, if present, must be treated. Persistent proteinuria at three months postpartum must make the physician aware of a possible underlying renal disease and necessitates evaluation by a nephrologist. However, if the level of proteinuria stays below 3 gram/day, further invasive diagnostic tests for underlying renal disease may be postponed until hypertension and/or proteinuria persist after two years postpartum. Further studies must focus on the correlation between time to resolution of hypertension and proteinuria, and remote cardiovascular risk.

Chapter 2.2

Associations between phenotypes of preeclampsia and thrombophilia



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ABSTRACT

Background Preeclampsia (PE) complicates 2-8% of all pregnancies. Studies on the association of PE with thrombophilia (TP) are conflicting. Clinical heterogeneity of the disease may be one of the explanations. The present study addresses the question whether different phenotypes of PE are associated with TP factors.

Materials and Methods We planned a retrospective cohort study. From 1985 until 2010 women with PE were offered postpartum screening for the following TP factors: anti-phospholipid antibodies (APA), APC-resistance (APC-r), protein C deficiency (PCD) and protein S deficiency (PSD), hyperhomocysteineamia (HHC), factor V Leiden (FVL) and Prothrombin gene mutation (F2M). Hospital records were used to obtain information on phenotypes of the PE and placental histology.

Results We identified 844 women with singleton pregnancies who were screened for TP factors. HELLP complicated 49% of pregnancies; IUGR complicated 61% of pregnancies. Early delivery (<34th week) occurred in 71% of pregnancies. Any TP factor was present in 29% of the women. Severe PE was associated with PSD (p=0.01). IUGR was associated with APA (p<0.01). Early onset PE was associated with APA (P=0.01). Extensive placental infarction (>10%) was associated with APA (p<0.01). Low placental weight (<5th percentile) was associated with HHC (p=0.03).

Discussion Severe and early onset PE, especially if complicated by IUGR, are associated with APA. Other phenotypes of PE, especially HELLP syndrome, were not associated with TP. We advise only to test for APA after severe, early onset PE, especially if complicated by IUGR. We suggest enough evidence is presented to justify no further studies are needed.

INTRODUCTION

Preeclampsia complicates 2-8% of all pregnancies[4]. The cause of preeclampsia has not yet been elucidated and is most probably heterogenic[4]. One possible cause is a maternal pro-thrombogenic state, leading to mal-adaptation of the spiral arteries in early pregnancy and placental thrombosis and infarction in mid- and late pregnancy[4]. A pro-thrombogenic state can be caused by inherited or acquired thrombophilia[98-100]. Maternal thrombophilia seems to be associated with preeclampsia in cohort studies. However, these results cannot be reproduced in larger prospective studies[4].

An explanation of these conflicting results might be that preeclampsia is a heterogenic disease with different phenotypes. Not only can preeclampsia be classified as mild or severe, it may also be complicated by hemolysis, elevated liver enzymes or low platelets (HELLP-syndrome) and/or intrauterine growth restriction (IUGR) and/or early onset preeclampsia. Histological examination of placentas of pregnancies complicated by preeclampsia may show extensive infarction, but also no abnormal findings at all[99]. Some authors suggest that early preeclampsia has another pathophysiological basis than late preeclampsia[101]. It might be that these different phenotypes of preeclampsia are differently associated with thrombophilia. If this is true, future research should be focused on the pathophysiology, prediction and ultimately prevention of preeclampsia in combination with these thrombophilia factors.

This retrospective cohort study addresses the question which phenotypes of preeclampsia are associated with thrombophilia.

MATERIAL AND METHODS

From 1985 until 2010 all patients with a singleton pregnancy who were admitted for mild or severe preeclampsia to the department of obstetrics of the Erasmus University Medical Center, University Medical Centre Rotterdam, were offered to be postpartum screened for thrombophilia factors. Preeclampsia was diagnosed according to the definition of the International Society for the Study of Hypertension (ISSHP). Severe preeclampsia was diagnosed if one or more of the following criteria were present: a blood pressure of 160 mmHg systolic or higher or 110 mmHg diastolic or higher proteinuria of 5 gram or more in a 24-hour urine specimen or dipstick urinalysis of 3+ or greater in two random urine samples collected at least 4 hours apart; cerebral or visual disturbances; elevated liver enzymes; thrombocytopenia; fetal growth restriction. HELLP was defined as a combination of platelet count $<100x10^9$/L, serum aspartate aminotransferase (ASAT) ≥30 U/L and serum alanine aminotransferase (ALAT) ≥30 U/L (2 SD above the mean in our hospital). Intrauterine growth restriction (IUGR) was defined as a birth weight below the 10th centile.

At least six weeks postpartum, patients were tested for: anti-cardiolipin antibodies, lupus anticoagulans, APC-ratio, levels of protein C and S, homocysteine and heterozygosity for factor V Leiden and Prothrombin gene mutation. None of the patients were using vitamin supplements during the period of testing.

The reference values for the coagulation assays were ascertained in a population of at least 40 normal male volunteers. Anti-cardiolipin antibodies were determined by enzyme-linked immunoassay (ELISA) according to the directives of Harris (normal values IgG and IgM <31 units GPL and <12 units MPL respectively). The presence of lupus anticoagulant was determined with the

diluted Prothrombin time (Recombiplastin, Instrumentation Laboratories, Italy, normal ratio < 1.20) and the activated partial thromboplastin time assay (Platelin, Organon Teknika, USA, normal value < 40 seconds). Effect of factor deficiency was eliminated by mixing 1:1 patient and normal pool plasma. Protein S (normal range 0.70-1.40 U/ml) was determined as protein S activity by a clotting assay (Diagnostica Stago, France) and as free protein S by an ELISA (Biopool, USA). Protein S deficiency is defined as an outcome of <0.70 (IU/ ml) for two assays at least 6 weeks apart without use of oral contraceptives. Protein C (normal range 0.70-1.40 U/ml) deficiency was determined by measuring protein C activity (IL Testkit ProclotTM Proclot, Instrumentation Laboratory, Italy) and protein C antigen by a house-made ELISA with the use of rabbit antihuman anti-protein C (Dako Cytomation, Denmark). Protein C deficiency is defined as an outcome of <0.70 (IU/ ml) for two assays at least 6 weeks apart.

Serum homocysteine concentrations were measured both after (an overnight) fasting and 6 hours after an oral loading dose of L- methionine (0.1 g/kg body weight). During the test the patients were given a standardized methionine-poor breakfast and lunch. EDTA-blood samples were kept on ice and plasma was separated within one hour for determination of homocysteine. Plasma total homocysteine was determined using HPLC with fluorescence detection. The patients were considered to have hyperhomocysteineamia if the fasting homocysteine concentration exceeded 15 µmol/L and/or the post-load value exceeded 45 µmol/L.

Factor V Leiden and Prothrombin gene mutation were determined by polymerase chain reaction.

Patients with an abnormal test result, except for factor V Leiden, Prothrombin gene mutation, and serum homocysteine concentrations were retested at least six weeks after the initial test. Only if the same abnormality was

confirmed a patient was considered positive for this coagulation abnormality. If a patient with an initial abnormal test result was not retested, the presence or absence of this coagulation abnormality was reported as missing.

The percentage of placental infarction was estimated by combining macroscopy and microscopy of the placenta. Placental weight was measured without umbilical cord and membranes. The percentile was calculated according to a previous study[102].

The thrombophilia factors were tested for associations. If more than one thrombophilia measurements were missing, the category 'one or more thrombophilia' was also marked as missing. The phenotypes of preeclampsia tested for associations were: HELLP syndrome, IUGR, early (<34 weeks) or late onset (≥ 34 weeks), minimal (<10%) versus extensive (≥10%) placental infarction and normal (>5th centile) versus low (≤5th centile) placental weight.

Furthermore, we did a factor analysis with a fixed 2-axis model. For this we defined 4 different subgroups with the 2 most important phenotypes of

Table 2.2.1. General characteristics (N=844); values are presented as % of the study population (n) or as median (range).

Maternal age at conception (years)	29	(17-43)
Nulliparous	74%	(627)
Gestational age at delivery (weeks)	31	(27-40)
Gestational age at onset of preeclampsia (weeks)	29	(15-40)
Severe preeclampsia	91%	(768)
HELLP syndrome	49%	(413)
Intra uterine growth restriction	61%	(512)
Eclampsia	3%	(28)
Placental abruption	4%	(30)
Birth weight (grams)	1090	(275-3720)
Birth weight percentile	3.1	(0-100)
Fetal death	14%	(116)
Information on placental histology	65%	(545)
Placental weight (grams)	235	(45-700)
Placental weight percentile	6.5	(0-100)
Placental infarction (%)	5	(0-90)

preeclampsia: IUGR and HELLP. The 4 subgroups were defined as IUGR-HELLP-, IUGR+, HELLP-, IUGR-, HELLP+ and IUGR+HELLP+. For the above mentioned 11 thrombophilia factors we used the continuous data for the analysis. If more than one sample was available, we used the result that was least abnormal.

Associations of thrombophilia factors with the different phenotypes of preeclampsia and the factor analysis were done with the statistical software package IBM SPSS Statistics Version 20 (IBM Corporation, 2011) using X^2-tests with continuity correction. Missing values were excluded for the analysis. A two-sided p-value of less than 0.05 was considered statistical significant.

RESULTS

A total of 844 women were tested for thrombophilia. The general characteristics of these patients are summarized in table 2.2.1. Placental histology was available for 545 women.

Table 2.2.2 shows the preeclampsia phenotypes and the prevalence of the thrombophilia. Overall 29% of the women had one or more abnormal thrombophilia results. Severe preeclampsia was significantly associated with a higher presence of one or more thrombophilia result (p=0.01) and with more prevalent Protein-S deficiency (p=0.01) compared to mild preeclampsia.

IUGR was significantly associated with a higher presence of one or more thrombophilia factors (p<0.01) and more prevalent anti-phospholipid antibodies (p<0.01) compared to normal grown fetuses. Early onset preeclampsia (gestational age <34weeks at delivery) was significantly associated with a higher presence of one or more thrombophilia factors (p<0.01) and more prevalent anti-phospholipid antibodies (p=0.01) compared to late preeclampsia (gestational age ≥ 34weeks at delivery). Increased placental infarction (≥ 10% of

Table 2.2.2. Prevalence of thrombophilia factors (figures presented as % (total tested in subgroup), bold and greyed numbers represent p < 0.05)

Factor	Overall	Preeclampsia severity		HELLP syndrome	
		Mild	Severe	Absent	Present
≥1 thrombophilia factor	239/740 (32.3%)	12/68 (17.6%)	227/672 (33.8%)	108/369 (29.3%)	131/371 (35.3%)
Anti-phospholipid antibodies	59/759 (7.8%)	3/72 (4.2%)	56/687 (8.2%)	27/391 (6.9%)	32/368 (8.7%)
Protein-C deficiency	6/778 (0.8%)	0/72 (0.0%)	6/706 (0.8%)	2/395 (0.5%)	4/383 (1.0%)
Protein-S deficiency	99/720 (13.8%)	2/66 (3.0%)	97/654 (14.8%)	43/354 (12.1%)	56/366 (15.3%)
APC Resistance (FVL excluded)	45/640 (7.0%)	6/56 (10.7%)	39/584 (6.7%)	20/321 (6.2%)	25/319 (7.8%)
Hyperhomocysteineamia	125/424 (29.5%)	6/30 (20.0%)	119/394 (30.2%)	51/193 (26.4%)	74/231 (32.0%)
Factor V Leiden (heterozygous)	38/807 (4.7%)	1/75 (1.3%)	37/732 (5.1%)	20/410 (4.9%)	18/397 (4.5%)
Prothrombin gene mutation (heterozygous)	25/806 (3.1%)	2/75 (2.7%)	23/731 (3.1%)	9/409 (2.2%)	16/397 (4.0%)

	IUGR		Gestational age	
	Absent	Absent	≥34 weeks	<34 weeks
≥1 thrombophilia factor	74/295 (25.1%)	163/443 (36.8%)	49/208 (23.6%)	190/532 (35.7%)
Anti-phospholipid antibodies	15/294 (5.1%)	44/463 (9.5%)	8/220 (3.6%)	51/539 (9.5%)
Protein-C deficiency	3/311 (1.0%)	3/464 (0.6%)	2/229 (0.9%)	4/549 (0.7%)
Protein-S deficiency	32/292 (11.0%)	67/425 (15.8%)	20/204 (9.8%)	79/516 (15.3%)
APC Resistance (FVL excluded)	15/246 (6.1%)	28/392 (7.1%)	12/182 (6.6%)	33/458 (7.2%)
Hyperhomocysteineamia	37/141 (26.2%)	88/283 (31.1%)	24/101 (23.8%)	101/323 (31.3%)
Factor V Leiden (heterozygous)	11/322 (3.4%)	27/482 (5.6%)	6/237 (2.5%)	32/570 (5.6%)
Prothrombin gene mutation (heterozygous)	9/321 (2.8%)	16/482 (3.3%)	4/237 (1.7%)	21/569 (3.7%)

	Placental infarction		Placental weight percentile	
	≥10%	<10%	≥10%	<10%
≥1 thrombophilia factor	120/351 (34.2%)	48/116 (41.4%)	82/217 (37.8%)	61/180 (33.9%)
Anti-phospholipid antibodies	22/353 (6.2%)	16/121 (13.2%)	16/221 (7.2%)	10/185 (5.4%)
Protein-C deficiency	3/368 (0.8%)	1/118 (0.8%)	1/230 (0.4%)	1/188 (0.5%)
Protein-S deficiency	55/336 (16.4%)	19/113 (16.8%)	42/209 (20.1%)	24/176 (13.6%)
APC Resistance (FVL excluded)	22/301 (7.3%)	6/103 (5.8%)	14/185 (7.6%)	9/159 (5.7%)
Hyperhomocysteineamia	66/200 (33.0%)	20/78 (25.6%)	28/111 (25.2%)	46/117 (39.3%)
Factor V Leiden (heterozygous)	21/380 (5.5%)	10/122 (8.2%)	12/237 (5.1%)	13/194 (6.7%)
Prothrombin gene mutation (heterozygous)	13/380 (3.4%)	6/121 (5.0%)	9/237 (3.8%)	8/193 (4.1%)

Table 2.2.3. Odds-ratios for phenotypes of preeclampsia, grey cells flag p < 0.05

Factor	Model 1	Model 2	Model 3
	IUGR without HELLP (cases = 241, controls = 190)		
One or more thrombophilia factor	2,02 (1,26-3,22)	1,87 (1,16-3,01)	1,79 (1,05-3,05)
Anti-phospholipid antibodies	1,6 (0,7-3,67)	1,43 (0,61-3,32)	0,99 (0,39-2,53)
Protein-C deficiency	0,85 (0,05-13,61)	0,98 (0,06-16,26)	2,93 (0,15-58)
Protein-S deficiency	2,21 (1,11-4,39)	2,01 (1-4,04)	1,87 (0,86-4,03)
APC Resistance (FVL excluded)	1,9 (0,71-5,07)	2,02 (0,74-5,53)	2,37 (0,8-7,01)
Hyperhomocysteineamia	1,38 (0,71-2,68)	1,46 (0,74-2,86)	1,62 (0,75-3,49)
Factor V Leiden (heterozygous)	1,58 (0,62-4,03)	1,45 (0,56-3,77)	1,16 (0,41-3,31)
Prothrombin gene mutation (heterozygous)	0,65 (0,17-2,47)	0,53 (0,13-2,13)	0,42 (0,09-1,92)
	HELLP without IUGR (cases = 138, controls = 190)		
One or more thrombophilia factor	1,54 (0,91-2,61)	1,41 (0,82-2,41)	1,39 (0,8-2,41)
Anti-phospholipid antibodies	0,92 (0,32-2,66)	0,98 (0,33-2,88)	0,82 (0,27-2,44)
Protein-C deficiency	2,81 (0,25-31,35)	2,43 (0,22-27,35)	2,22 (0,18-27,15)
Protein-S deficiency	2,06 (0,97-4,34)	1,81 (0,85-3,87)	1,97 (0,89-4,33)
APC Resistance (FVL excluded)	2,11 (0,73-6,12)	1,89 (0,64-5,55)	1,81 (0,61-5,41)
Hyperhomocysteineamia	1,5 (0,7-3,18)	1,58 (0,73-3,4)	1,68 (0,77-3,67)
Factor V Leiden (heterozygous)	0,77 (0,22-2,7)	0,68 (0,19-2,41)	0,51 (0,14-1,85)
Prothrombin gene mutation (heterozygous)	1,09 (0,29-4,14)	1,01 (0,26-3,89)	0,98 (0,25-3,87)
	HELLP and IUGR (cases = 271, controls = 190)		
One or more thrombophilia factor	2,21 (1,41-3,47)	2,05 (1,29-3,26)	2 (1,15-3,45)
Anti-phospholipid antibodies	2,16 (0,98-4,73)	2,1 (0,95-4,67)	1,15 (0,46-2,88)
Protein-C deficiency	1,45 (0,13-16,13)	1,4 (0,12-15,99)	3,11 (0,11-91,97)
Protein-S deficiency	2,17 (1,12-4,23)	1,67 (0,84-3,34)	1,92 (0,85-4,35)
APC Resistance (FVL excluded)	1,59 (0,6-4,24)	1,76 (0,64-4,83)	2,81 (0,89-8,89)
Hyperhomocysteineamia	1,63 (0,88-3,03)	1,79 (0,95-3,36)	1,9 (0,91-3,97)
Factor V Leiden (heterozygous)	1,47 (0,58-3,71)	1,41 (0,55-3,65)	0,84 (0,28-2,5)
Prothrombin gene mutation (heterozygous)	1,76 (0,61-5,07)	1,63 (0,55-4,79)	1,51 (0,43-5,25)

Controls: no IUGR and no HELLP

Model 1: crude estimates

Model 2: adjusted for maternal age at conception and nulliparous

Model 3: model 2 + adjusted for gestational age at onset of preeclampsia

total volume) was significantly associated with more prevalent anti-phospholipid antibodies ($p<0.01$) compared to normal placental infarction (< 10% of total volume). A low placental weight (≤ 5th percentile) was significantly associated with more prevalent hyperhomocysteineamia ($p=0.03$) compared to normal placental weight (> 5th percentile). HELLP was not associated with any thrombophilia. The following thrombophilia factors were not associated with any phenotype of preeclampsia: Protein-C deficiency, APC-resistance, factor V Leiden mutation and Prothrombin gene mutation.

Table 2.2.3 shows adjusted odds-ratios for thrombophilia factors if only HELLP or only IUGR is present. After adjusting for gestational age at onset of preeclampsia, correlations with IUGR disappear for Protein-S deficiency.

The factor analysis with fixed 2-axis model performed poorly, only explaining 34% of the variance in the results of thrombophilia factors.

DISCUSSION

Thrombophilia was more present if the preeclampsia was severe, combined with IUGR, a delivery before the 34th week of gestation, placental infarction was more than 10% or placental weight was lower than the 5th centile. To our knowledge this is the largest cohort-study so far, testing for the association between different phenotypes of preeclampsia and thrombophilia.

Previous studies show wide ranges in the prevalence of thrombophilia factors as shown in table 2.2.4. This is probably caused by differences in known confounders[103] like laboratory methods, chosen cut-off points to define abnormal results, definition of the presence of thrombophilia factors (one or two positive tests), timing of the testing and heterogeneity of the cases race, gestational age at delivery and preeclampsia severity.

If preeclampsia was severe, we found a higher prevalence of Protein-S deficiency. Associations disappeared when testing for the other of preeclampsia. Two previous studies also found a significant association between severe preeclampsia compared to normal controls[104 105].

If preeclampsia was accompanied with IUGR, we found a higher prevalence of anti-phospholipid antibodies. Yasuda et al[106] found similar results in 22 women with IUGR without preeclampsia, while another study did not find this association in 25 women[107]. Other studies did not perform a comparative analysis[108] or were unable to do so because of a 94% incidence of IUGR in their cohort[109].

In early preeclampsia, we found a higher prevalence of anti-phospholipid antibodies. Another study did not show a difference in anti-phospholipid antibodies in women with preeclampsia that delivered before and after the 28th gestational week[110].

In case of increased placental infarction >10% we found a higher prevalence of anti-phospholipid antibodies. No previous study tested this association.

In case of a low placental weight ≤ 5th percentile we found a higher prevalence of hyperhomocysteineamia. Only one previous study found an association between elevated homocysteine levels and placental vasculopathy[138]. One study showed an increased placental weight when folic acid supplementation was started preconceptionally[139]. Since folic acid lowers homocysteine levels, these and our results suggest that elevated homocysteine levels could impair placental growth capability.

We found no association between HELLP and any kind of thrombophilia, unlike other studies[99 105 116]. The factor analysis did not show any association in the continuous results also.

Table 2.2.4. Overview of studies on preeclampsia and thrombophilia (C= cohort study, C-C= Case-control study, PC= prospective cohort study, SR= systematic review, SPE= severe preeclampsia, MPE= mild preeclampsia, PlacPath= placental pathology, ACA= anti-cardiolipin antibodies, LAC= lupus anti-coagulans,

Study	Study-Type	Comparisons	n (PE)	AFS All	AFS ACA	AFS LAC	AFS PCD
Current	C	*	890	32.9%	9.0%	1.9%	0.7%
1995, Dekker et al[104]	C	±SPE	101		28.4%	0.0%	1.2%
2001, Many et al[111]	C	±SPE, ±IUGR, ±PlacPath	25	48.0%			
2002, Sikkema et al[99]	C-C	±PlacPath	47	68%		4%	7%
2005, Mello et al[105]	C-C	±SPE, ±MPE	402	16.7%	3.2%		
2006, Van Rijn et al[112]	C	PE±HELLP, PE±IUGR, ±28w	120	24%		0.8%	2.5%
2008, Muetze et al[113]	C	±HELLP	68				
2009, Facchinetti et al[114]	C	±SPE	60	46.7%	35%	20%	
2009, Kahn et al[115]	C-C	±PE	113				
2010, Sep et al[116]	C	PE±HELLP	75		8%	3%	0%
2010, Sep et al[116]	C	PE±HELLP	40		9%	0%	3%
Robertson 2006[117]	SR	±PE, ±IUGR	481		8.9%	9.1%	2.9%
1995, Yasuda et al[106]	PC	PE±S, ±IUGR	22			31.2%	
1998, Nagy et al[118]	C-C	±SPE	69				
1999, Kupferminc et al[119]	C-C	±SPE, ±IUGR	34				
1999, Mello et al[120]	C-C	±PE	46			2.2%	2.2%
1999, O'Shaughnessy et al[121]	C	±PE	283				
1999, Van Pampus et al[110]	C-C	±SPE, ±28w	345				
2000a, Kupferminc et al[122]	C-C	±SPE, ±MPE, ±IUGR	80				
2000b, Kupferminc et al[123]	C-C	±SPE	63	66.7%		3.2%	
2001, Alfirevic et al[107]	C-C	±SPE, ±IUGR	63			14.3%	9.5%
2001, Dreyfus et al[124]	C-C	±PE	180			3.9%	0.6%
2002, Agorastos et al[125]	C-C	±PE, ±IUGR	16				
2002, Benedetto et al[126]	C-C	±PE, PE±HELLP, PE±IUGR	111				
2002, Currie et al[127]	C-C	±SPE	48				
2002, D'Elia et al[128]	C-C	±PE	58				
Rodger 2010[129]	SR	±PE, ±IUGR	1060				
2000, Murphy et al[130]	PC	±PE, ±IUGR	12				
2004, Salomon et al[131]	PC	±PE, ±IUGR	29	34.5%			
2005, Dizon-Thownson et al[132]	PC	±PE, ±IUGR	134				
2006, Lindqvist et al[133]	PC	±PE, ±IUGR, ±33w	34				
2008, Karakantza et al[134]	PC	±PE, ±IUGR	8				
2008, Dudding et al[135]	PC	±PE, ±IUGR	243				
2008, Clark et al[136]	PC	±PE, ±IUGR	66				
2010, Silver et al[137]	PC	±PE, ±IUGR	129				

PCD= Protein-C deficiency, PSD= Protein-S deficiency, rAPC= APC-resistance, HHC= hyperhomocysteineamia, MLT= methionine loading test, FVL= factor V Leiden, PGM= Prothrombine gene mutation)

PSD	rAPC	HHC	FVL +/-, +/+	PGM +/-, +/+	Country (Ethnicity)	Special remarks
13.5%	7.1%	28.9%	5.0%	2.9%	Netherlands	91% severe PE, 2*positive = positive
24.7%	16%	17.7%			Netherlands	100% severe, FVL not yet known
					Israel	Placental parameters
13%	9%	57%	21%		Netherlands	SPE and/or IUGR <34w, 1*pos = pos
			3.2%	4.0%	Italy, 100% Caucasian	100% mild PE
1.7%	3%	17%	11%		Netherlands	100% early onset PE, 1*pos = pos; Only total thrombophilia factors compared
			16.9%	4.2%	Germany	100% HELLP
		11.7%	28.3%	20%	Italy, 100% Caucasian	60% severe PE, 2*pos = pos; Only total thrombophilia factors compared
		5.4%	14.3%	2.7%	Montreal, Canada	?% severe PE
4%			2.0%	3%	Netherlands	100% HELLP
3%			13.0%	17%	Netherlands	100% PE without HELLP
5.0%	32.1%	11.3%	7.2%%	3.5%	-	
					Japan	36% severe PE
			18.8%		Hungary, 100% Cauc	100% severe PE
			26.5%	5.9%	Israel, 44% Ashkenazi	100% severe PE
4.3%	26.1%		26.1%%		Italy, 100% Caucasian	
			5.3%		UK	
	11.3%	12.1%	6.0%		Netherlands	100% severe, 1*pos = pos
				8.8%	Israel, 96% Ashkenazi	Severe PE (n=55); PGM 9.1% Mild PE (n=25): PGM = 8.0%
7.9%			23.8%	7.9%	Israel, 25% Ashkenazi	100% Severe PE
	28.6%		1.6%		UK, 88% Caucasian	100% Severe PE
					France	35% Severe PE
			18.8%	0.0%	Greece	
			7.2%	7.2%	Italy	PE+HELLP (n=32): FVL 15.6%, PGM 6.4% PE+IUGR (n=31): FVL 9.6%, PGM 3.2%
			8.3%		Australia	100% Severe PE
			5.2%	1.7%	Italy	
			5.1%	4.0%		
			0.0%		Ireland	
					Israel	(only LAC, FVL, PGM)
			3.7%		US, 69% Cauc, 10% African Amer, 19% Hisp	
		5.9%			Sweden	
			0.0%	0.0%	Greece	
			7.0%	2.1%	Australia	
			4.7%		Scotland	
				4.7%	US, 31% Cauc, 34% African Amer, 33% Hisp	

Our study found no association between any of the preeclampsia phenotypes and factor V Leiden. Previous cohort and case-control studies showed conflicting results on the association between the occurrence of preeclampsia and factor V Leiden[105 107 113 115 116 118-120 123 125-128]. However, reported prevalence range widely from 2% to 28%. Ethnicity may explain some of this variance, next to small study groups and bias due to study design. In larger studies[110 121] as well as in prospective cohort studies (systematically review by Rodger et al[129]) prevalence ranged from 3-7%, showing no association with preeclampsia and are in line with our findings. This leaves factor V Leiden only a possible associated factor in Ashkenazi-Jews, but not in Caucasians.

We found no associations with Prothrombin gene mutations. Previous cohort and case-control studies showed conflicting results[105 113 115 116 119 122 123 125 126 128]. However, a systematic reviews of only prospective cohort studies[129], showed no associations.

We found no associations with Protein-C deficiency and (non-factor V Leiden) APC-resistance. Although the incidence in our population was very low, it confirms the findings in other studies[107 116 120 123 124 133].

This study has several limitations. Firstly, bias in patient inclusion before 2006 could not be excluded. Until 2006 mainly severe cases of preeclampsia were being screened for thrombophilia. Since 2006 screening for thrombophilia is offered to all women with preeclampsia. Secondly, placental infarction was not scored using a standardized protocol, lowering the power of the findings with regard to placental infarction. Thirdly, the tests of association we performed were numerous, causing multiple-testing. Forth, abnormality of some factors of thrombophilia had a low prevalence in this population (Protein-C), leading to a probable power-problem. On the other hand, the low prevalence indicates a low clinical value, sustaining our conclusion.

The most important strength of this study is the high number of cases, which enabled comparisons between preeclampsia phenotypes.

Overall, severe preeclampsia is associated with anti-phospholipid antibodies. This is mainly explained by the association with placental insufficiency (placental infarction and IUGR), but not with HELLP syndrome. We hypothesize that this is due to the fact that this thrombophilic factor does not act through systemic coagulation pathways, but at the placental side. Ernst et al report on the pathophysiologic mechanisms of anti-phospholipid syndrome[140]. The primary hypothesis is that anti phospholipid antibodies cause placental thrombosis, leading to placental infarction. The associations we found between anti phospholipid antibodies and placental infarctions, impaired fetal growth and deliveries before the 34th gestational week confirm this hypothesis, since the one phenotype is very likely to result from the other.

One acting mechanism might be through Beta-2GP1 molecule, present on the surface of trophoblastic cell membranes. It appears to inhibit thrombosis by reducing the conversion of Prothrombin to thrombin on platelets and inhibiting the activation of the intrinsic coagulation cascade[140]. Beta-2GP1 antibodies block the Beta-2GP1 molecule, so it can no longer inhibit thrombosis. Another acting mechanism might be the disruption of annexin V, that normally binds to the phospholipid molecules on the surface of the trophoblastic membrane, preventing thrombosis by forming a protective protein coat.

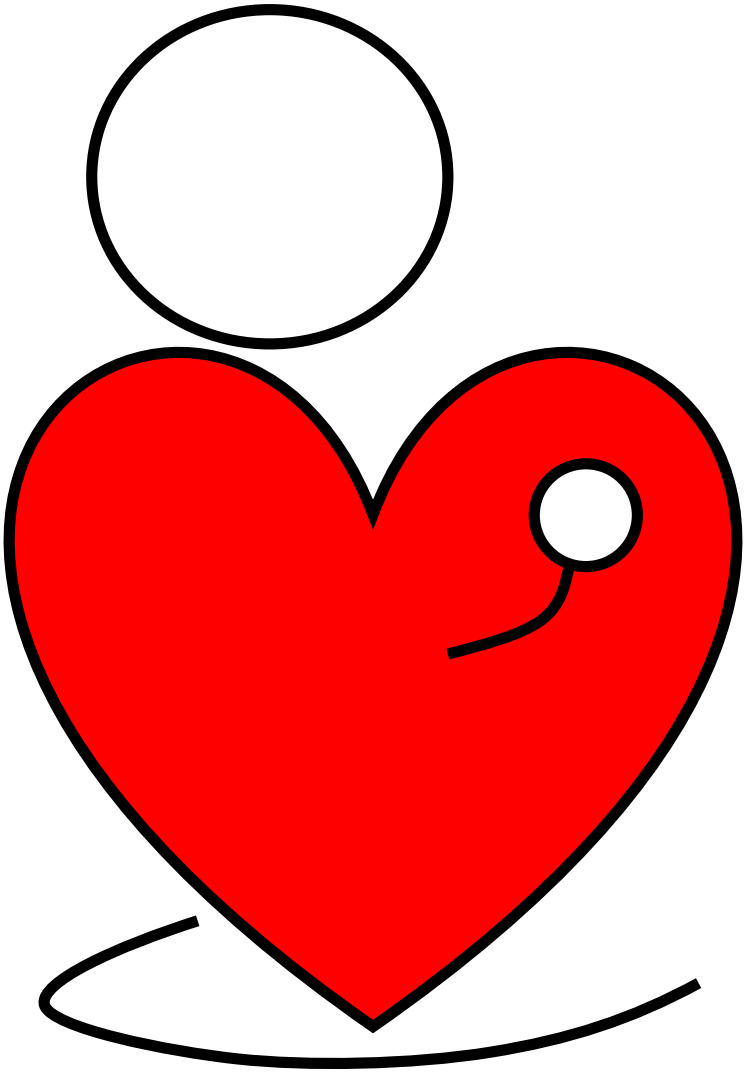
In 2012 the FRUIT-study, a randomized controlled trial studying the effect of low-molecular weight heparin on recurrence risk of preeclampsia in women with thrombophilia, suggests that if inheritable thrombophilia like Protein-S deficiency are present, administration of aspirin and low molecular weight heparin during a next pregnancy may decrease the recurrence risk[141]. Studies measuring the effect of low-molecular weight heparin on the recurrence risk of

preeclampsia in thrombophilic women with acquired thrombophilia like anti-phospholipid syndrome are currently being conducted.

In conclusion, phenotyping of preeclampsia can help to determine if screening for thrombophilia is warranted. We advise to screen for anti-phospholipid antibodies after early onset preeclampsia, especially if complicated by IUGR. We do not recommend routine screening for thrombophilia and screening after other phenotypes of preeclampsia. We suggest that enough evidence is presented to conclude that associations between preeclampsia and thrombophilia are not clinically important and further studies should not be conducted.

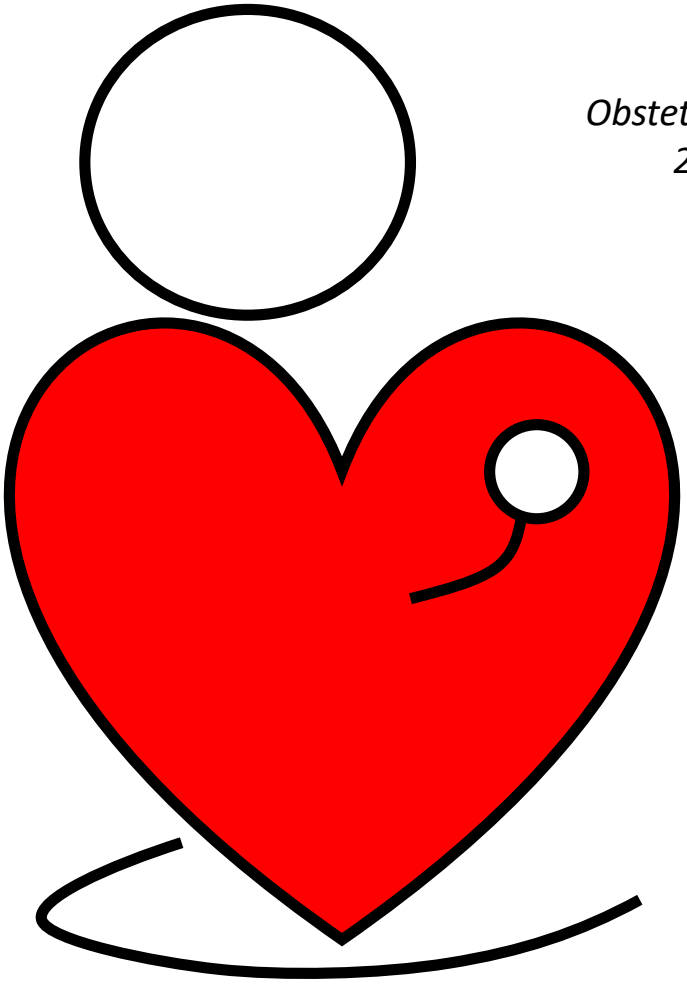
Part Three

Lifestyle intervention after cardiometabolic complicated pregnancy



Chapter 3.1

Effect of Postpartum Lifestyle Interventions on Weight Loss, Smoking Cessation, and Prevention of Smoking Relapse: A Systematic Review



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ABSTRACT

Postpartum lifestyle interventions are recommended for women after pregnancies complicated by preeclampsia, intrauterine growth restriction, and/or gestational diabetes, since they are at increased cardiovascular risk. To identify potential intervention strategies to reduce this risk, a systematic review of the literature is presented on the effectiveness of postpartum lifestyle interventions aimed at weight loss, smoking cessation, and smoking relapse prevention. The main characteristics of these postpartum lifestyle interventions are briefly described. The PubMed, Embase, Web of Science, PsychInfo, and Cinahl databases were searched for studies on the effects of postpartum lifestyle interventions on weight loss, and smoking cessation or prevention of smoking relapse, initiated for up to 1 year postpartum. No studies on the effectiveness of postpartum lifestyle interventions after the aforementioned specific pregnancy complications were found. However, 21 studies are included that describe existing postpartum lifestyle interventions, which were applied to unselected (on the basis of pregnancy complications) postpartum women. Six of 8 weight loss interventions, 4 of 5 smoking cessation interventions, and 4 of 8 smoking relapse prevention interventions were effective. Individually tailored counseling, group counseling sessions, and use of diaries or other correspondence materials were shown to be effective. Currently, postpartum lifestyle interventions tailored specifically for women who experienced the pregnancy complications are lacking. While awaiting their development, it seems reasonable to utilize existing lifestyle interventions shown to be effective in unselected postpartum women.

INTRODUCTION

Women who have experienced preeclampsia, intrauterine growth restriction, and/or gestational diabetes are at increased risk to develop cardiovascular disease later in life compared with women who did not experience these complications[1-3 10]. Women with such complications more often exhibit cardiovascular risk factors, including higher circulating concentrations of fasting insulin, increased blood pressure, increased lipids, increased body mass index, and increased insulin resistance[21 24 26 31 142-144]. It has been suggested that women who have experienced these complications during pregnancy should be screened for postpartum cardiovascular risk factors, and should be offered a postpartum lifestyle intervention to reduce future cardiovascular morbidity and mortality[24 142]. Moreover, after a pregnancy complicated by preeclampsia, intrauterine growth restriction, and/or gestational diabetes, the immediate postpartum period is considered to be a window of opportunity for preventive interventions[1]. Lifestyle interventions have been effective in ameliorating risk factors for cardiovascular disease, by promoting smoking cessation and weight loss[145 146], with substantial effects on cardiovascular risk reduction[147].

To date, however, few data are available to inform the choice of specific lifestyle interventions for promoting a healthy postpartum lifestyle after complicated pregnancy. Considering the specific challenges that women who have experienced complications face, such lifestyle interventions would ideally be tailored to the specific needs, characteristics, and preferences of these high-risk women in order to promote participation and adherence to the intervention. For example, compared with women with an uncomplicated pregnancy, women who experienced pregnancy complications more frequently experience

emergency caesarean section, preterm birth, and admission to an intensive care unit. Furthermore, in the postpartum period, women who have experienced pregnancy complications more frequently report physical symptoms (e.g., headache and fatigue)[148], cognitive difficulties (e.g., problems with concentration and memory)[149], and emotional duress[150 151]. These postpartum problems can be important barriers to the adoption of a healthy lifestyle.

In order to select an effective intervention strategy, an overview of the effects of existing postpartum lifestyle interventions is needed. Therefore, we present a systematic review of the literature on the effects of postpartum lifestyle interventions targeted at weight loss, smoking cessation, and smoking relapse prevention. The characteristics of these postpartum lifestyle interventions are also briefly described. After completion of this educational activity, physicians should be better able to counsel patients on how to apply existing postpartum intervention strategies aimed at weight loss, smoking cessation, and smoking relapse prevention to lower cardiovascular risk.

METHODS

Literature Search

A systematic review of the literature up to May 2010 was conducted using the following computerized databases: PubMed, Embase, Web of Science, PsychInfo, and Cinahl. First, these databases were searched for literature on the effects of postpartum lifestyle interventions on weight loss, smoking cessation, and the prevention of smoking relapse, with specific regard to women who experienced preeclampsia, intrauterine growth restriction, and/or gestational diabetes.

Since no articles on the effects of lifestyle interventions after these

pregnancy complications were found, a broader search, focusing on the effects of postpartum lifestyle interventions on weight loss, smoking cessation, and smoking relapse in unselected women was conducted using the following terms: puerperium or postpartum period or postpartum or postpartum and lifestyle or life style or risk reduction behavior or risk reduction behavior or health promotion or smoking cessation or weight loss or weight reduction or smoking relapse prevention. Articles retrieved from this search were copied to a reference library (EndNote) and duplicates, if any, were deleted.

Selection Procedure

First, the titles and abstracts of the retrieved articles were screened and labeled in EndNote. Articles were excluded when they were not written in the English language, when non-human research was described, when the study was not an original research article (e.g., a review article), when the study did not deal with the postpartum period, and when the study did not describe the effect of a lifestyle intervention.

Second, the full texts of the remaining articles were examined. Additionally, a manual search of the reference lists of these articles was conducted. We included original research articles describing effects of postpartum lifestyle interventions that were initiated up to 1 year after delivery. Only articles that described the effects of postpartum lifestyle interventions for weight loss, smoking cessation, and smoking relapse prevention were included, since they address the established cardiovascular risk factors of overweight/obesity and smoking. Articles on the effects of lifestyle interventions on other outcome measures (e.g., fruit and vegetable intake or physical activity) were excluded, since our focus was on the effect of lifestyle interventions for established modifiable cardiovascular risk factors only. Furthermore, studies

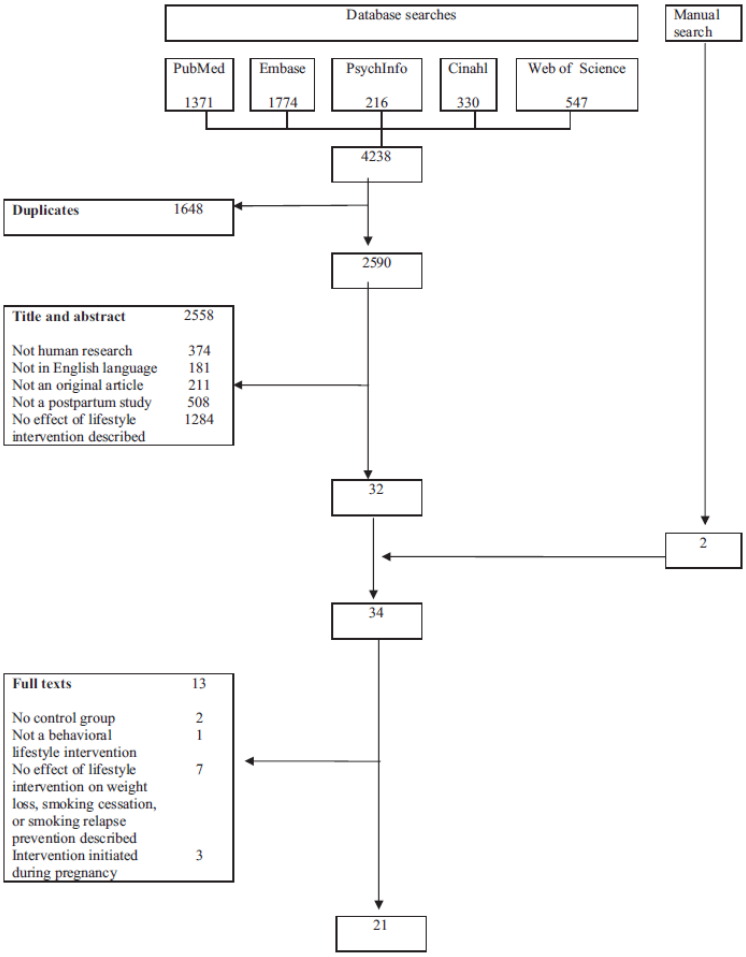
without a control group, studies that did not describe the effect of a behavioral lifestyle intervention (e.g., that described the effect of reduced nicotine cigarettes), and studies on the effect of lifestyle interventions initiated during pregnancy were also excluded.

Data Extraction

For the articles included in the present review, the following characteristics were recorded: first author and year of publication, country, study design, interventions, participant demographics, sample sizes, measurements, and the effects of the interventions in terms of weight loss, smoking cessation, and smoking relapse prevention. With regard to weight loss, reported outcome measures were mean weight loss or weight retention in kilograms (kg) at follow-up, mean weight loss per time unit, and percentage of women who returned to their pre-pregnancy weight at follow-up. With regard to smoking cessation, reported outcome measures were number of cigarettes smoked (self-reported or biochemically validated), salivary cotinine levels, self-reported and biochemically validated 7-day abstinence, 4-week point prevalence abstinence rates, quit rates, daily smoking rates, and percentages of women who reported sustained or continuous cessation. With regard to smoking relapse prevention, the following outcome measures were reported: relapse rates, percentage of nonsmokers, and percentage of women who reported sustained or continuous cessation.

All reported outcome measures in the intervention group were compared to a control group. An intervention was considered to be effective when a significant difference ($P < 0.050$ was found between the intervention and control group for the outcome measure at follow-up. Study results were also interpreted in the context of the study design. A randomized controlled trial (RCT) was

Figure 3.1.1. Diagram showing the reasons for exclusion from the review and the number of excluded articles



considered to be the preferred study design with regard to interpretation of the effectiveness of the study.

Additionally, when available, the following intervention characteristics were described: type of intervention, duration of the intervention, participant contact during the intervention (such as the number/type of contacts, e.g., face-to-face or telephone contact), by whom the intervention was delivered, type of counseling, the materials and methods used during counseling, and (when applicable) the theoretical background of the counseling.

RESULTS

Study Selection

After removal of duplicates, the searches in PubMed, Embase, Web of Science, PsychInfo, and Cinahl resulted in a total of 2590 articles. Of these, 33 full texts were examined. The manual search provided an additional 2 full texts. From the 35 full texts screened, 21 articles were suitable for inclusion in this review (Figure 3.1.1).

Data Extraction

Table 3.1.1 gives an overview of the effectiveness of the included intervention studies. Details on the effects and characteristics of interventions aimed at weight loss are given in Table 3.1.2, and those aimed at smoking cessation or smoking relapse prevention in Table 3.1.3.

Postpartum Lifestyle Interventions

Weight Loss

Tables 3.1.1 and 3.1.2 give an overview of 10 articles describing the effect of 8 lifestyle interventions on postpartum weight loss[152-161]. Of these interventions, 6 were diet and exercise interventions[153-155 157-159 161], of which 5 described statistically significant effects on weight loss[153-155 157 159 161]. In these latter studies, mean weight loss ranged from 1.9 kg[157] to 7.8 kg[154]. One study reported no significant effect on weight loss[158]; however, a positive relation was found between the number of visits attended and weight loss (P = 0.01).

Of the 2 other studies, 1 described the effect of an exercise intervention

Table 3.1.1. Summary of the Effectiveness of the Included Intervention Studies

First Author, year	Country	P
Weight loss		
Diet Intervention		
De Castro, 2009[160]	Brazil	*
Exercise intervention		
Lovelady, 1995[156] and Dewey, 1994[152]	USA	NS
Combined diet and exercise intervention		
Kinnunen, 2007[153]	USA	#
Leermakers, 1998[154]	USA	#
Lovelady, 2000[155] and Lovelady, 2006[161]	USA	*
McCrory, 1999[157]	USA	*
Ostbye, 2009[158]	USA	NS
O'Toole, 2003[159]	Finland	#
Smoking		
Smoking cessation		
Fossum, 2004[162]	Sweden	#@
Smoking relapse prevention		
French, 2007[163]	USA	#
Van 't Hof, 2000[167]	USA	NS
Johnson, 2000[164] and Ratner, 2000[165]	Canada	#$
Suplee, 2005[166]	USA	NS
Combined smoking cessation and relapse prevention		
Hannover, 2009[170]	Germany	
Smoking cessation		#
Smoking relapse prevention		NS
Roske, 2008[171]	Germany	
Smoking cessation		#
Smoking relapse prevention		#
Severson,1997[168] and Wall, 1995[169]	USA	#$
Smoking cessation		&$
Smoking relapse prevention		
Winickoff, 2010[172]	USA	NS
Smoking cessation		NS
Smoking relapse prevention		

Significance of the intervention effect *P<0.001, &P<0.01, #P<0.05, NS=Not Significant
@This study reported conflicting results: while salivary cotinine levels indicated an effect on the smoking cessation intervention, the self-reported cessation rate indicated no intervention effect.
$These interventions showed a significant intervention effect at 6 months postpartum.

only, which had no significant effect on weight loss[152 156], and 1 study described the effect of a diet intervention only, which did have a significant effect on weight loss[160].

Smoking Cessation and Smoking Relapse Prevention

Tables 3.1.1 and 3.1.3 give an overview of 11 articles describing the effect of 9 interventions on smoking cessation and smoking relapse prevention[162-172]. One article described the effect of a postpartum smoking cessation intervention only[162]. Results of this study were contradictory. Although salivary cotinine levels indicated an effect of the smoking cessation intervention, the self-reported cessation rate indicated an opposite effect[162].

Five articles described the effect of 4 postpartum smoking relapse prevention interventions[163-167]. Of the 4 smoking relapse prevention interventions, 2 showed no significant effect on smoking relapse prevention[166 167]. One smoking relapse prevention intervention was shown to be effective in preventing smoking relapse at 3 and 6 months postpartum[163]. Smoking abstinence at both 3 and 6 months postpartum was 18.2% in the intervention group compared with 5.2% in the control group. In this study, a prospective 2-group design (not an RCT) was used to evaluate intervention efficacy[163]. The other smoking relapse prevention intervention was shown to have a significant intervention effect at 6 months postpartum. Daily smoking was reported in 34% of the intervention group, compared with 48% in the control group[164 165]. However, this intervention effect was not sustained at 12 months postpartum[164 165].

Five other articles described 4 interventions aimed at both smoking cessation and smoking relapse prevention[168-172]. An intervention aimed at both smoking cessation and the prevention of smoking relapse evaluated in 2 studies

was shown to be effective in promoting smoking cessation and preventing smoking relapse at 6 months postpartum ($P < 0.01$)[169]. A 7-day abstinence rate was reported by 5.9% in the intervention group, compared with 2.7% in the control group; 45% of the intervention group reported smoking relapse compared with 55% of the control group. At 12 months postpartum, this effect was not sustained[168]. While 1 intervention demonstrated a significant effect on both smoking cessation and smoking relapse prevention at 6 months postpartum[171], another failed to show significant effects at 3 months postpartum on either outcome measures[172]. The fourth intervention reported a small effect on smoking cessation (sustained abstinence rate of 3% in the intervention group compared with 0% in the control group) and no effect on smoking relapse[170].

Characteristics of the Interventions

Of the 21 included articles, 14 were conducted in the United States[152 154-159 161 163 166-169 172] and the remaining 7 were conducted in Finland[153], Sweden[162], Canada[164 165], Brazil[160] and Germany[170 171]. Apart from 1 study that used a prospective 2-group design[163] and one that used a prospective cohort design[160], the studies were RCTs. The number of participants per study ranged from 33[152 156] to 1875[168].

Weight Loss

Of the 6 effective weight loss interventions, 5 were individually tailored[153-155 157 159 161]. The duration of these 6 effective interventions ranged from 11 days[157] to 9 months[159]. Only 1 study reported the use of a lifestyle intervention that was based on a theoretical background[153]. This latter study used the theoretical models of Laitakari and Asikainen[173], PRECEDE-PROCEED[174], and Stages of Change[175].

Table 3.1.2. Description of postpartum lifestyle interventions and their effect on weight loss

First Author, Year, Country	Study Design	Groups and Sample Sizes (n)	Participants	Follow-Up
Diet				
De Castro, 2009, Brazil[160]	Prospective cohort	High-protein (HP) diet n=261 Low-protein (LP) diet n=160	Pp women, recruited 1-3d after delivery Mean age (SD): HP: 25.5 (6.0) LP: 26.7 (5.9)	At 2, 6 and 9 mo pp
Exercise				
Lovelady, 1995, USA[156] and Dewey, 1994, USA[152]	RCT	I: Regular supervised exercise, n=18 C: Exercise restricted to once a week, n=15	Exclusively breastfeeding women, recruited 6-8weeks pp Mean age: I: 31.1 C: 29.7	At 12-14 wk pp and at 18-20 wk pp
Diet and Exercise				
Kinnunen, 2007, Finland[153]	RCT	I: Diet and physical activity, n=53 C: Usual care, n=39	Primiparas, recruited through public child health clinics at 3 mo pp Mean age (SD): I: 29.5 (3.9) C: 28.3 (4.4)	10 mo pp

Intervention Description	Mean baseline Weight in kg (SD)	Weight Loss
High-protein (HP) diet: protein intake above or equal to 1.2 g per kg per day of body weight. Low-protein (LP) diet: protein intake below 1.2 g per kg per day of body weight.	HP: 59.4 (10.4) LP: 67.9 (11.6)	At 6 mo pp, women with and HP diet lost more body weight than women with an LP diet 1.69 (3.7) vs 0.77 (4.3) kg (p=0.08). Mean difference in body weight loss form baseline to 9 mo pp between the HP and LP groups was 0.84 kg (p=0.17). Women with an HP diet lost more (324 [0.06] g) per mo than women with a LP diet (P<0.00001).
Regular supervised aerobic exercise (at a level of 60%-70% of the heart rate reserve) for 45 min/d, 5d/wk for 12 wk. Individually tailored exercise sessions. The program began with 20-min sessions, with 5-min increments every 3 d until the woman could complete 45 min of continuous exercise at the target heart rate.	I: 67.3 C: 67.0	At 12-14wk pp, women in the intervention group lost 0.60 kg, while women in the control group lost 1.00 kg. At 18-20 wk pp both women in the intervention group and in the control group had lost 1.60 kg Differences between the intervention group and the control group at both time points were NS.
Individual counseling on diet and physical activity delivered by a public health nurse. Five visits at 2, 3, 5, 6, and 10 mo pp. Counseling was based on the theoretical models of Laitakari and Asikainen[173], PRECEDE-PROCEED[174] and Stages of Change[175]. Individual physical activity counseling consisted of one primary counseling session (20-30 min) at the 2 mo pp and 4 booster sessions (10-15 min) at 3, 5, 6 and 10 mo pp. An individual weekly physical activity plan was composed, adherence to this plan was assessed and the plan was revised if needed. Also: option to attend supervised group exercise sessions, developed specifically for pp women, held once a week for 45-60 min. The dietary counseling consisted of one primary counseling session (20-30 min) at 3 mo pp and 3 booster sessions (10 min) at 5, 6 and 10 mo pp. After comparing the personal habits to the recommendations, the public health nurse and the participant discussed the need for dietary changes, as	I: 67.1 (11.1) C: (64.7 (7.8) Weight retention (kg): I: 4.3 (4.0) C: 4.2 (3.9)	Of the women in the I group, 50% (n=23) returned to their pre-pregnancy weight at follow-up (weight retention ≤ 0 kg), while 30% (n=11) of the women in the C group did (p=0.06). OR 3.89 (95% CI: 1.16-13.04, p=0.03). Mean weight retention in the I group (1.8 [4.3] kg) was not significantly different from weight retention in the C group (1.0 [4.4] kg)

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Table 3.1.2. *Continued*

First Author, Year, Country	Study Design	Groups and Sample Sizes (n)	Participants	Follow-Up
Leermakers, 1998, USA[154]	RCT	I: Behavioral weight loss intervention, n=47 C: no treatment, n=43	3-12mo pp non-lactating women, exceeded pre-pregnancy weight by at least 6.8 kg; BMI ≥ 22 Mean age (SD): I: 32.4 (4.5) C: 30.3 (5.6)	Directly after end at 6 mo
Lovelady, 2000, USA[155]	RCT	I: diet and exercise, n=21 C: no intervention, n=19	Breastfeeding women, overweight (BMI 25-30) recruited at 4 wk pp Mean age (SD): I: 31 (4) C: 33 (4)	14 wk pp

Intervention Description	Mean baseline Weight in kg (SD)	Weight Loss
well as opportunities for and barriers to making the changes. Also received two take home leaflets on healthy diet. Weekly record of compliance with the individual objectives was kept.		
Diet: consisting of 1000-1500 kcal/d, with fat restricted to 20% of caloric intake. Physical activity: Aerobic exercise program: gradually increasing the frequency and duration of walking, until 2 miles/d on at least 5d/wk was reached. Consistent with guidelines of all adults, American College of Sports Medicine (ACSM)[187]. Included 3 components: (1) Two group sessions (at beginning and at 2 mo). Discussion of eating and exercise progress and problem solving. (2) Correspondence materials. Consisted of 16 written lessons about nutrition, exercise and behavior change strategies. These lessons were sent weekly for the first 12 wk, biweekly for the next 4 wk and monthly for the last 8 wk. Women were asked to monitor their calorie and fat intake and their exercise on a daily basis throughout the 6-mo program and return their record by mail. Behavioral lessons, which focused on strategies to modify diet and exercise behaviors, were tailored to the special needs of the new mothers. Each lesson included a 1 to 2-page homework assignment, which was to be completed and returned with the self-monitoring diaries. (3) Brief telephone contacts, 5-15 min, weekly or biweekly, depending on the participants' desires and needs. The discussions focused on eating and exercise progress, goal setting and problem solving.	I: 78.7 (11.2) C: 82.9 (15.2)	Weight loss among women in the I group (7.8 kg) differed significantly form weight loss in the C group (4.9 kg) at follow-up (p=0.03). Significantly more women in the I group (33%) returned to their pre-pregnancy weight at follow-up than women in the control group (11.5%) (p<0.05).
Diet: 500 kcal fewer than daily energy requirements. Diet prescription: 25% of energy from fat, 20% from protein, 55% from carbohydrate, with no less than 1800 kcal (7531 kJ) total per day. Trained graduate research assistants used the Food Guide Pyramid[188] to meet dietary recommendations. Food models were used to demonstrate portion size. Cognitive and behavioral strategies were discussed at individual weekly sessions. Six low-fat, low-calorie frozen dinners were provided each week. Exercise: brisk walking, jogging, or aerobic dancing at 65-80% of maximum	I: 75.9 (9.3) C:76.8 (7.8)	Women in the intervention group lost significantly more weight (4.8 [1.7] kg) than women in the control group (0.8 [2.3] kg), (p<0.001)

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Table 3.1.2. *Continued*

First Author, Year, Country	Study Design	Groups and Sample Sizes (n)	Participants	Follow-Up
Lovelady, 2006, USA[161]	RCT	I: diet and exercise, n=19 C: no intervention, n=16	Breastfeeding women, overweight (BMI 25-30) recruited at 4 wk pp	14 wk pp
McCrory, 1999, USA[157]	RCT	Diet (D): n=22 Diet and exercise (D+E): n=22 C: n=23	Exclusively breastfeeding women, recruited at 12 (4) wk pp Mean age (SD): 32 (5)	At 12 (4) wk pp + 11 d
Ostbye, 2009, USA[158]	RCT	I: n=225 C: n=225	Overweight or obese women BMI ≥25, recruited at 6 wk pp. Mean age (SD): I: 30.6 (5.8) C: 31.2 (5.3)	1 mo after end at 12 mo pp

Intervention Description	Mean baseline Weight in kg (SD)	Weight Loss
heart rate 4 times per week during 10 wk. Initial exercise session 15 min. The following sessions increased by 2 min/d until women were exercising with their target heart rate for 45 min.		
Same as Lovelady, 2000[155]	I: 75.9 (9.8) C: 77.2 (8.3)	Women in the intervention group lost significantly more weight (4.8 [1.6] kg) than women in the control group (0.8 [1.8] kg), (p<0.001)
D: Aimed at 35% energy deficit. Diets were individually tailored and food was provided in preweighted amounts. D+E: Aimed at 35% net energy deficit, 60% by dietary restriction and 40% by additional exercise. Exercise was prescribed in terms of a target heart rate range (50%-70% of maximal heart rate) and total time. Exercise sessions were self-supervised. Energy expended in exercise (based on heart rate monitoring) was checked every 1-3d during the intervention period, and the prescription was adjusted as necessary. C: Asked to maintain their weight during the intervention by maintaining their usual diet and activity patterns.	D: 68.3 (10.2) D+E: 69.0 (12.8) C: 68.5 (8.5)	Women in the D group had lost 1.9 kg, and women in the D+E group lost 1.9 kg at follow-up, while the women in the C group had lost 0.2 kg (p < 0.00001)
Diet: Eight healthy-eating classes to reduce total caloric intake, increase in fruit and vegetable consumption. In the classes, women were taught practical skills shown to facilitate weight loss, including making choices that decrease consumption of high-fat, high-sugar foods and beverages; learning appropriate portion sizes; cooking easy, low-fat meals; making appropriate choices at fast-food restaurants; and avoiding over-eating in stressful situations. Participants were provided with a study notebook with exercises and recipes. Ten physical activity classes: increasing physical activity to the recommended 30 min a day, 5 times a wk. Counseling sessions by a trained counselor: every 6 wk, lasting 20 min each, delivered primary over the phone, but occasionally in person. Consistent with motivational interviewing, the counselor utilized reflective listening techniques, self-motivational statements, and change talk to elicit participants' personal behavioral goals and troubleshoot barriers to achieving them. Participants	I: 88.7 (18.8) C: 88.4 (18.5)	Mean weight at follow-up in I group was 87.8(20.7) kg, and in the C-group 88.1 (20.2) kg. Mean weight loss was 0.9 (5.1) kg in the I group and 0.4 (4.9) kg in the C group; this difference was NS. There was a positive association between classes attended and weight loss (p=0.01). There were no significant differences between the 2 groups in other measures of weight change, including return to pre-pregnancy weight and percent weight loss.

Continues on next page

Table 3.1.2. *Continued*

First Author, Year, Country	Study Design	Groups and Sample Sizes (n)	Participants	Follow-Up
O'Toole, 2003, USA[159]	RCT	I: Structured diet and physical activity C: Self-directed diet and physical activity, n=40	6 wk-6 mo pp overweight women Mean time since delivery (SD): I: 12 (5) wk C: 14 (4) wk Mean age (SD): I: 30.8 (4.2) C: 32.2 (4.9)	At 1 yr pp

Pp = postpartum; BMI = Body mass index; kg = Kilo grams; I = Intervention group; C = Control group; SD = Standard deviation; NS = Not significant; RCT = Randomized controlled trial; min = Minute(s); d = Day(s); wk = Week(s); mo = Month(s); yr = Year(s)

Intervention Description	Mean baseline Weight in kg (SD)	Weight Loss
received a pedometer and a sport stroller. Control: biweekly newsletter with general tips for pp mothers.		
Diet: individualized from baseline measurement by a dietician to a deficit of at least 350 kcal/d. Exercise: individualized physical activity prescriptions from baseline measurement by an exercise physiologist to increase energy expenditure by at least 150 kcal/day. Kept daily food and activity diaries and met for group educational sessions dealing with nutrition and physical activity strategies. Group sessions: weekly for the first 12 wk, biweekly for the following 2 mo, monthly thereafter until 1 yr pp. Self-directed intervention: met individually with a dietician and exercise physiologist for a single 1-h educational session about diet and physical activity. Received copies of the American Dietetic Association Brochure Nutrition and Health for women[189], and the Food Guide Pyramid[188]. Also received copies of the ACOG brochure Exercise and Fitness: A Guide for Women[190].	I: 78.6 (1.6) C: 85.4 (3.5)	After 12 wk of intervention, women on the I group had lost 5.6 kg, and women on the C group had lost 0.6 kg ($p<0.05$). After 1 yr pp, women in the I group had lost 7.3 kg, while women in the C group had lost 1.3 kg ($p<0.05$).

Table 3.1.3. Description of postpartum lifestyle interventions and their effect on smoking cessation and smoking relapse

First Author, Year, Country	Study Design	Groups and Sample Sizes (n)	Participants	Follow-Up
Smoking cessation				
Fossum, 2004, Sweden[162]	RCT	I: "smoke-free children" counseling, n=26 C: Usual care, n=15	Smoking mothers, recruited 0-4 wk pp at child health center	At 3 mo pp
Smoking relapse prevention				
French, 2007, USA[163]	Prospective 2-group design	I: brief intervention, n=122 C: Usual care, n=97	Women who had quit smoking during their pregnancy, and at least 7 d before deliver. Recruited during pp hospitalization.	
Van 't Hof, 2000, USA[167]	RCT	I: relapse prevention, n=141 C: Usual care, n=146	Smoking during the 30 d before pregnancy and quit during pregnancy	At 6 mo pp

Intervention Description	Baseline values	Weight Loss
Counseling method "Smoke-free children" developed by Swedish child centers[191]. Based upon a client-centered approach. Based on the principles developed by Greenberg et al[192]. Delivered by a child health nurse. Contacts at child health centers. Aimed at increasing self-efficacy. Five key elements: (1) asking what the mothers themselves know about the effects of smoking on children. (2) suggesting to the mothers that they register how much tobacco smoke there is in the child's proximity. (3) discussing the results of the mothers' survey and asking what they think about present smoking habits and whether they heave suggestions about possible changes. (4) supporting any attempt they might carry out to change smoking habits and discussing problems that may emerge. (5) supporting women who have stopped smoking during pregnancy to continue to refrain from smoking.	Self-reported number of cigarettes: I: 13.1 (6.5) C: 10.8 (5.7) Biochemically validated number of cigarettes: I: 12.7 (6.6), n=22 C: 8.4 (3.9), n=8 Mean cotinine level: I: 185 ng/mL C: 245 ng/mL	In the I group, the number of self-reported cigarettes smoked was reduced with 0.3 at follow-up, compared to 2.6 in the C group ($p<0.05$). Mothers reported more smoking in the I group than in the C group. When biochemically validated, the number of cigarettes smoked in the I group increased with 0.2, while the number of smoked cigarettes in the C group decreased with 1.3 however, salivary cotinine levels indicated a decrease of 20 ng/mL cotinine in the I group compared to a n increase of 101 ng/mL in the C group ($p=0.03$). Weak correlations between self-reported smoking and cotinine-levels were found.
Home visiting program during hospitalization (5 min), home visit at 1 wk pp (15 min) and 2 follow-up telephone calls or home visits (15 min). Delivered by a nurse. Based on the principles of motivational interviewing[193 194], Use of the US public health service clinical practice guideline: 5A's[177 178]. Use of the 5 A's of asking if the women smoked, advising her to quit, assessing her willingness to quit, assisting her in quitting and arranging a follow-up. Topics included: relapse prevention, stress management, skills building, trigger avoidance, relapse rehearsal, pp depression. 4-part intervention: pp hospitalization: brief intervention (congratulations and encouragement) home visit at 1 wk pp (smokers: 5A's, non-smokers: encouragement and further problem solving) and 2 follow-up telephone calls or home visits (same status-dependent content).	All women had quit smoking during pregnancy: 100% abstinence	Smoking abstinence at 3 mo pp was 26.4% in the I group, compared to 12.4% in the C group (OR 2.4, 95% CI 1.16-4.98). Smoking abstinence at 6 mo pp was 21.5% in the I group compared to 10.2% in the C group (OR 2.5, 95% CI 1.13-5.71). Smoking abstinence at both 3 and 6 mo pp was 18.2% in the I group compared to 5.2% in the C group (OR 2.4, 95% CI 1.16-4.93). Biochemically verified (salivary cotinine level < 14 ng/mL).
Counseling delivered by nurse and the pediatric provider: during the hospital stay (15-30 min), 2wk pp and at 2 "well baby" visits (2 and 4 mo pp). The nurse delivered counseling during the first visit, the pediatric	287 quitters	41% of the women in the I group relapsed to smoking (any smoking during the last 7 d), compared to 37% of the women in the C group

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Table 3.1.3. *Continued*

First Author, Year, Country	Study Design	Groups and Sample Sizes (n)	Participants	Follow-Up
Johnson, 2000, Canada[164]	RCT	I: brief in-hospital intervention C: Usual care, n=254	Recruited while admitted to hospital for delivery. Stopped smoking at least 6 wk before delivery. Age 15-40 yr	At 3 and 6 mo pp
Ratner, 2000, Canada[165]	RCT	n=251		At 12 mo pp
Suplee, 2005, USA[166]	RCT	I: counseling C: no intervention, n=62	Enrollment during pregnancy, smoking cessation during pregnancy. Mean age: 22.6, range 14-45 yr	At 4-8 wk pp

Intervention Description	Baseline values	Weight Loss
provider delivered counseling during the other 3 visits. Counseling about reason for maintaining cessation and help in developing a plan for doing so. Reinforcement if they quit and if not, given encouragement and a plan to try to quit again.		(NS). Biochemically validated with cotinine.
Face-to-face in-hospital counseling sessions at birth, followed by 8 telephone follow-up sessions, home visits, or face-to-face visits outside the home during the first 3 mo pp. Delivered by a nurse. Sessions were weekly during the first mo pp and biweekly during the second and third mo pp. Counseling based on principles derived from Marlatt's relapse model[176 180]. Aim counseling: teaching women to identify high-risk situations for smoking relapse and determining strategies to manage those situations, thereby strengthening their smoking cessation self-efficacy. The nurse supported efforts to maintain smoking abstinence, reviewing high-risk situations encountered and reviewed the lessons learned from any relapses. Supplemented with written materials.	All women had stopped smoking during pregnancy. 100% abstinence.	Continuous abstinence rate at 3 and 6 mo pp was 38% in the I group, compared to 27% in the C group. OR 1.63, 95% CI 0.96-2.78. At 6 mo pp, daily smoking was reported in 34% of the I group, compared to 48% of the C group, OR 1.80, 95% CI 108-2.99. Validated with CO in expired air.
		At 12 mo, daily smoking was 41.2% in the I group and 50.4% in the C group, OR 1.45, 95% CI 0.87-2.43. Continuous abstinence rate at 6 and 12 mo pp was 12% in the I group and 18.5% in the C group, OR 1.17, 95% CI 0.62-2.22. Significant intervention effect at 6 mo was not sustained at 12 mo pp.
One brief (10-20 min) counseling session provided during the immediate pp hospitalization in the participants' hospital room, delivered by a researcher. Using empowerment techniques, motivational interviewing[193 194], identification of stressors and individual coping strategies, and educational material. Personal Rulers Worksheet[61], Marlatt and Gordon's relapse prevention model[176 180]. The participant received 4 different educational brochures developed by the American Lung Association and Agency for Health Care Policy and Research.	All non-smoking	Relapse rate in the I group was 63%, compared to 75% in the C group (NS). Quit rate in the I group was 37%, compared to 25% in the C group (NS).

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Table 3.1.3. *Continued*

First Author, Year, Country	Study Design	Groups and Sample Sizes (n)	Participants	Follow-Up
Smoking cessation and smoking relapse prevention				
Hannover,2009,Germany[170]	RCT	I: smoking cessation and relapse prevention, n=299 C: Usual care, n=345	Pp women who smoked prior to or in pregnancy and who had quit no longer than 4 wk prior to pregnancy. Recruited directly after birth in maternity wards. Mean age (SD): I: 26.2 (5.7) C: 26.0 (5.4)	At 6, 12, 18 and 24 mo pp
Roske, 2008, Germany[171]	RCT	I: smoking cessation and relapse prevention, n=239 C: n=272	Pp women who had smoked before pregnancy. Recruited at the time of giving birth. Mean age (SD): I: 26.7 (2.7) C: 26.0 (5.4)	At 4 wk, 6 mo and 12 mo pp
Severson, 1997, USA[168]	RCT (MOMS-study)	Smokers: I: n=1073 C: n=802 Quitters: I: n=609 C: n=417	Enrollment at 10-14 d pp Smoking 1 mo prior to becoming pregnant	At 12 mo pp

Intervention Description	Baseline values	Weight Loss
I: face-to-face counseling 40 d pp plus telephone counseling calls 4 and 12 wk later. Motivational interviewing[193 194] and relapse prevention[176] served as principles for the intervention. Counseling incorporated: information on the health effects of smoking and environmental tobacco smoke, balancing of the pros and cons of smoking, self-efficacy for behavioral change, reflecting previous, observed or imagined behavioral changes, exploring high-risk situations and relapse prevention strategies and the abstinence violation effect. C: usual care plus self-help material for each parent.	Median = 35 d pp Smokers: I: n=151 (51%) C: n=187 (54%) Mean number of cigarettes per day (SD): I: 11.6 (6.9) C: 11.8 (7.5)	With regard to smoking cessation, 4 wk point prevalence abstinence rates were higher in the I group compared to the C group at 6, 12 and 18 mo (7% vs 1%, 7% vs 2% and 9% vs 1% respectively), p<0.05. Sustained abstinence was higher in the I group at 6 mo follow-up (3% vs 0%), p<0.05. Small effect with regard to smoking cessation. No effect with regard to relapse prevention.
I: home counseling sessions 4-6wk pp and 2 telephone counseling sessions 4 and 12 wk later. The counseling was conducted by 4 trained study co-workers. It was based on the principles of motivational interviewing[193 194] and tailored to the motivation stage of change. Both the I and C group received: a self-help manual addressing maternal smoking, smoking cessation and relapse prevention; and a manual addressing the partner of the participating women.	Non-smokers: I: n=134 (56.1%) C: n=145 (53.3%)	Women in the I group were significantly more likely to be non-smokers 6 mo after the intervention (p<0.05). Membership in the I group significantly predicted non-smoking at 6 mo, but no 1 yr pp, after controlling for demographic, smoking and pp risk variables.
Same intervention as Wall[169]	Smokers: n=1875 Quitters: n=1026	Smokers: at 12 mo pp 5.5% of the women in the I group reported to have quit smoking, vs. 4.7% of the women in the C group (NS). Continuous quit at both 6 and 12 mo pp was 2.3% in the I group and 1.2% in the C group (p<0.05). However, no effect was found on sustained quitting (OR 1.78, 95% CI 0.84-3.74). Quitters: at 12 mo pp 42.9% in the I group reported to still have quit, vs. 39.1% in the C group. (NS). Continuous quit at both 6 and 12 mo pp was 32.8% in the I group and 26.1% in the C group (p<0.05). No intervention effect was found on sustained quitting (OR 1.25, 95% CI 0.93-1.68). The effect of the intervention at 6 mo pp was reduced at 12 mo pp.

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Table 3.1.3. *Continued*

First Author, Year, Country	Study Design	Groups and Sample Sizes (n)	Participants	Follow-Up
Wall, 1995, USA[169]	RCT (MOMS-study)	I: extended intervention, smokers n=842; quitters n=514 C: minimal intervention, smokers n=636; quitters n=344	Enrollment at 10-14 d pp Smoking 1 mo prior to becoming pregnant	At end at 6 mo pp
Winickoff, 2010, USA[172]	RCT	I: n=42 (32 women) C: Usual care, n=53 (35 women)	Parents (both fathers and mothers) who were current smokers (1 cigarette, even a puff, in past 30 d) or recent quitters (smoked since 1 mo before conception) Recruited directly pp Median age: I: 28 C: 30	At 3 mo pp

Pp = postpartum; BMI = Body mass index; kg = Kilo grams; I = Intervention group; C = Control group; SD = Standard deviation; NS = Not significant; PC = Prospective cohort; RCT = Randomized controlled trial; min = Minute(s); d = Day(s); wk = Week(s); mo = Month(s); yr = Year(s)

Intervention Description	Baseline values	Weight Loss
Pediatric office-based smoking intervention, delivered by a pediatrician. Implemented during 'well baby' office visits at 2 wk, 2, 4 and 6 mo pp. Duration of counseling 1-2 min. Hospital packet containing written information about passive smoking and a letter advising them to quit + oral and written advice. Content of advice: adverse health effects of passive smoking, hints for quit strategies, role modeling and a letter to the fathers. Videotape: potential health effects of passive smoking, benefits of quitting. Brief discussion about amount smoked, barriers to quitting and results of past quit attempts. Smokers were asked whether they were willing to set a quit date. If mothers expressed a willingness to set a quit date, they were given the Freedom From Smoking materials developed by the American Lung Association and a list of local resources for assistance in quitting. They were encouraged to follow through and a project quit kit was distributed. Quitters were encouraged to stay quit.	Smokers: n=1478 Quitters: n=858	Smokers: at 6 mo pp, 5,9% of the women in the I group reported a 7-d abstinence compared to 2.7% of the women in the C group ($p<0.01$). OR 1.82, 95% CI 1.02-3.25. Quitters: At 6 mo pp, 45% of the I group reported smoking relapse, compared to 55% in the C group, OR 1.56, 95% CI 1.16-2.10.
I: one 15-min in-person counseling session delivered by trained study staff working from adapted materials and messages specifically tailored for parental smokers (available at: www.ceasetabacco.org); offer of enrollment in a proactive state-of-the-art telephone counseling session (QuitWorks, the Massachusetts statewide quitline) and letters faxed to the newborn's pediatrician, parents' primary care provider and mothers' obstetrician indicating the parents' tobacco use status and their readiness to quit and recommending useful strategies to facilitate parental cessation, the need for ongoing support and medication prescription when appropriate. The overall strategy was based on the 5A model[177 178] and tailored to the circumstances of the parental smoker in the hospital setting when their child is hospitalized.	Smokers: I: 69% (63% female) C: 62% (54% female) Median number of cigarettes per d: I: 4.4 C: 5.0	At 3 mo postpartum self-reported 7-d point abstinence decreased from 31% to 25% among I parents vs 38% to 23% among C subjects (effect size 9.4%, NS). Among current smokers at baseline who were reached at follow-up (n=36), self-reported cotinine-confirmed 7-d abstinence rates at follow-up were 9% in the I group and 3% in the C group (NS). Among mothers who were smokers at baseline, 10% in the I group and 5% in the C group self-reported 7-d abstinence at the 3 mo follow-up (NS).

Participants were recruited as early as 1 day after delivery[160] and up to 12 months postpartum[154]. Of the 6 effective intervention studies, 5 had specific participant inclusion criteria: 1 intervention included exclusively breast-feeding women[157], 2 interventions recruited breast-feeding, overweight women[155 161], 1 intervention included non-breast-feeding, overweight women[154], and another intervention included overweight women irrespective of breast-feeding[159].

Effective diet interventions consisted of a high-protein diet[160], group sessions[154 159], correspondence materials (e.g., homework assignments)[154], telephone contact[154], food diaries[154 159], and individual counseling sessions[153 161]. In some interventions, food was provided in preweighed amounts[155 157 161]. Diet interventions were delivered by a dietician[159], a public health nurse[153], or a trained graduate research assistant[161].

Effective physical activity interventions consisted of self-supervised exercise sessions[157], an aerobic exercise program[154], an individualized activity plan[159], correspondence materials[154], telephone contact[154], physical activity diaries[154 159], individual counseling sessions[153] and individualized exercise sessions[161]. Physical activity interventions were delivered by an exercise physiologist[159], a public health nurse[153], or a research assistant[161].

Smoking Cessation and Smoking Relapse Prevention

A smoking cessation and smoking relapse prevention intervention that was found effective was office-based, delivered by a pediatrician, and implemented during 4 routine "well baby" office visits (from 2 weeks to 6 months postpartum)[168 169]. This intervention consisted of a hospital packet (containing written information about passive smoking and a letter advising women to quit), a videotape, and a brief discussion. Another effective intervention consisted of a home counseling session and 2 telephone counseling sessions, and was based

on the principles of motivational interviewing and motivational stages of change[171]. A third smoking cessation and smoking relapse prevention intervention that was shown to be effective in smoking cessation, but not in preventing smoking relapse, consisted of face-to-face and telephone counseling sessions based on the principles of motivational interviewing and relapse prevention[170].

One effective smoking relapse prevention intervention consisted of 9 contacts during 3 months: one face-to face counseling session at birth followed by 8 telephone counseling sessions or home visits delivered by a nurse[164 165]. This intervention was based on Marlatt's relapse model[176]. Another effective smoking relapse prevention intervention was also delivered by a nurse, and consisted of 4 home visits or telephone contacts over 2 months[163]. This intervention was based on the principles of motivational interviewing, and the "5As"[177 178]. Motivational interviewing is a directive patient-centered counseling technique that aims to promote intrinsic motivation for behavior change[179]. The "5As" refer to asking if the women smoked, advising her to quit, assessing her willingness to quit, assisting her in quitting, and arranging a follow-up.

The smoking cessation intervention that reported conflicting results was based on a client-centered approach and aimed at increasing self-efficacy[162]. It was delivered by a child health nurse.

DISCUSSION

This extensive literature search identified existing postpartum lifestyle interventions that were shown to be effective in lowering cardiovascular risk factors in general populations of postpartum women. Although the immediate postpartum period after a pregnancy complicated with pre-eclampsia,

intrauterine growth restriction, and/or gestational diabetes is considered to be a window of opportunity for preventive interventions, no studies were identified which have specifically examined the effects of postpartum lifestyle interventions among women with such complications. Whether the interventions aimed at general populations of postpartum women identified in our present study will also be effective in women who have experienced complicated pregnancies should be the subject of further research. Awaiting the results of such future studies, utilization of lifestyle interventions that have been shown to be effective in postpartum women in general should be considered for use in women who have experienced complicated pregnancies.

Specifically, the current review suggests that individually tailored postpartum weight loss interventions with both a diet and an exercise component might be used, since 5 out of the 6 interventions included in this review were effective. Group sessions, correspondence materials, telephone contact, food diaries, or individual counseling sessions may be effective in improving postpartum diet. Self-supervised exercise sessions, an aerobic exercise program, an individualized activity plan, correspondence materials, telephone contact, activity diaries, and counseling sessions could be used to promote postpartum physical activity. Home visits, face-to-face counseling, and telephone counseling, might be used to promote postpartum smoking cessation and prevent smoking relapse.

Furthermore, the results of this literature study suggest that a theoretical background can be used to develop postpartum lifestyle interventions. For example, the theoretical models of Laitakari and Asikainen[173], Precede-Proceed[174], and Stages of Change[175] might be used in the development of weight loss interventions. Smoking cessation and smoking relapse prevention interventions could be based on the principles of motivational interviewing (49),

the "5As"[177 178], and Marlatt's relapse model[176 180]. However, a theoretical framework that takes into account the context of the lives of women after pregnancies complicated by preeclampsia, intrauterine growth restriction, and/or gestational diabetes may more specifically contribute to the development of effective interventions to reduce cardiovascular risk in these women (56). To our knowledge, such a theoretical framework has not yet been described.

Besides the interventions identified in his study, the results of other research, such as research on lifestyle and related factors among women with a recent pregnancy complicated by gestational diabetes, could also provide useful information to be taken into account when developing effective interventions for women who experience a complicated pregnancy[181-185]. For example, lack of time and childcare duties have been identified as barriers to physical activity, suggesting that interventions should preferably be delivered at variable hours and should entail minimal travel time. Also, involvement of family (e.g., to provide child care) is suggested to enhance participation.

To our knowledge, only 1 study has explored the needs, ideas, and opinions of women who have experienced preeclampsia, intrauterine growth restriction, and/or gestational diabetes as they relate to postpartum lifestyle counseling[186]. This study showed that these women do perceive a need for postpartum lifestyle counseling and prefer to receive a combination of face-to-face personal counseling, supported by computer-tailored lifestyle advice offered on the internet[186].

Methodological Considerations/Limitations

Although the most relevant articles on the effectiveness of postpartum lifestyle interventions are probably in the English language, relevant non-English

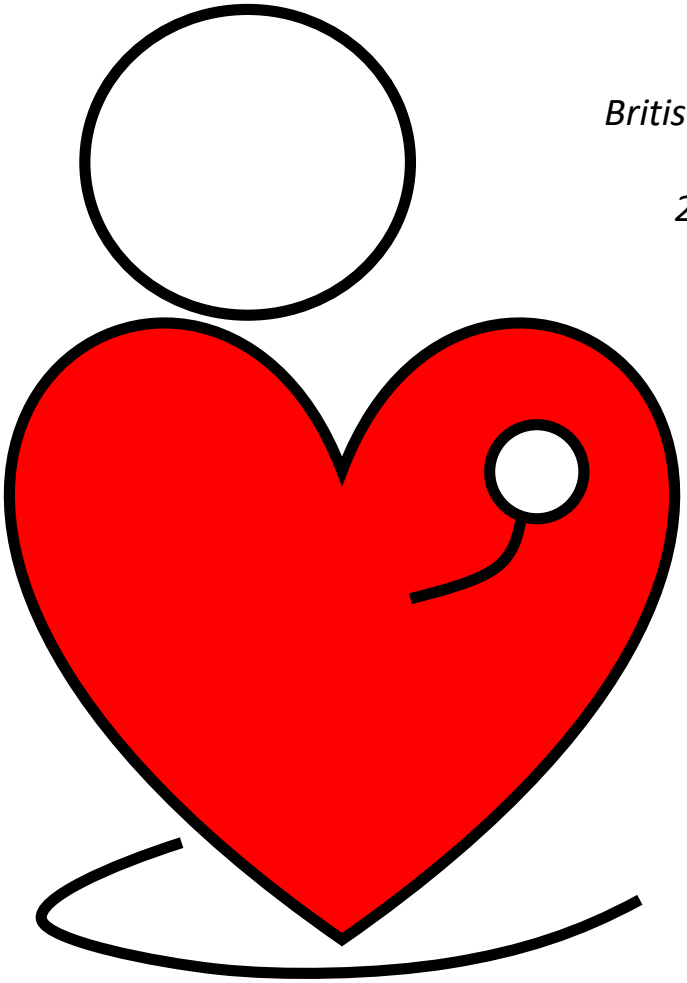
literature might have been missed for inclusion in the present review. Additionally, although studies reporting nonsignificant results were retrieved in the literature search, due to publication bias ineffective interventions might have been underreported. Another limitation is that we did not assess the quality of the included studies. However, all included studies incorporated a control group in their design, and most of them were RCTs. Since the participants of the included studies were diverse (e.g., they differed with regard to breast-feeding and baseline weight) and the interventions used were mostly unique across the included studies, we could not estimate overall mean effects in a meta-analysis.

CONCLUSION

In conclusion, existing postpartum lifestyle interventions might be used to achieve weight loss, smoking cessation, or to prevent smoking relapse in women who have experienced preeclampsia, intrauterine growth restriction, and/or gestational diabetes. Ideally, lifestyle interventions tailored for these high-risk women will be developed and tested. The interventions identified in this study could provide a solid starting point for the development of such tailored interventions. Future research should also focus on the long-term effectiveness of such interventions.

Chapter 3.2

RISK OF CARDIOVASCULAR DISEASE AFTER PREECLAMPSIA AND THE EFFECT OF LIFESTYLE INTERVENTIONS: A LITERATURE-BASED STUDY



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ABSTRACT

Objective This study addresses the following questions. Do cardiovascular risk factors fully explain the odds-ratio of cardiovascular risk after preeclampsia? What is the effect of lifestyle interventions (exercise, diet and smoking cessation) after preeclampsia on the risk of cardiovascular disease?

Design Literature based study.

Methods Data for the calculations were provided by studies, identified by Pubmed searches. First, the differences in cardiovascular risk factors after preeclampsia compared to an uncomplicated pregnancy were estimated. Second, the effects of lifestyle interventions on cardiovascular risk were estimated. Validated risk prediction models were used to translate these results into cardiovascular risk.

Results After correction for known cardiovascular risk factors, the odds-ratio of preeclampsia for ischaemic heart disease is 1.89(1.76-1.98), and for stroke it is 1.55(1.40-1.71). Lifestyle interventions after preeclampsia on exercise, dietary habits and smoking cessation decreases cardiovascular risk with an odds-ratio of 0.91 (0.87-0.96).

Conclusion Cardiovascular risk factors do not fully explain the risk of cardiovascular disease after preeclampsia. The gap between estimated and observed odds-ratios may be explained by an additive risk of cardiovascular disease by preeclampsia. Furthermore, lifestyle interventions after preeclampsia seem effective in decreasing cardiovascular risk. Future research is needed to overcome the numerous assumptions we had to make in our calculations.

INTRODUCTION

Preeclampsia occurs as a complication in 2-8% of pregnancies[4]. After preeclampsia, women have an increased risk of cardiovascular disease, including ischaemic heart disease and stroke[2]. Moreover, since preeclampsia and cardiovascular disease share most risk factors like hypertension, obesity, diabetes, and hypercholesterolemia[195 196], preeclampsia functions as a marker for cardiovascular risk[1]. However, it is not yet known whether preeclampsia itself independently adds to cardiovascular risk[197 198]. If this is true, then preeclampsia would be an independent risk factor, and not just a marker for cardiovascular disease.

Furthermore, the burden of cardiovascular disease in women is high. In 2004 cardiovascular disease accounted for 57.0% of global female mortality[199]. This emphasises the need for preventive lifestyle (or medical) interventions. Early detection of high-risk individuals maximises the effect of such interventions. After preeclampsia, women are thought to be good subjects for such interventions, since they are young and probably well motivated. Other authors have indeed suggested postpartum lifestyle interventions after preeclampsia to lower cardiovascular risk[4 197]. However, although previous research has shown that lifestyle interventions are effective if cardiovascular risk factors are already present[200], the effect remains uncertain in the absence of cardiovascular risk factors[201]. Thus, since the majority of women after preeclampsia have no cardiovascular risk factors[202] and studies of post-preeclamptic lifestyle interventions are lacking, possible effects remain unknown. However, effects of lifestyle interventions after preeclampsia could be estimated.

This study addressed the following questions. Do cardiovascular risk

factors fully explain the increased odds-ratios of cardiovascular risk after preeclampsia? What is the effect of lifestyle interventions after preeclampsia on the risk of cardiovascular disease?

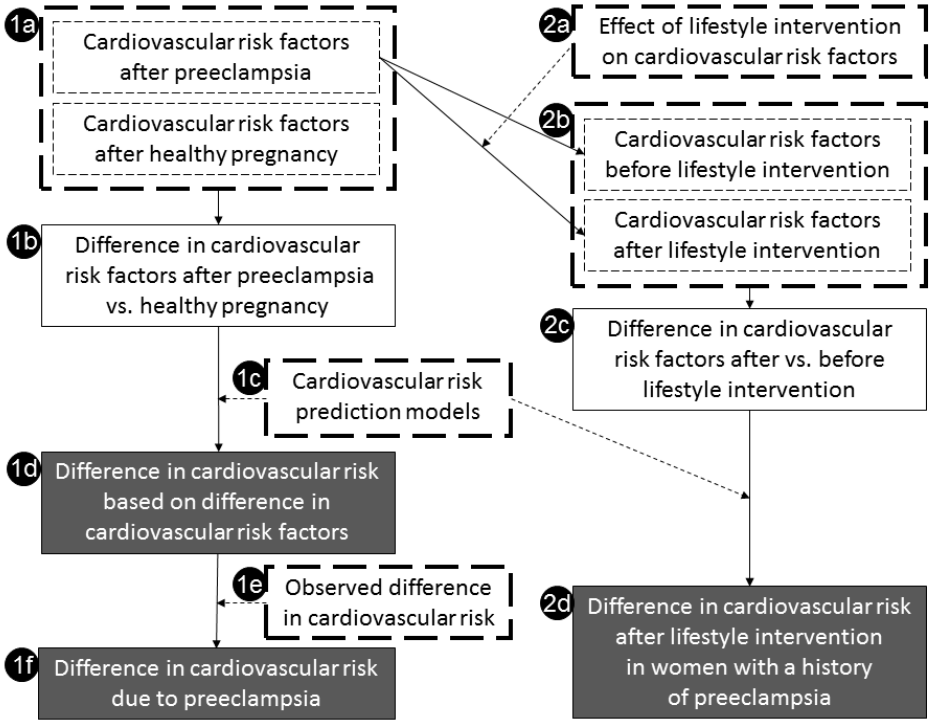
MATERIAL AND METHODS

Estimating both the contribution of cardiovascular risk factors, as well as preeclampsia itself, on cardiovascular risk and the effect of lifestyle interventions on cardiovascular risk involves a number of steps. The estimation process is visualised in figure 3.2.1.

Cardiovascular risk after preeclampsia (steps 1a-1f)

In step 1a we searched for studies that reported on differences in cardiovascular risk factors between women with a history of preeclampsia compared to women with a history of an uncomplicated pregnancy. We focused on cardiovascular risk factors used in the prediction models in step 1c: systolic and diastolic blood pressure, cholesterol levels, weight, smoking, diabetes, familial cardiovascular disease and the level of C-reactive protein. A Pubmed search with the term "*preeclampsia AND risk factors AND cardiovascular disease"* was used to identify original case/control studies that reported on these cardiovascular risk factors after preeclampsia, see Figure 2. Preeclampsia was according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria, defined as a blood pressure of 140/90 mmHg or higher and proteinuria of at least 300 mg/day at a gestational age of at least 20 weeks. Studies with women with chronic hypertension were allowed, but we excluded studies that included women with pre-existing renal or cardiovascular disease. As for this and all other searches (steps 1c and 2a), publications until January

Figure 3.2.1. Steps in estimating the contribution of cardiovascular risk factors, additive cardiovascular risk of preeclampsia and the effect of lifestyle interventions on future cardiovascular disease (numbers correspond with numbered steps in text).



2010 were included, and Non-English and non-human studies were excluded.

In step 1b we calculated the difference in cardiovascular risk factors between women with a history of preeclampsia and women with a history of a healthy pregnancy by subtraction. For each cardiovascular risk factor, the median value and interquartile range of the reported differences was calculated. This resulted in a collection of median differences of the cardiovascular risk factors as shown in the first column of table 3.2.1.

In step 1c we searched for cardiovascular risk prediction models. A recent review by Cui et al[203] was used to identify validated cardiovascular risk prediction models. An additional hand search provided the Framingham 30-years prediction model[39]. We used the original articles that reported on the

coefficients that were used in the prediction models. The following models were used: MONICA[37], PROCAM[34], SCORE[35], Eurostroke[38], CUORE[36], Framingham 30-years prediction model[39] and Reynolds Risk Score[40].

In step 1d we calculated the odds-ratios of cardiovascular risk between women with a history of preeclampsia and women with a history of a healthy pregnancy, based on the differences in cardiovascular risk factors as provided in step 1b. Here for we used the cardiovascular risk prediction models as supplied by step 1c. The interquartile range in step 1b was used to calculate a confidence interval of the odds-ratios.

In step 1e the meta-analysis of Bellamy et al[2] was used to provide the observed risk of cardiovascular disease after preeclampsia. This study reported separately on ischaemic heart disease and stroke.

In step 1f we calculated the additive effect of preeclampsia on of cardiovascular risk, corrected for the cardiovascular risk factors as mentioned in step 1a. To obtain this effect the observed odds-ratios (step 1e) were divided by the calculated odds-ratios (step 1d), both for ischaemic heart disease and stroke.

Estimated effect of lifestyle interventions on cardiovascular risk after preeclampsia (steps 2a-2d)

In step 2a we searched PubMed for studies that reported on the effect of lifestyle interventions on cardiovascular risk factors. The recent review by our research group provided us with studies reporting on weight reduction and smoking cessation after pregnancy[204]. For improving the lipid profile and lowering blood pressure, we used the identical Pubmed search strategy as in the review: "*(puerperium OR postpartum period OR postpartum OR post-partum) AND (lifestyle OR life style OR risk reduction behaviour OR risk reduction behaviour OR health promotion OR <specific search term>)"*. As specific search

Figure 3.2.2. Pubmed searches (all searches included studies until January 2010).

Search: *preeclampsia AND risk factors AND cardiovascular disease*

	Pubmed hits	**Title and abstract**	**Full text articles**	**Included**
	878 →	723 →	21 →	13
Exclusions (overlapping categories)				
Non-human	11			
Non-English	146			
No report on outcome		699	7	
Double dataset			1	

Search: *(puerperium OR postpartum period OR postpartum OR post-partum) AND (lifestyle OR life style OR risk reduction behavior OR risk reduction behavior OR health promotion OR lowering blood pressure OR hypertension)*

	Pubmed hits	**Title and abstract**	**Full text articles**	**Included**
	2576 →	182 →	29 →	0
Exclusions (overlapping categories)				
Non-human	266			
Non-English	342			
No trial	2384			
No lifestyle interventions		153		
No report on outcome			29	

Search: *(puerperium OR postpartum period OR postpartum OR post-partum) AND (lifestyle OR life style OR risk reduction behavior OR risk reduction behavior OR health promotion OR lowering lipids OR dyslipidaemia OR hypercholesterolemia)*

	Pubmed hits	**Title and abstract**	**Full text articles**	**Included**
	1134 →	105 →	28 →	0
Exclusions (overlapping categories)				
Non-human	123			
Non-English	87			
No trial	1026			
No lifestyle interventions		77		
No report on outcome			28	

term we used "*lowering lipids OR dyslipidaemia OR hypercholesterolemia"* and "*lowering blood pressure OR hypertension"*, respectively. Non-human studies and non-English articles were excluded. However, neither search provided any usable studies (figure 3.2.2). Therefore, we used the Cochrane Library to select studies reporting on the effects on lipid profile and blood pressure after primary interventions[205]. We selected studies reporting on effects in women aged 30-60 years. Studies were categorised according to cardiovascular risk factor (table 3.2.4). Next, for each cardiovascular risk factor the median value of the reported effects was calculated. This resulted in a collection of median effects of lifestyle intervention on the cardiovascular risk factors as shown in the second column of table 3.2.1. For each risk factor, a 1st and 3rd quartile value was calculated.

In step 2b we calculated the difference in cardiovascular risk factors between women with a history of preeclampsia with or without lifestyle interventions. The same studies as found in step 1a were used. The reported values of women with a history of preeclampsia were considered to be without the effect of lifestyle interventions. To compile a new fictive dataset with values of women with a history of preeclampsia that would have had lifestyle interventions, the collection of median effects of lifestyle interventions (step 2a) was used to recalculate the values of the cardiovascular risk factors into new values, as if these women would have had lifestyle interventions after preeclampsia.

In step 2c we calculated the difference in cardiovascular risk factors between women with a history of preeclampsia with or without lifestyle interventions. For each cardiovascular risk factor the median value and interquartile range of the difference between the original and the fictive, recalculated values as provided in step 2b was calculated by subtraction. This resulted in a collection of median differences of the cardiovascular risk factors

(values not shown).

In step 2d we used the risk prediction models found in step 1c to calculate the odds-ratios of cardiovascular risk between women with a history of preeclampsia with or without lifestyle interventions, based on the differences of cardiovascular risk factors as provided in step 2c. The interquartile range in step 2c was used to calculate a confidence interval of the odds-ratios.

Table 3.2.1. Differences in cardiovascular risk factors in women 1 to 30 years after preeclampsia compared to controls without preeclampsia and estimated effects of lifestyle interventions programs.

Risk factor	Differences of risk factors after preeclampsia compared to controls* Median (IQR)	Effect of lifestyle interventions ** Median (IQR)
Potentially modifiable risk factors		
Systolic blood pressure (mmHg)	7.5 (6.3-10.5)	-2.4 (-5.7– -1.3)
Diastolic blood pressure (mmHg)	7.0 (5.0-9.0)	-1.8 (-4.5 – -0.9)
Total cholesterol (mg/dl)	11.5 (5.0-18.0)	-2 (-16 – -2)
HDL-Cholesterol (mg/dl)	0.0 (-1.5-0.0)	0 (-3 – -1)
Body mass index (kg/m2)	2.8 (1.8-3.0)	-1.0% (-3.6% – 0.0%)
Smoking (%)	-10.9% (-18.0%-5.0%)	-2.2% (-7% – -0.7%)
Diabetes mellitus (%)	1.7% (0.0%-3.0%)	No Data
Treatment for hypertension (%)	15.4% (12.3%-22.6%)	No Data
Non-modifiable risk factors		
Familial CVD (<60y) (%)	22.2% (21.8%-26.3%)	
(hs-)CRP (mg/l)	0.5 (0.42-0.59)	

IQR = Interquartile Range, CVD = cardiovascular disease, CRP = C-reactive protein
*Based on reported studies listed in table 3.2.3.
**Paired analysis before vs. after interventions, based on reported studies listed in table 3.2.4.

RESULTS

Cardiovascular risk after preeclampsia

The search in Step 1a resulted in 878 articles. As shown in figure 3.2.2, 13

Table 3.2.2. Calculated odds-ratios (OR) for cardiovascular disease (CVD).

	OR for CVD after preeclampsia (preeclampsia vs. control)		OR for CVD of hypothetical lifestyle interventions after preeclampsia (before vs. after)	
Risk prediction model	**OR**	**(Q1-Q3*)**	**OR**	**(Q1-Q3*)**
Ischemic Heart Disease				
MONICA[37]	1.23	(1.19-1.36)	0.92	(0.84-0.96)
PROCAM[34]	1.09	(0.98-1.23)	0.94	(0.88-0.97)
SCORE[35]	1.14	(1.02-1.30)	0.87	(0.81-0.96)
Stroke				
EuroStroke[38]	1.17	(1.06-1.29)	0.96	(0.91-0.98)
Ischemic Heart Disease and stroke				
CUORE[36]	1.31	(1.16-1.57)	0.88	(0.85-0.99)
Reynolds Risk Score[40]	1.42	(1.25-1.71)	0.87	(0.80-0.98)
Framingham 30y-BMI[39]	1.27	(1.10-1.46)	0.95	(0.87-0.98)
Framingham 30y-Lipids[39]	1.25	(1.10-1.49)	0.87	(0.83-0.98)

articles were included. Screening the references of these articles resulted in an additional 3 studies. Table 3.2.3 lists all 16 studies included in the analysis categorised by cardiovascular risk factor. Of each cardiovascular risk factor the median and interquartile range of the difference between former preeclamptic women and women without a former preeclamptic pregnancy is shown in table 3.2.1.

The calculated odds-ratios based on these values are shown in table 3.2.2. For ischaemic heart disease a median odds-ratio of 1.14 was calculated based on the differences of cardiovascular risk factors after a history of preeclampsia compared to a healthy pregnancy. Dividing the observed odds-ratio of 2.16 with this calculated odd-ratio of 1.14, an odds-ratio of 1.89 (1.76-1.98) remained as the additive effect of preeclampsia to risk of ischaemic heart disease, corrected for cardiovascular risk factors. For stroke, an odds-ratio of 1.17 was calculated based on the difference of cardiovascular risk factors after a history of preeclampsia compared to a healthy pregnancy. Dividing the observed odds-

ratio of 1.81 with this calculated odds-ratio of 1.17, an odds-ratio of 1.55 (1.40-1.71) remained as the additive effect of preeclampsia to risk of stroke, corrected for cardiovascular risk factors.

Estimated effect of lifestyle interventions on cardiovascular risk after preeclampsia

The included studies are listed in table 3.2.4 categorised by cardiovascular risk factor. Table 3.2.1 shows the median and interquartile range of the effects for each cardiovascular risk factor.

Based on these values we estimated the odds-ratios for cardiovascular disease after lifestyle interventions in former preeclamptic women to be between 0.87-0.96 (table 3.2.2).

DISCUSSION

Main findings

Our estimates showed that cardiovascular risk factors used in the prediction models did not fully explain the risk of cardiovascular disease after preeclampsia. A major part of the observed odds-ratios of cardiovascular disease after preeclampsia remained after adjustment for these cardiovascular risk factors.

According to our estimates, lifestyle interventions after preeclampsia will decrease the cardiovascular risk by 4-13%. This might be an underestimation, since we had to use studies that did not account for possible motivational effects of having had preeclampsia[186 205 206]. On the other hand, the duration of follow-up of the studies was well below the time-span of the prediction models. Thus, a possible rebound effect after cessation of the interventions would lower the

effect on cardiovascular risk. This might have led to an over-estimation of the possible effect.

Interpretation

We hypothesise that preeclampsia itself is a true risk factor, rather than a marker, for cardiovascular disease. Since transient endothelial dysfunction can last up to 2 years after preeclampsia[202], it is likely that preeclampsia has a permanent effect on cardiovascular health. This may partly be reflected by permanent effects on cardiovascular risk factors. Indeed, Romundstad et al showed that the difference in cardiovascular risk factors of women after preeclampsia compared to women with a healthy pregnancy is 28-60% higher than the pre-pregnant difference[207]. However, preeclampsia may also directly increase cardiovascular risk through other yet unknown pathways.

Another explanation of the found independent additive effect of preeclampsia on cardiovascular risk might be a higher prevalence of thrombophilic factors in formerly preeclamptic women. Indeed, thrombophilic factors like Protein-C and -S deficiencies increase the risk of early-life cardiovascular disease[208 209]. However, whether these thrombophilic factors are more prevalent in formerly preeclamptic women is still unclear, but is modest at best[4].

The studies we included to calculate the differences in cardiovascular risk factors between women with a history of preeclampsia and women with a healthy pregnancy (Table 3.2.3), were very heterogeneous. Preeclampsia has different phenotypes. For instance, preeclampsia can be early or late, severe or mild, with or without HELLP or IUGR. The observed odds-ratios we used were also based on very heterogeneous studies[2]. It is to be expected that each phenotype is differently associated with cardiovascular disease.

Limitations and strengths

To calculate our results, we had to make several assumptions. The first assumption we made was that cardiovascular risk factors have the same effect on cardiovascular risk in women as they do in men, since the cardiovascular risk prediction models used were mainly based on male cohorts. However, it is suggested that cardiovascular disease in women might have a different pathogenesis than cardiovascular disease in men[210]. The second assumption we made was that the effects of lifestyle interventions after preeclampsia are the same as the effects of lifestyle interventions in general or after any pregnancy, because specific literature was lacking. The third assumption we made was that the effects of lifestyle interventions will last for the time-span of the cardiovascular risk prediction models (10-30 years) since the studies we could use lasted for at most 6 years.

Our study has several limitations. First, the above-mentioned assumptions we had to make weaken the results of our study. Second, we only included studies that were published in Pubmed registered journals and that were written in English. This could have resulted in an overestimation in our calculations of the contribution of cardiovascular risk factors and effects of lifestyle interventions, due to publication-bias. Third, we were limited to use only cardiovascular risk factors that were used in the prediction models. Other cardiovascular risk factors, like ethnicity, apolipoproteins and others, we could not use in our model. This could have led to an over-estimation of the independent effect of preeclampsia on cardiovascular risk. Forth, due to heterogeneity of the included studies in table 3.2.3 and table 3.2.4, we could not perform meta-analyses for each risk factor. We therefor used less accurate medians and interquartile ranges in our calculations.

CONCLUSION

Cardiovascular risk factors do not fully explain the risk of cardiovascular disease after preeclampsia. The gap between estimated and observed odds-ratios may be explained by an additive risk of cardiovascular disease by preeclampsia. Furthermore, lifestyle interventions after preeclampsia seem effective in decreasing cardiovascular risk.

Further studies should focus on the effects of post-preeclamptic lifestyle interventions on cardiovascular risk and cardiovascular risk factors. Preferably, follow-up would last for 10 to 30 years. This would eliminate the necessity to make the above-mentioned assumptions in our model.

Since we found an additive effect of preeclampsia on future cardiovascular disease, possible prevention of preeclampsia by preconception or early-pregnancy lifestyle modification is of even greater importance.

Table 3.2.3. Cardiovascular risk factors in women after preeclamptic pregnancies compared to normal pregnancies.

	PE	Control	ΔPE-Control	ln(PE)	ln(Contr)
Systolic blood pressure (mmHg)					
He 1999[21]	120	108	12	4,79	4,68
Sattar 2003[25]	124	116	8	4,82	4,75
Wolf 2004[27]	111	105	6	4,71	4,65
Kaaja 2005[22]	134	128	6	4,90	4,85
Girouard 2007[20]	115	108	7	4,75	4,68
Manten 2007[24]	127	116	11	4,84	4,75
Berends 2008[18]	126	121	5	4,84	4,80
Gaugler-Senden 2008[19]	130	115	15	4,87	4,75
Magnussen 2009[23]	132	125	7	4,88	4,83
Smith 2009[26]	120	111	9	4,79	4,71
Diastolic blood pressure (mmHg)					
He 1999[21]	74	65	9	4,30	4,17
Sattar 2003[25]	83	76	7	4,42	4,33
Wolf 2004[27]	73	68	5	4,29	4,22
Kaaja 2005[22]	79	76	3	4,37	4,33
Girouard 2007[20]	75	70	5	4,32	4,25
Manten 2007[24]	84	75	9	4,43	4,32
Berends 2008[18]	81	75	6	4,39	4,32
Gaugler-Senden 2008[19]	83	75	8	4,42	4,32
Smith 2009[26]	81,5	72	9,5	4,40	4,28
Use of anti-hypertensive drugs (%)					
Sattar 2003[25]	17,5	5,0	12,5		
Wilson 2003[7]	26,7	14,5	12,2		
Berends 2008[18]	19,1	0,9	18,2		
Gaugler-Senden 2008[19]	35,0	0,0	35,0		
Magnussen 2009[23]	9,6	2,2	-7,4		
Smoking (%)					
He 1999[21]	20,0	38,0	-18,0		
Sattar 2003[25]	22,5	15,0	7,5		
Wolf 2004[27]	7,0	3,0	4,0		
Kaaja 2005[22]	21,5	22,5	-1,0		
Manten 2007[24]	31,0	38,0	-7,0		
Berends 2008[18]	22,0	49,1	-27,1		
Gaugler-Senden 2008[19]	10,0	15,0	-5,0		
Edlow 2009[211]	8,8	20,0	-11,2		
Magnussen 2009[23]	26,4	37,3	-10,9		
Total cholesterol (mg/dl)					
Sattar 2003[25]	201	182	19	5,30	5,20
Girouard 2007[20]	184	176	8	5,22	5,17
Manten 2007[24]	201	182	19	5,30	5,20

ΔIn(PE)-In(Control)	Mean or median time after PE (y)	Mean age at follow-up (y)	Special remarks
0,11	4,5	37,5	56% severe preeclampsia
0,07	19,0	42,0	Mainly late-onset preeclampsia
0,06	1,5	35,2	
0,05	17,5	47,9	
0,06	8,1	35,8	
0,09	0,8	40,8	Early-onset preeclampsia
0,04	7,0	36,2	Mainly late-onset preeclampsia
0,12	5,5	37,7	Severe, early-onset preeclampsia
0,05	16,6	39,9	
0,08	1,0	31,5	51% severe preeclampsia
0,13	4,5	37,5	56% severe preeclampsia
0,09	19,0	42,0	Mainly late-onset preeclampsia
0,07	1,5	35,2	
0,04	17,5	47,9	
0,07	8,1	35,8	
0,11	0,8	40,8	Early-onset preeclampsia
0,08	7,0	36,2	Mainly late-onset preeclampsia
0,10	5,5	37,7	Severe, early-onset preeclampsia
0,12	1,0	31,5	51% severe preeclampsia
	19,0	42,0	Mainly late-onset preeclampsia
	32,0	56,2	
	7,0	36,2	Mainly late-onset preeclampsia
	5,5	37,7	Severe, early-onset preeclampsia
	16,6	39,9	
	4,5	37,5	56% severe preeclampsia
	19,0	42,0	Mainly late-onset preeclampsia
	1,5	35,2	
	17,5	47,9	
	0,8	40,8	Early-onset preeclampsia
	7,0	36,2	Mainly late-onset preeclampsia
	5,5	37,7	Severe, early-onset preeclampsia
	0,6	26,6	
	16,6	39,9	
0,10	19,0	42,0	Mainly late-onset preeclampsia
0,04	8,1	35,8	
0,10	0,8	40,8	Early-onset preeclampsia

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Table 3.2.3. *Continued*

	PE	Control	ΔPE-Control	ln(PE)	ln(Contr)
Berends 2008[18]	186	209	-23	5,23	5,34
Gaugler-Senden 2008[19]	193	189	4	5,26	5,24
Smith 2009[26]	181	166	15	5,20	5,11
HDL-cholesterol (mg/dl)					
Sattar 200325	60	56	4	4,09	4,03
Girouard 200720	51	55	-4	3,93	4,01
Manten 200724	53	53	0	3,97	3,97
Berends 200818	50	50	0	3,91	3,91
Gaugler-Senden 200819	62	62	0	4,13	4,13
Magnussen 200923	56	58	-2	4,03	4,06
Smith 200926	57	58	-1	4,04	4,06
BMI (kg/m2)					
Marin 2000212	29,8	26,5	3,3	3,40	3,28
Sattar 200325	27,0	26,0	1,0	3,30	3,26
Wolf 200427	29,2	24,0	5,2	3,37	3,18
Kaaja 200522	27,7	26,2	1,5	3,32	3,27
Girouard 200720	26,9	24,7	2,2	3,29	3,21
Manten 200724	26,0	23,0	3,0	3,26	3,14
Berends 200818	27,2	24,4	2,8	3,30	3,20
Gaugler-Senden 200819	25,7	22,7	3,0	3,25	3,12
Edlow 2009211	29,3	29,3	0,0	3,38	3,38
Magnussen 200923	27,4	25,3	2,1	3,31	3,23
Smith 200926	29,0	26,0	3,0	3,37	3,26
Diabetes (%)					
Marin 2000212	1,9	2,3	-0,4		
Kaaja 200522	3,4	1,7	1,7		
Berends 200818	4,3	0,0	4,3		
Gaugler-Senden 200819	0,0	0,0	0,0		
Edlow 2009211	8,0	5,0	3,0		
Familial cardiovascular disease (<60y) (%)					
Roes 2005213	53,9	31,7	22,2		
Rigo 2006214	43,2	16,5	26,7		
Valdés 2009[215]	42,2	20,5	21,7		
(hs-)CRP (mg/l)					
Girouard 2007[20]	1,8	1,2	0,6	0,59	0,18
Gaugler-Senden 2008[19]	2,0	1,5	0,5	0,69	0,41
Smith 2009[26]	2,9	2,5	0,4	1,08	0,93

Δln(PE)-ln(Control)	Mean or median time after PE (y)	Mean age at follow-up (y)	Special remarks
-0,12	7,0	36,2	Mainly late-onset preeclampsia
0,02	5,5	37,7	Severe, early-onset preeclampsia
0,09	1,0	31,5	51% severe preeclampsia
0,07	19,0	42,0	Mainly late-onset preeclampsia
-0,08	8,1	35,8	
0,00	0,8	40,8	Early-onset preeclampsia
0,00	7,0	36,2	Mainly late-onset preeclampsia
0,00	5,5	37,7	Severe, early-onset preeclampsia
-0,04	16,6	39,9	
-0,02	1,0	31,5	51% severe preeclampsia
0,12	14,2	43,3	
0,04	19,0	42,0	Mainly late-onset preeclampsia
0,20	1,5	35,2	
0,06	17,5	47,9	
0,09	8,1	35,8	
0,12	0,8	40,8	Early-onset preeclampsia
0,11	7,0	36,2	Mainly late-onset preeclampsia
0,12	5,5	37,7	Severe, early-onset preeclampsia
0,00			
0,08	16,6	39,9	
0,11	1,0	31,5	51% severe preeclampsia
	14,2	43,3	
	17,5	47,9	
	7,0	36,2	Mainly late-onset preeclampsia
	5,5	37,7	Severe, early-onset preeclampsia
	0,6	26,6	
	N/A	34,0	Severe preeclampsia
	N/A	28,7	Severe preeclampsia
	N/A	60,9	
0,41	8,1	35,8	
0,29	5,5	37,7	Severe, early-onset preeclampsia
0,15	1,0	31,5	51% severe preeclampsia

Table 3.2.4. Effects of lifestyle intervention programs

	Type of study	Intervention	n	% women
Systolic blood pressure (mmHg)				
Gillet 1987[216]	RCT	Tailored intensive aerobic exercise (I) vs commercial aerobic exercise (C)	20	100%
HPTR group 1990[217]	RCT	Dietary counselling (I) vs no dietary counselling (C)	841	35%
Eriksson 1991[218]	RCT	Dietary treatment and increased activity with annual check-ups (I) vs no intervention (C)	181	-
Sjostrom 1999[219]	PC	Diet & exercise (I) vs no intervention (C)	380	100%
Stevens 2001[220]	RCT	Group meetings and individual counselling for 3 years (I) vs usual care (C)	595	34%
Diastolic blood pressure (mmHg)				
Gillet 1987[216]	RCT	Tailored intensive aerobic exercise (I) vs commercial aerobic exercise (C)	20	100%
HPTR group 1990[217]	RCT	Dietary counselling (I) vs no dietary counselling (C)	841	35%
Eriksson 1991[218]	RCT	Dietary treatment and increased activity with annual check-ups (I) vs no intervention (C)	181	-
Sjostrom 1999[219]	PC	Diet & exercise (I) vs no intervention (C)	380	100%
Stevens 2001[220]	RCT	Group meetings and individual counselling for 3 years (I) vs usual care (C)	595	34%
Smoking cessation (% of women)				
Wall 1995[169]	RCT	Oral and written information and advice at 4 visits (I) vs written information once (C)	1478	100%
Severson 1997[168]	RCT	Oral and written information and advice at 4 visits (I) vs oral information and advice once (C)	1875	100%
Glasgow 2000[221]	RCT	Video, counselling and follow-up telephone calls (I) vs advice only (C)	1154	100%
Solomon 2005[222]	RCT	Free nicotine patches & proactive tel support (I) vs patches only (C)	171	100%
Solomon 2005[223]	RCT	Free nicotine patches & proactive tel support (I) vs patches only (C)	171	100%

Age Group (y)	Duration of Follow-up	Lost to follow-up	Effect	Special remarks
43,8 (5,7)	16 weeks	6,0%	0,0	
25-40	3 years	12,0%	-2,4	
-	6 years	-	-8,8	Men and women with IGT
-	5 years	-	-5,7	
30-54	4 years	11,0%	-1,3	
43,8 (5,7)	16 weeks	6,0%	0,0	
25-40	3 years	12,0%	-1,8	
-	6 years	-	-5,0	Men and women with IGT
-	5 years	-	-4,5	
30-54	4 years	11,0%	-0,9	
-	6 months	-	-2,2%	2 weeks postpartum women
-	12 months	-	-0,7%	2 weeks postpartum women
15-35	6 months	10,0%	0,0%	Women attending planned parenthood clinics Biochemically validated
33,7(8,9)	3 months	6,0%	-17,0%	Low-income women Self-reported abstinence
33,7(8,9)	6 months	13,0%	-7,0%	Low-income women; Self-reported abstinence; Measurements 3 months after stop program

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Table 3.2.4. *Continued*

	Type of study	Intervention	n	% women
Total cholesterol (mg/dl)				
Gillet 1987[216]	RCT	Tailored intensive aerobic exercise (I) vs commercial aerobic exercise (C)	20	100%
Baron 1990[224]	RCT	Nutritional advice (I) vs no advice (C)	179	100%
Manning 1991[225]	RCT	Strength training 3 sessions (I) vs no training (C)	16	100%
Simkin 1995[226]	RCT	Dietary & behavior intervention (I) vs no intervention (C)	253	100%
Janssen 2002[227]	RCT	Dietary treatment & aerobic exercise (I) vs dietary treatment only (C)	11	100%
Janssen 2002[227]	RCT	Dietary treatment & resistance exercise (I) vs dietary treatment only (C)	14	100%
Cheng 2004[228]	RCT	Monthly dietary counselling (I) vs no counselling (C)	175	69%
Wister 2007[229]	RCT	Health report card and counselling by telephone (I) vs usual care (C)	315	45%
HDL-cholesterol (mg/dl)				
Baron 1990[224]	RCT	Nutritional advice (I) vs no advice (C)	179	100%
Manning 1991[225]	RCT	Strength training 3 sessions (I) vs no training (C)	16	100%
Simkin 1995[226]	RCT	Dietary & behavior intervention (I) vs no intervention (C)	253	100%
Janssen 2002[227]	RCT	Dietary treatment & aerobic exercise (I) vs dietary treatment only (C)	11	100%
Janssen 2002[227]	RCT	Dietary treatment & resistance exercise (I) vs dietary treatment only (C)	14	100%
Weight loss (% of baseline weight)				
Lovelady 1995[156]	RCT	Aerobic exercise 45min/d for 5d/w (I) vs no exercise	33	100%
Leermakers 1998[154]	RCT	Behavioral intervention	90	100%
McCrory 1999[157]	RCT	35% reduction in dietary energy intake (I) vs no reduction (C)	45	100%
McCrory 1999[157]	RCT	Combined 35% reduction in dietary energy intake and increased exercise (I) vs no reduction (C)	45	100%
Lovelady 2000[155]	RCT	Dietary restriction of 500 kCal/d & exercise 45 mins/d for 4d/w (I) vs no restriction or exercise (C)	40	100%

Age Group (y)	Duration of Follow-up	Lost to follow-up	Effect	Special remarks
35-57	16 weeks	6,0%	0	Sedentary, overweight women
25-60	1 year	9,0%	-2	
22-57	12,5 weeks	8,3%	0	Sedentary, obese women
44-50	6 months	2,8%	-13	
24,8 (5,8)	16 weeks	0,0%	-16	Overweight, obese women
24,8 (5,8)	16 weeks	0,0%	-23	Overweight, obese women
52,80	4 months	16,0%	-15	Hypercholesterolemic, non-medicated patients
55,80	1 year	11,7%	-16	10y-framingham score >= 10%
25-60	1 year	9,0%	0	
22-57	12,5 weeks	8,3%	-3	Sedentary, obese women
44-50	6 months	2,8%	-2	
24,8 (5,8)	16 weeks	0,0%	-1	Overweight, obese women
24,8 (5,8)	16 weeks	0,0%	-3	Overweight, obese women
30,5	12 weeks	-	0,0%	Breastfeeding women
32,4 (4,5)	6 months	23,0%	-4,0%	Women at 3-12 months postpartum
32 (5)	11 days	-	-2,5%	Breastfeeding women
32 (5)	11 days	-	-2,0%	Breastfeeding women
31 (4)	10 weeks	16,7%	-5,3%	Breastfeeding, overweight women

Continues on next page

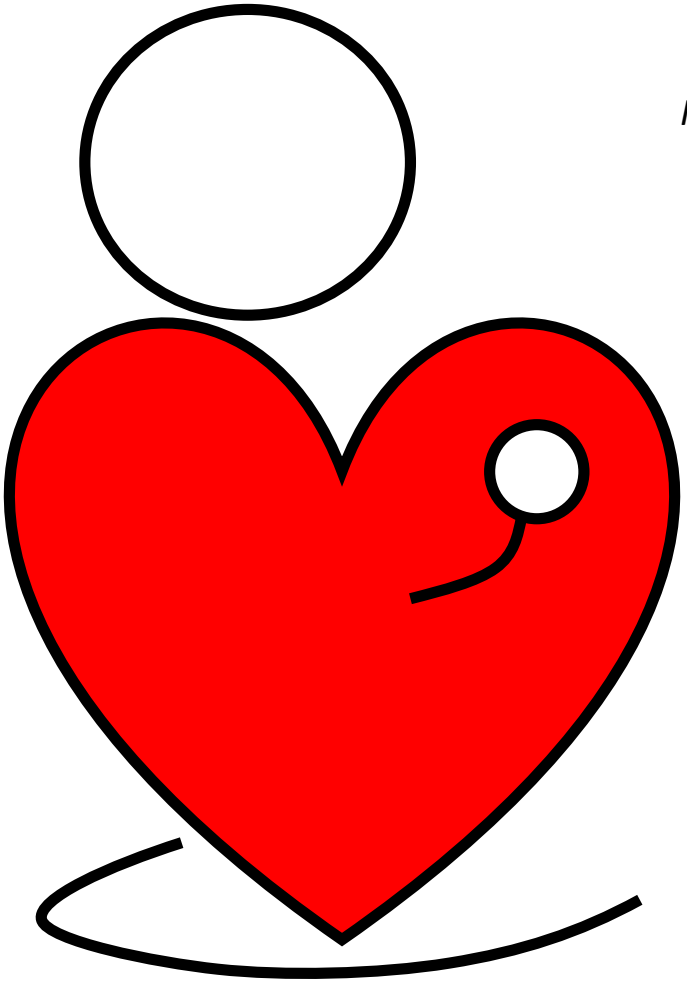
Table 3.2.4. *Continued*

	Type of study	Intervention	n	% women
O'Toole 2003[159]	RCT	Weekly counselling of diet and physical activity (12 weeks total) and daily food and activity diaries (I) vs 1-hour educational session (C)	40	100%
Lovelady 2006[161]	RCT	Dietary restriction of 500 kCal/d & exercise 45 mins/d for 4d/w (I) vs no restriction or exercise (C)	45	100%
Kinnunen 2007[153]	RCT	5 counselling sessions on diet and physical activity (I) vs usual care (C)	92	100%
De Castro 2009[160]	PC	High Protein-intake (I) vs low-protein intake (C)	421	100%
Ostbye 2009[158]	RCT	18 health classes and 6 telephone counselling sessions (I) vs no intervention (C)	450	100%

Age Group (y)	Duration of Follow-up	Lost to follow-up	Effect	Special remarks
31,5 (4,6)	1 year	-	-7,8%	1-6 months postpartum, overweight women
-	5 years	-	0,0%	Breastfeeding, overweight women
29,0 (4,1)	8 months	-	0,0%	2 months postpartum women
	9 months	-	0,0%	1-3 days postpartum women
30,9 (5,6)	10 months	-	0,0%	2 months postpartum, overweight women

Chapter 3.3

PREFERENCES FOR POSTPARTUM LIFESTYLE COUNSELING AMONG WOMEN SHARING AN INCREASED CARDIOVASCULAR AND METABOLIC RISK: A FOCUS GROUP STUDY



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ABSTRACT

Objective To describe women's preferences for postpartum lifestyle counseling after a pregnancy complicated by preeclampsia, intrauterine growth restriction and/or gestational diabetes.

Methods

Thirty-six women who had experienced these pregnancy complications participated in six focus group interviews.

Results All women expressed a need for participation in postpartum lifestyle counseling. They preferred participation to be tailored to individual preferences. A combination of face-to-face counseling supported by computer-tailored lifestyle advice appealed to them.

Conclusion Postpartum lifestyle counseling aimed at these women should be tailored to individual needs and preferences.

INTRODUCTION

Epidemiological data indicate that an obstetric history of preeclampsia, intrauterine growth restriction and/ or gestational diabetes is associated with a significantly increased risk for remote cardiovascular diseases, such as hypertension, myocardial infarction, ischemic heart disease, and cerebrovascular accidents[230]. Women who have experienced these pregnancy complications share cardiovascular and metabolic risk factors, such as abdominal obesity, insulin resistance, atherogenic dyslipidemia, and elevated blood pressure[51].

It is suggested that lifestyle-related risk factors should primarily be targeted to reduce cardiovascular and metabolic risk in women who have experienced these pregnancy complications[51]. Research in other high-risk groups has shown that lifestyle interventions have been effective in lowering risk factors for cardiovascular disease[231-234] and diabetes mellitus type II[58 59]. Potentially modifiable lifestyle-related risk factors associated with cardiovascular disease are consumption of saturated fat, fruit, vegetables, and alcohol, physical activity, smoking, and psychosocial factors[235].

Currently, in the health care setting, tailored interventions (such as face-to-face counseling) are widely applied. Such interventions are intended to reach one specific person, are based on characteristics that are unique to that person, are related to the outcome of interest, and have been derived from an individual assessment[236 237].

However, in the last decades, potentially important new channels for health communication have emerged, such as computers and the Internet[238]. Computer-tailored lifestyle counseling (e.g., computer-tailored nutrition education) can provide people with both individualized feedback and advice on

personal performance levels (e.g., nutritional intake) and awareness of their own performance, as well as personal motivation to change, goals, outcome expectations, subjective norms, self-efficacy, self-regulation processes and other possible behavioral determinants[237 239]. Now that computer-tailored health education is recognized as a promising health education strategy, computer-tailored lifestyle interventions for various behaviors are currently offered on the World Wide Web[65 240 241].

Considering the individual differences in pregnancy complications and their consequences, physical and psychological recovery, and other personal factors (e.g., education and family composition), the use of tailored lifestyle interventions seems to be highly suitable. For example, face-to-face lifestyle counseling or computer-tailored lifestyle advice might be offered. Moreover, tailoring a lifestyle intervention to the specific characteristics and preferences of these high-risk women is expected to promote participation and adherence to the intervention. In the process of developing such a tailored intervention, opinions, needs, and ideas of women who have recently experienced such pregnancy complications should be taken into account.

Although the postpartum period after a pregnancy complicated with preeclampsia, intrauterine growth restriction and/or gestational diabetes, is considered to be a window of opportunity for preventive interventions shortly after delivery[1 230], little is known about what the lifestyle interventions aimed at these high-risk women should consist of. Up to now, little information is available about women's preferences regarding postpartum lifestyle counseling. Therefore, we conducted focus group interviews among women after a pregnancy complicated with preeclampsia, intrauterine growth restriction and/or gestational diabetes in order to document their needs, opinions, and ideas regarding postpartum lifestyle counseling. Two different types of lifestyle

interventions were discussed: face-to-face counseling by a health care specialist and computer-tailored lifestyle counseling.

METHODS

Participants

Patients with pregnancies complicated by preeclampsia, intrauterine growth restriction and/or gestational diabetes who had given birth in the Erasmus University Medical Center in Rotterdam between November 2004 and October 2006, were eligible for participation in the focus group interviews. By searching hospital records, 182 eligible patients were selected and invited by mail to participate in the focus groups.

Preeclampsia was diagnosed according to ISSHP criteria. Intrauterine growth restriction due to placental insufficiency was defined when the ultrasonic fetal abdominal circumference was below the 5th percentile in combination with abnormal Doppler patterns of the umbilical artery (pulsatility index above the 95th percentile and/or in case of absent or reversed end diastolic flow)[242]. Patients were diagnosed with gestational diabetes when 1-hour postprandial glucose level was above 7.0 mmol/l[243].

A complication was defined as severe when delivery occurred at a gestational age of 32 weeks or less, when the newborn was admitted to the neonatal intensive care unit, or in case of perinatal mortality[83].

Procedure

The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center. Focus group interviews were held at the Erasmus University Medical Center in December 2006 and February 2007, and lasted

about 60 minutes each. Prior to the interviews, participants provided informed consent and completed a questionnaire assessing ethnicity (Dutch, non-Dutch), level of education (primary school, secondary school, and higher education) smoking (yes, no), and self-reported weight and height. A moderator (M.H.), assisted by a facilitator (D.B/ W.B), led the focus group interviews. Interviews were audiotaped, and were held in line with focus group principles provided by Morgan et al[244]. A semi structured focus group discussion guide was used to structure discussion topics.

Analysis

Questionnaire

Self-reported weight and height were used to calculate the body mass index (BMI). A BMI of 25 or higher was defined as overweight and 30 or higher as obesity. Birth weight and gestational age at delivery were retrieved from hospital records. A participant was designated to be of non-Dutch ethnic origin if one of her parents was born abroad[245]. Educational level was assessed by the highest completed education and reclassified into three categories: 1) primary school, 2) secondary school and 3) higher education[246].

Interviews

Focus groups were audiotaped, transcribed verbatim, and checked for accuracy. After transcripts were made, a qualitative data analysis program (the software package QSR Nvivo, version 7) was used to analyze the transcripts in accordance with content analysis principles[244]. Discussion topics were identified, sorted, and labeled according to the technique of content analysis. A systematic summary of what each group said about a topic was made. Discussion topics

were examined across groups and for all groups combined. Discussion topics addressed in the interview guide were preferred characteristics of the postpartum lifestyle counseling, face-to-face lifestyle counseling, and computer-tailored lifestyle counseling. To illustrate some findings, quotations are reported.

Table 3.3.1. Demographic data and clinical characteristics of the study participants.

	n	(%)	Mean (SD)	Range
Women				
Age (years)	36		32.7 (4.5)	22 -41
Ethnicity				
Dutch	20	(55.6%)		
Educational level				
Primary school	5	(14.7%)		
Secondary school	15	(44.1%)		
Higher education	14	(41.2%)		
Smoking				
Yes	3	(8.3%)		
Body mass index			24.8 (4.9)	17.1-39.3
25-30	12	(36.4%)		
≥ 30	4	(12.1%)		
Pregnancy complication				
Preeclampsia	21	(16.7%)		
Intrauterine growth restriction	4	(58.3%)		
Gestational diabetes	5	(11.1%)		
Preeclampsia and intrauterine growth restriction	6	(13.9%)		
Offspring				
Birth weight (g)	36		2352 (1155)	(690-4360)
Gestational age at delivery (days)	36		246 (4.9)	(184- 290)

RESULTS

Participants

Of the 36 women participating in the focus group interviews, 21 had experienced preeclampsia, 4 intrauterine growth restriction, 5 gestational diabetes, and 6 women had experienced both preeclampsia and intrauterine growth restriction. The number of participants per group ranged from 4 to 10 (average 6). See table 3.3.1 for demographic data and clinical characteristics of the study participants.

Postpartum Lifestyle Counseling

All women expressed a need for postpartum lifestyle counseling. *"Every piece of advice, guidance and information after delivery is very valuable."* Generally, women said that they would like to receive personal feedback on their current health status and their future risk. *"It would help if someone would say: You are too heavy, these are the consequences of being too heavy, and this is what you can do to lose weight".* However, all stated that postpartum lifestyle counseling should preferably not be too time consuming and should not cost too much effort.

All preferred to receive tailored postpartum lifestyle advice. In addition, women mentioned that participation in postpartum lifestyle counseling should preferably be tailored to personal preferences regarding the frequency, onset, duration, and the length of personal guidance. For example, some reported that they would like to be able to decrease the frequency of counseling visits after a certain time after delivery. Also, women who had experienced a prolonged period of recovery, preferred to postpone participation in a lifestyle counseling

program until completely recovered from their pregnancy. The idea that prolonged guidance might decrease a woman's fear of recurrence of the condition and hence their threshold for a next pregnancy, was mentioned as a reason for the desire for lifestyle support until the next pregnancy.

Particularly women who experienced a severe complication expressed a need for more and longer physical and psychological guidance after their complicated pregnancy as part of postpartum counseling: *"Such counseling is a step in the right direction towards better follow-up care".*

Face-to-Face Counseling

All women indicated that they would like to receive postpartum lifestyle counseling from a health care specialist. Face-to-face counseling from a health care specialist was perceived as effective and motivating. Women said that they would feel motivated to show the counselor what progress they had made. They would like to receive support from the counselor and they would like to receive reminders of why it is important to improve their lifestyle. *"Regularly being reminded of what you are doing it for would help".* Furthermore, they would like the idea of their lifestyle being monitored by a health care specialist; they would prefer regular moments of evaluation; and they would like to be able to observe progress from participating in lifestyle counseling.

A preferred counsellor was reported to be someone who had sufficient and extensive knowledge about lifestyle, and about the pregnancy complications and their consequences. Women mentioned that the counsellor must be experienced, and should be familiar with experiences of other women who had the same complications during pregnancy. *"It must be someone who knows how to put our experiences into perspective."*

Several health care specialists were mentioned as potential counselors:

specialized nurses, general practitioners, gynecologists, and midwives. A gynecologist was perceived as sufficiently specialized, but overqualified to apply lifestyle counseling. The general practitioner was perceived as easily accessible, but not sufficiently specialized. Women generally stated that a nurse might be easier to talk to than a physician. Additionally, they would like the counselor to be able to provide information, and both medical and psychological support, when needed. When the counselor cannot provide this support, he or she should preferably be able to transfer the patient to other health care specialists (e.g., a psychologist or a dietician).

Most women said that they would rather receive counseling from the same person so that they can build a relationship on mutual trust. Others indicated they would not mind if they would receive counseling from multiple counselors, because they might profit from the variance in both the level and the nature of knowledge between counselors. For most women, the gender of the counselor was irrelevant.

Women generally preferred the location of the counseling to be close to home. *"As a young mother, you're not very flexible in making appointments."* Suggested locations for the counseling included: the general practitioner's premises, the infant welfare center, and a nearby hospital. Additionally, women suggested that lifestyle counseling might also be administered at home, or that counseling might take place by telephone. Others suggested that counseling could take place at a location where they could meet fellow sufferers.

Finally, they said that it would be practical to combine a counseling visit with one of the standard postpartum visits to a healthcare specialist (e.g., gynecologist or pediatrician) that they have already planned. This was particularly the case for women who had experienced a severe complication, since they generally had more postpartum hospital visits. However, some

women preferred a separate visit so that they could pay full attention to counseling (and could choose whether or not to bring their child). All women stated that they were willing to pay a separate visit (or extra visits) for lifestyle counseling.

Computer-Tailored Counseling: Alternative or Supplement?

The use of computer-tailored lifestyle counseling was perceived as appealing. Women reported that a computer-tailored lifestyle promotion program should be readable, comprehensible and accurate. It would be appreciated if the progress of their lifestyle behaviors could be registered on the computer-tailored lifestyle promotion program. It was suggested that lifestyle behavior could be monitored and displayed in a graph, so that progress could be made "visible". Women said this would stimulate them to (re)gain control and responsibility over their own lifestyle behavior.

The majority preferred a computer-tailored advice to be accessible on the Internet, so that they could complete the intervention wherever and whenever convenient. "*Internet is widespread and universally accessible; when you're not able to complete the intervention at home, there are lots of places where you can."* Moreover, it was suggested that a computer-tailored lifestyle program on the Internet could provide a forum. Such a forum was mentioned as an easy way to get in contact with other women who had experienced the same pregnancy complication. Others, however, perceived making contact with fellow suffers by means of a forum on the Internet as too impersonal.

Although the Internet was generally thought to be a suitable medium to offer computer-tailored lifestyle advice, it was mentioned that caution should be paid to safety on the Internet. The Internet connection has to be secure, and privacy has to be guaranteed. "*It has to be a personal, protected space on the*

Internet, not everyone should be able to read what's on it." With regard to lifestyle questionnaires, a minority preferred the use of paper and pencil to the use of a computer, or keeping a "lifestyle" diary. They thought the Internet would be too impersonal and not motivating enough. "*Internet could be too undisciplined.*" Moreover, women mentioned that lack of access to the Internet and lack of skills to adequately surf on the Internet could be barriers towards computer-tailored counseling on the Internet. They also mentioned that, although the Internet is widespread, not everyone has a computer at home or a fast connection on the Internet.

Thus, although a computer was seen as an attractive medium to provide tailored lifestyle counselling, the use of a computer-tailored advice alone was considered to be too minimal, perhaps less effective and not suited for longer-term purposes, because *"the computer doesn't answer back".* Computer-tailored advice was seen as a way to support face-to-face counselling. A combination of face-to-face personal counselling supported by computer-tailored lifestyle advice offered on the Internet appealed to women. This combination was perceived as desirable, effective, and motivating.

DISCUSSION

This first study exploring the needs, ideas and opinions on postpartum lifestyle counseling of women who had experienced preeclampsia, intrauterine growth restriction, and/or gestational diabetes shows that these women have a need for postpartum lifestyle counseling. They preferred to receive tailored lifestyle advice. According to these women, participation in postpartum lifestyle counseling should preferably be tailored to individual preferences regarding the location, onset, duration, length, and the frequency of personal guidance. A

combination of face-to-face personal counselling, supported by computer-tailored lifestyle advice offered on the Internet, appealed to these women.

Our results show that women, who are at increased cardiovascular and metabolic risk after they have experienced a pregnancy complication, are motivated to participate in postpartum lifestyle interventions. Women reported that they would like to be guided in adopting a healthy lifestyle, and that they would like their lifestyle to be monitored by a health care specialist. This is in line with the window of opportunity for preventive interventions in women after a pregnancy complicated with preeclampsia, intrauterine growth restriction and/or gestational diabetes, as demonstrated earlier[1].

To our knowledge, our study is the first to describe preferences for postpartum lifestyle support among women who have experienced preeclampsia, intrauterine growth restriction and/or gestational diabetes. However, we found one other study that investigated preferred types of lifestyle support among women with recent gestational diabetes in order to improve the development of diabetes prevention strategies. The results of this study by Zehle et al[182] show that advice from a dietician and telephone support from a health educator were the most preferred forms of health assistance to improve dietary and physical activity habits. The results of our study confirm the conclusion of Zehle et al that dietary change programs, informed by the beliefs and circumstances of this high-risk population, need to be developed[182].

The finding that the Internet might be a suitable medium to offer lifestyle counseling supports previous research. It was earlier concluded that the Internet can be a valuable tool to support physicians and nurses in the field of adolescent preventive care[247]. The use of a combination of face-to-face counseling and computer-tailored counseling is also supported by previous research. In the field of child preventive health care, Internet-tailored fruit and vegetable education

was combined with brief counseling[248]; this integrated two-component intervention induced positive changes in knowledge and awareness of intake levels of fruit and vegetables among schoolchildren.

In addition to individual counseling, our results seem to indicate that group counseling might be suitable for these women as well. However, this needs to be further examined. During the focus group meetings, women reported that they would like to share their experiences with fellow sufferers. Their preference for a location where they could meet fellow sufferers, and their preference for a forum to get in touch with fellow sufferers, reflects this desire. This is also demonstrated by the fact that, after the focus group interviews, participants exchanged their e-mail addresses. In their social environment, women generally seem to lack the company of women who have experienced the same pregnancy complication(s), probably because of lack of knowledge and lack of understanding about the complication and its consequences. Due to this lack of social support, during participation in lifestyle counseling they would like contact with other women who have experienced the same pregnancy complication(s).

Some methodological considerations of the present study need to be addressed. Some selection bias may have occurred since only patients who gave birth in the Erasmus University Medical Center (a tertiary referral hospital) were invited to participate; despite efforts to prevent bias (e.g., by having random, consecutive participant selection), a volunteer bias might have occurred. In addition, an investigator bias may have arisen; although using more than one analyst might have improved the consistency or reliability of the analyses, the appropriateness of the interrater reliability concept in qualitative research is still debated[249].

CONCLUSION

The results of our study suggest that postpartum lifestyle counseling aimed at women who had experienced preeclampsia, intrauterine growth restriction, and/or gestational diabetes should be tailored to individual needs and preferences. However, further quantitative studies should be conducted to determine the relative importance of the reported preferences.

Postpartum lifestyle counseling aimed at these women should preferably be developed in collaboration with a multidisciplinary team of health care specialists and in close collaboration with potential users, should address important behavioral determinants, and should be both theory and evidence based. Further research is needed to establish whether women who have experienced different pregnancy complications also differ in their preferences for postpartum lifestyle counseling.

Based on our results, we conclude that postpartum lifestyle promotion among women who have experienced these pregnancy complications deserves more attention in clinical practice. Gynecologists should play a central role in informing women of their increased cardiovascular and metabolic risk. Before evidence-based interventions are developed specifically for this high-risk group, they could already emphasize the importance of adopting a healthy postpartum lifestyle.

Practice Implications

The efficacy of a developed lifestyle counseling strategy should eventually be tested in a randomized controlled trial. Meanwhile, the preferences reported in the present study provide a basis for desired health promotion support. These preferences can be implemented in the process of developing and implementing

a lifestyle promotion program for use in this high-risk group. Addressing these preferred lifestyle-counseling characteristics might promote participation in and adherence to postpartum lifestyle counseling aimed at women who have experienced these pregnancy complications.

Table 3.3.2. Prompts to explore women's preferences for postpartum lifestyle counseling after a pregnancy complicated with preeclampsia, intrauterine growth restriction and/or gestational diabetes.

To what extent do you need postpartum lifestyle counseling?

What would be your preferred characteristics of a lifestyle promotion program?

Face-to-face counseling

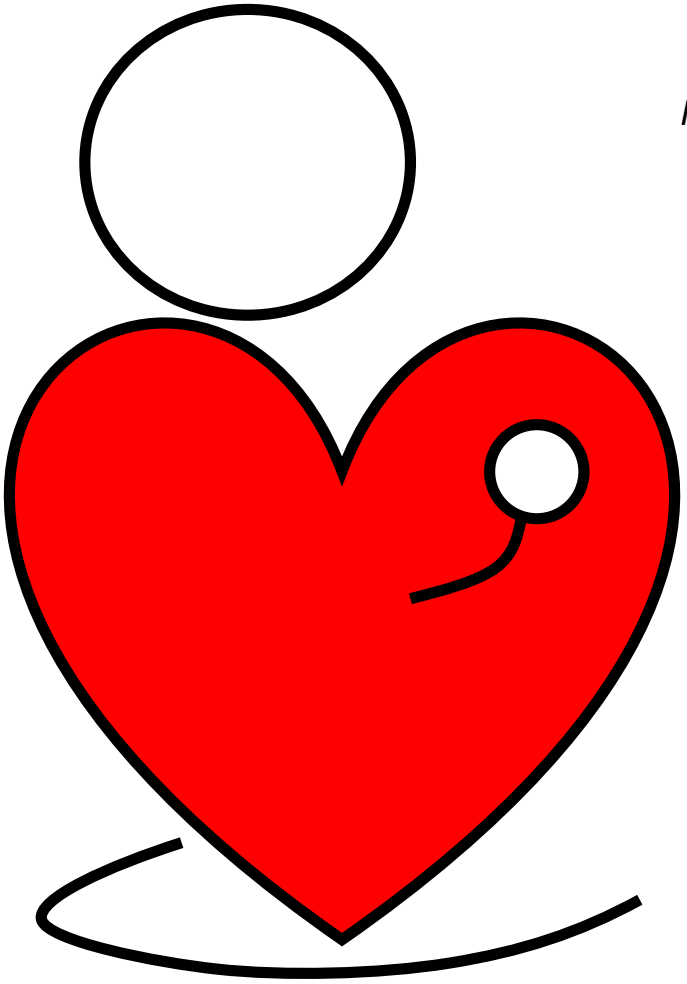
- By whom would you prefer the lifestyle counseling to be offered?
- Would you prefer your counselor to be a man or a woman?
- What profession would you prefer the counselor to have?
- Would you prefer seeing the same counselor across visits? Would you prefer multiple counselors?
- Where would you prefer the lifestyle counseling to take place?
- When would you prefer the lifestyle counseling to be offered?
- Would you prefer a separate visit for counseling or would you prefer to combine visits?
- What would you prefer with regard to the frequency of counseling visits?

Computer-tailored counseling

- What do you think about offering computer-tailored counseling on the Internet?
- What do you think of combining lifestyle counseling with a computer-tailored lifestyle promotion program?

Chapter 3.4

MOTIVATORS AND BARRIERS TO A HEALTHY POSTPARTUM LIFESTYLE IN WOMEN AT INCREASED CARDIOVASCULAR AND METABOLIC RISK: A FOCUS GROUP STUDY



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ABSTRACT

Objective To describe motivators and barriers to the adoption of a healthy postpartum lifestyle after a pregnancy complicated by preeclampsia, intrauterine growth restriction, and/or gestational diabetes.

Methods 36 women with complicated pregnancies participated in six focus group interviews that aimed to explore perceptions of modifiable determinants of postpartum lifestyle.

Results Although women expressed that they intended to live a healthy postpartum lifestyle, it was generally not achieved. Motivators included improving their own current health condition as well as modeling a healthy lifestyle for their children. Important barriers were reported to be lack of knowledge, poor recovery and lack of professional support after delivery.

Conclusions The reported motivators and barriers can be used to develop a postpartum lifestyle intervention.

INTRODUCTION

Cardiovascular disease and diabetes mellitus type II continue to be major causes of mortality and morbidity. Women who have experienced pregnancy complications like preeclampsia, intrauterine growth restriction and/or gestational diabetes are not only at an increased risk for recurrence of these complications in a subsequent pregnancy[250-252], but they share an increased risk to develop cardiovascular disease or diabetes mellitus type II later in life[2 3 10 26]. Furthermore, maternal placental syndromes, such as preeclampsia and intrauterine growth restriction more often occur in women with metabolic risk factors for cardiovascular disease, such as obesity, hypertension, and diabetes mellitus[2 3].

Risk factors for cardiovascular disease and diabetes mellitus type II, such as dyslipidemia, hypertension and obesity, are significantly related to lifestyle behaviors[59 235 253]. Lifestyle interventions have proven to be effective in reducing these risk factors for cardiovascular disease[253] and diabetes mellitus type II[58 254]. For example, improving poor nutrition, smoking cessation, and increasing physical activity can delay or prevent the onset of diabetes mellitus type II[3 255].

Guidelines recommend lifestyle measures to reduce cardiovascular risk[256]. More specifically, current literature suggests adoption of a healthy postpartum lifestyle to ameliorate cardiovascular and metabolic risk in women who have experienced these pregnancy complications[83]. However, it remains unclear how postpartum lifestyle can best be promoted in this women. In order to understand how a healthy postpartum lifestyle can best be promoted, women's perceptions of modifiable determinants of postpartum lifestyle need to be explored. Therefore, focus group interviews were held to describe motivators and barriers to the adoption of a healthy postpartum lifestyle.

METHODS

Participants

Patients with pregnancies complicated by preeclampsia, intrauterine growth restriction and/or gestational diabetes, who delivered in the Erasmus University Medical Center in Rotterdam between November 2004 and October 2006, were invited to participate in the focus group interviews. After searching hospital records, 182 patients were selected and invited by mail.

Preeclampsia was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP): development of systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg after 20 weeks of gestation in a previous normotensive woman plus proteinuria. Proteinuria was defined as a 24-hour urine collection containing at least 300 mg of protein[5].

Intrauterine growth restriction due to placental insufficiency was defined as an ultrasonic fetal abdominal circumference below the fifth percentile in combination with a pulsatility index of the umbilical artery > p 95 or absent or reversed end diastolic flow[242]. Gestational diabetes was diagnosed in case of at least one abnormal result (fasting>= 7.0 mmol/l or two hours>= 7.8 mmol/l) of a two-hour 75-gram oral glucose tolerance test[257 258].

A pregnancy complication was defined as severe if the gestational age at delivery was less than 32 weeks, the newborn was admitted to the Neonatal Intensive Care Unit, or resulted in perinatal death.

Procedure

Six focus group interviews were held at the Erasmus University Medical Center, Rotterdam, the Netherlands, between December 2006 and February

2007. Four of the group interviews consisted of patients with either mild or severe preeclampsia or isolated intrauterine growth restriction. One group interview consisted of women diagnosed with severe preeclampsia. Another group interview consisted of women diagnosed with gestational diabetes. Prior to the interviews, participants provided informed consent and completed a questionnaire regarding ethnicity, level of education, smoking habits, and self-reported weight and height. A moderator (M.H.), assisted by a facilitator (D.B./W.B.), led the focus group interviews. Interviews were held in line with the focus group principles provided by Morgan et al[244]. A semi-structured focus group discussion guide was used to structure discussion topics (see Table 3.4.2). Topics addressed in the semi-structured discussion guide were motivators and barriers to adoption of a healthy postpartum lifestyle. Additionally, components of the Theory of Planned Behavior were addressed: attitude, subjective norm, perceived behavioral control, and intention (see theoretical framework below). Interviews were audio taped and each lasted about 60 minutes. The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center.

Theoretical framework

Interpretation of results was theoretically framed within the Theory of Planned Behavior. The topics in the semi-structured interview guide were derived from the components of the Theory of Planned Behavior, according to which attitude, subjective norm, and perceived behavioral control determine intention to behavior. Attitude is defined as the degree to which performance of the behavior is positively or negatively valued. Subjective norm is the perceived social pressure to engage or not to engage in a behavior. And perceived behavioral control refers to people's perceptions of their ability to perform a

given behavior. Intention to behavior is a person's readiness to perform a given behavior[259 260]. Behavior is a function of compatible intentions and perceptions of behavioral control. Perceived behavioral control moderates the effect of intention on behavior, such that a favorable intention produces the behavior only when perceived behavioral control is strong.

Table 3.4.1. Demographic data and clinical characteristics of the study participants.

	n	(%)	Mean (SD)	Range
Women				
Age (years)	36		32.7 (4.5)	22 -41
Ethnicity				
Caucasian	22	(60.1%)		
African	8	(22.2%)		
Asian	6	(16.7%)		
Educational level				
Primary school	5	(14.7%)		
Secondary school	15	(44.1%)		
Higher education	14	(41.2%)		
Smoking				
Yes	3	(8.3%)		
Body mass index			24.8 (4.9)	17.1-39.3
25-30	12	(36.4%)		
≥ 30	4	(12.1%)		
Parity				
Nulliparous	18	(50%)		
Multiparous	18	(50%)		
Pregnancy complication				
Preeclampsia	21	(16.7%)		
Intrauterine growth restriction	4	(58.3%)		
Gestational diabetes	5	(11.1%)		
Preeclampsia and intrauterine growth restriction	6	(13.9%)		
Offspring				
Birth weight (g)	36		2352 (1155)	(690-4360)
Gestational age at delivery (days)	36		246 (4.9)	(184- 290)

Analysis

Ethnicity was classified according to Heart and Stroke Foundation criteria[261]. Educational level was assessed by the highest completed education and reclassified into three categories: primary school, secondary school and higher education[262]. Self-reported weight and height was used to calculate body mass index (BMI); a BMI of 25 or higher was defined as overweight, and 30 or higher as obesity. Birth weight and gestational age at delivery were retrieved from hospital records.

Focus groups were audio taped, transcribed verbatim and checked for accuracy. After transcripts were made, a qualitative data analysis program (the software package QSR Nvivo, version 7) was used to analyze the transcripts in accordance with content analysis principles[249 263]. Content analyses is a methodology to systematically analyze the content of communication. It's commonly used to analyze recorded transcripts of interviews. Discussion topics were identified, sorted and labeled according to the technique of content analysis. Discussion topics were examined across groups and for all groups combined.

RESULTS

Participants

Recruitment rate was 19.8%. Of the 36 women that participated in the focus group interviews, 21 had preeclampsia, 4 intrauterine growth restriction, 5 gestational diabetes, and 6 women had both preeclampsia and intrauterine growth restriction. The number of participants per group ranged from 4 to 10 (average 6). Women were 5.8 to 19.0 months postpartum at the time of the focus groups. Demographic data and clinical characteristics of the participants

are shown in table 3.4.1.

Attitude and intention

Women considered the main components of a healthy lifestyle to be a healthy diet, sufficient physical activity, no smoking, limited alcohol use, little stress, and a healthy environment to live in. All participants expressed the desire for living a healthy postpartum lifestyle, and most stated that they had the intention to adopt a healthy lifestyle shortly after delivery.

Motivators and subjective norm

After their complicated pregnancy, women felt that they were more aware of the vulnerability of their health condition, the importance of being in good health, and of the importance of a healthy lifestyle: *"I've never been so conscious of my health as after my pregnancy."* A healthy lifestyle after delivery was perceived as important, desirable, and a way of taking good care of themselves and their children. By adopting a healthy lifestyle women expected to promote both their physical and psychological health condition and to feel more energetic. The desire to be a good role model for their children also motivated them to adopt a healthy lifestyle. Women who were breastfeeding stated that a healthy diet was considered important because of the direct influence of their diet on the nutrition of their newborn.

Promotion of a future health condition was also reported to be a motivator for adopting a healthy postpartum lifestyle. Women stated that they wanted to live a healthy lifestyle to prevent recurrence of the old complication: *"If I want to have another baby in two years, I believe I have to improve my weight and physical condition - just in case it all goes wrong again, and I have another too small baby".* Furthermore, the majority said that their increased

cardiovascular and metabolic risk was an important reason for wanting to adopt a healthy postpartum lifestyle: *"Because of the increased risk, I don't eat too much fat, I avoid smoky places, and I have enough exercise. I'm aware of it - it's not that I think: I'll see what will happen in 10 years".* Furthermore, women perceived that a healthy lifestyle was also considered important and desirable by their partner, family, friends and their healthcare specialists.

Barriers and perceived behavioral control

The vast majority did not feel confident in their ability to be able to adopt a healthy lifestyle, and perceived it as difficult to achieve. Most women reported that they did not succeed in adopting a healthy postpartum lifestyle; this also applied to those who were living a healthy lifestyle prior to their pregnancy.

All women characterized their postpartum physical and psychological health condition as being worse than that prior to their pregnancy. This was more pronounced in women who had experienced a severe complication: *"After delivery, I've never had the feeling of being my old self again"*. Frequently reported complaints were fatigue, forgetfulness, low mood, sleep disturbance, emotional lability, and reliving events surrounding their complicated pregnancy. Women felt they were not yet recovered from their pregnancy, both physically and psychologically. This was reflected in the complaints they reported, even up to 19 months after delivery. This reported lack of recovery from their complicated pregnancy was mentioned to be the main barrier to adopt and maintain a healthy lifestyle. This was more often the case among women who had experienced preeclampsia compared with women who experienced gestational diabetes, since women who had experienced preeclampsia more often reported postpartum complaints and lack of recovery form their pregnancy: *"It was a battle to get out of bed, let alone thinking about eating two*

pieces of fruit and two ounces of vegetables a day." The pregnancy complications and their consequences were experienced as stressful life events, and the processing of and coping with these life events contributed to lack of recovery. In particular, the burden of emotional damage and the importance of psychological recovery were mentioned. Women also reported feelings of loss of control over their own body, and feelings of loss of confidence in their own body. Women reported that the recovery process as well as the adoption of a healthy postpartum lifestyle was hindered by a lack of postpartum support from health care providers, lack of knowledge, and lack of understanding about the pregnancy complication and its consequences: *"That's something I've missed, women who have been through the same thing to share experiences with, to be able to process my experiences." "Nobody around me indicated what had happened to me, what I could expect to happen after delivery, and what kind of help could be offered to me when needed."*

Compared with women who experienced preeclampsia and intrauterine growth restriction, women with gestational diabetes struggled with a healthy postpartum diet for different reasons. Whereas maintaining the diet prescribed by a dietician was associated with feelings of solitude, dullness, and isolation from their family or friends among women who had gestational diabetes, women who had preeclampsia and intrauterine growth restriction generally struggled with a healthy diet because of lack of recovery.

Other perceived barriers included lack of time and energy caused by daily demands such as taking care of their offspring, housekeeping, working, and frequent hospital visits. "I was already very pleased that I could run my household and to go to work. And that was all I could cope with at the time. For nine months I was worn out just by doing that". Frequent hospital visits were a particular challenge for women who had had intrauterine growth restriction,

since their offspring had more frequently been admitted to a neonatal care facility.

DISCUSSION

Our results show that even though most women reported that they had the intention, the majority did not succeed in adopting a healthy lifestyle. Barriers included poor postpartum physical and psychological recovery, and lack of postpartum medical and psychological support from their healthcare specialists. This suggests that there is a need for professional support in the adoption of a healthy lifestyle after pregnancies complicated by preeclampsia, intrauterine growth restriction and/or gestational diabetes. Professional support should focus on provision of knowledge about the pregnancy complications, their consequences, and what to expect after delivery.

The finding that poor postpartum recovery is a barrier to live a healthy lifestyle confirms previous research[148 264]. According to the participants in the present study, after delivery more information is needed about the complication and its consequences, about what to expect regarding its course, and how to deal with the complication and postpartum recovery. This is especially the case in severe complications. Women also prefer to receive more psychological and physical guidance to support their recovery, and would like to be guided in adopting a healthy lifestyle. They expect such information and guidance from their healthcare specialists. Healthcare specialists could be assisted and exonerated in the application of a lifestyle intervention directly after delivery, as previously proposed by Sattar et al[1].

It has been suggested that pregnancies complicated by preeclampsia, intrauterine growth restriction, and/or gestational diabetes may provide a

window of opportunity to apply a lifestyle intervention shortly after delivery[1]. Our study provides a list of motivators and barriers of postpartum lifestyle. This list can be used to develop a lifestyle intervention aimed at women who have experienced these pregnancy complications. However, the reported findings are descriptive and provide information that should be further evaluated in quantitative research in representative samples. Further quantitative research is needed to be able to determine the prevalence and the relative importance of the reported benefits and barriers. In addition, research should be focused on the determinants of participation in health promotion programs and preferred program characteristics in order to develop an effective evidence-based lifestyle intervention for implementation in this high-risk group

Study limitations and strengths

Selection bias might have occurred, as only patients who gave birth in the Erasmus University Medical Center (a tertiary referral hospital) were invited to participate. Patients who are admitted to this university hospital generally experience more severe complications compared to other hospitals in the surrounding area. Despite efforts to prevent bias (e.g. by having random, consecutive participant selection), a volunteer bias could have occurred. There was a low recruitment rate. Reasons for non-participation included insufficient understanding of the Dutch language and inability to be present at the time of the focus group interviews.

In addition, an investigator bias may have arisen. Although using more than one analyst might have improved the consistency or reliability of the analyses, the appropriateness of the inter-rater reliability concept in qualitative research is still debated[249 265].

Our finding that women did not succeed in living a healthy lifestyle,

despite their positive attitude, their motivation to comply to the beliefs of important referents, and their favorable intention, can be explained by applying the Theory of Planned Behavior. According to this theory, these women did not achieve a healthy postpartum lifestyle because of their low perceived behavioral control. This suggests that a healthy lifestyle can be promoted in these women by improving their perceived behavioral control. Perceived behavioral control might be increased by lowering or removing perceived barriers, such as lack of postpartum guidance, and poor physical and psychological recovery. Thus, a healthy postpartum lifestyle may be promoted by supporting postpartum recovery and by providing better postpartum guidance.

Table 3.4.2. Discussion guide to explore women's perceptions of postpartum lifestyle after a pregnancy complicated by preeclampsia, gestational diabetes, and/or intrauterine growth restriction

Opening questions
- What comes to mind when you think of a healthy lifestyle?
- What do you consider to be a healthy lifestyle?

Attitude
- To what extend is the adoption of a healthy lifestyle important to you?
- What makes a healthy lifestyle important to you?
- To what extent do you want to adopt a healthy lifestyle?

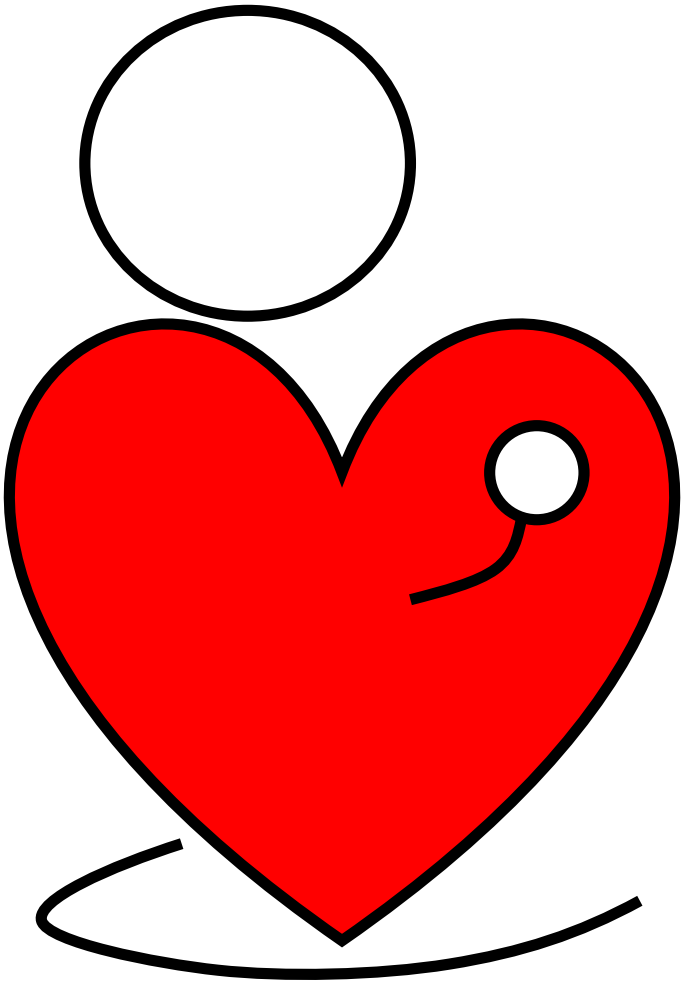
Intention
- To what extent do you intent to adopt a healthy lifestyle?

Motivators
- What motivates you to adopt a healthy lifestyle?
- What would be the reason for you to adopt a healthy lifestyle?
- To what extent does your social environment motivate you to adopt a healthy lifestyle (subjective norm)?

Barriers
- To what extent wo you think you are able to adopt a healthy lifestyle (perceived behavior control)?
- Why do you think you may not be able to adopt a healthy lifestyle?
- To what extent does your social environment not allow you to adopt a healthy lifestyle (subjective norm)?

Chapter 3.5

FEASIBILITY AND EFFECTIVENESS OF A LIFESTYLE INTERVENTION AFTER COMPLICATED PREGNANCIES TO IMPROVE RISK FACTORS FOR FUTURE CARDIOMETABOLIC DISEASE



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ABSTRACT

Objectives To evaluate the feasibility and effectiveness of a postpartum lifestyle intervention after pregnancies complicated by preeclampsia, fetal growth restriction (FGR) and/or gestational diabetes mellitus (GDM) to improve maternal risk factors for future cardiometabolic disease.

Design A specific pre-post controlled design.

Setting One tertiary care hospital and three secondary care hospitals (intervention group); one secondary care hospital (control group).

Participants Two hundred and six women six months postpartum following a pregnancy complicated by preeclampsia, FGR or GDM.

Intervention Lifestyle intervention program, consisting of a computer-tailored health education program in combination with three individual counselling sessions during seven months.

Main outcome measures Primary outcome measure of feasibility was the proportion of eligible women who complied with the intervention. Primary outcome measure of effectiveness was weight change during the intervention.

Results The proportion of eligible women who complied with the intervention was 23%. Major barrier was lack of time. Adjusted weight change attributed to lifestyle intervention was -1.9 kg (95%-CI -4.3 to -0.3). Further significant changes were observed in BMI (-0.9 kg/m^2 (95%-CI -1.4 to -0.3)), waist-to-hip ratio (-0.04 cm/cm (95%-CI -0.06 to -0.03)), blood pressure medication use (19% (95%-CI 9% to 28%)), HOMA2-score (59 %S (95%-CI 18 to 99)) and total fat intake (-2.9 gr (95%-CI -4.6 to -1.2)).

Conclusions The results support feasibility and effectiveness of a lifestyle intervention after complicated pregnancies to improve maternal cardiometabolic risk factors. The proportion of eligible women who complied with the intervention was twice as high as in other primary lifestyle intervention studies. Further randomized controlled studies are needed with longer follow-up to confirm our findings and evaluate durability. In the meantime, we suggest health care professionals to offer lifestyle interventions to women after complicated pregnancies.

INTRODUCTION

After pregnancies complicated by preeclampsia, fetal growth restriction and/or gestational diabetes mellitus, women are at an increased risk to develop cardiometabolic disease in later life. Women with a history of preeclampsia suffer from a two-fold increased risk of ischemic heart disease and stroke[80]. This increased risk may be due to shared risk factors, or an independent association between preeclampsia and cardiometabolic disease in later life[1]. Women with fetal growth restriction have an up to three-fold increased risk of future cardiovascular disease if it was the only pregnancy complication and an up to seven-fold increased risk in combination with preeclampsia[3 11 14 16]. Women with a history of gestational diabetes mellitus have a 20-60% risk of developing diabetes mellitus 5 to 10 years later[266].

Based on these observations pregnancy could be interpreted as a stress-test for cardiometabolic health[1]. As stress-test, pregnancy could identify young women with a high risk of future cardiovascular disease. So far, the scientific focus has been to examine differences in cardiometabolic risk factors between women with a history of complicated pregnancies and those with uncomplicated pregnancies[17].

As a stress-test for cardiometabolic health, a complicated pregnancy could identify 'high-risk' women at a young age. This provides opportunities to prevent future cardiometabolic disease. In addition, the complicated pregnancy might boost a woman's motivation to prevent future disease, thus providing a window of opportunity for starting a lifestyle intervention program[4].

Focus group studies have confirmed that women are willing to participate in a lifestyle intervention after pregnancy complications[186 206 267]. However, lifestyle interventions after pregnancies complicated by preeclampsia or fetal

growth restriction have not been evaluated yet[204].

The primary aim of this study is to evaluate the feasibility of a lifestyle intervention program after complicated pregnancies associated with an increased risk of future cardiometabolic disease by comparing the proportion of eligible women who completed the intervention to other lifestyle intervention programs. Secondary aim is to test effectiveness of this intervention in improving maternal cardiometabolic risk factors by analysing change in weight and other cardiometabolic risk factors before and after the intervention.

MATERIALS AND METHODS

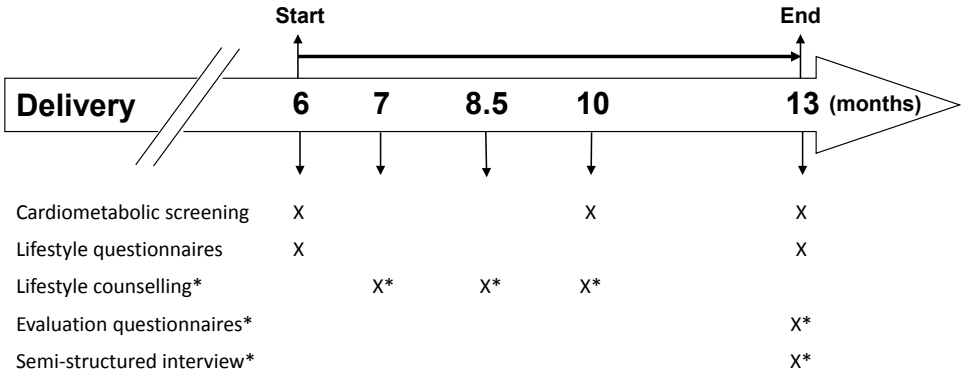
The Postpartum Rotterdam Appraisal of Cardiometabolic health and Tailored Intervention (PRo-ACTIve) study is a feasibility study to develop and evaluate a postpartum lifestyle intervention program. It was designed as a multicentre, specific pre-post controlled study[268] to develop and evaluate the lifestyle intervention. During the first year of the study a control cohort was considered to be a vital part of the effect evaluation of the intervention.

Women with pregnancies complicated by preeclampsia, fetal growth restriction and/or gestational diabetes mellitus were included between February 2007 and September 2010. Preeclampsia was defined according to ISSHP-criteria[5]: blood pressure of 140/90 mmHg or higher and proteinuria of at least 300 mg/day after a gestational age of at least 20 weeks. Severe preeclampsia was defined according to ACOG-criteria[83]: a blood pressure of 160 mmHg systolic or higher or 110 mmHg diastolic or higher; proteinuria of 5 gram or more in a 24-hour urine specimen or dipstick urinalysis of 3+ or greater in two random urine samples collected at least 4 hours apart; cerebral or visual disturbances; elevated liver enzymes; thrombocytopenia; fetal growth restriction. Fetal growth

restriction was defined according to ACOG-criteria[269]: fetal abdominal circumference < 5th percentile and umbilical artery Doppler with a pulsatility index ≥ 95th percentile and/or absent or reversed end-diastolic flow on last ultrasonic examination before delivery. Gestational diabetes mellitus was defined according to the 2003 report of the international expert committee of the American Diabetes Association on the diagnosis and classification of diabetes mellitus[243]: a fasting glucose > 6.1 mmol/L or a 2-hour glucose > 7.8 mmol/L after a 75-grams oral glucose tolerance test. Other inclusion criteria were age ≥ 18 years at time of inclusion, Dutch, Turkish or Moroccan ethnicity and mastery of the Dutch language. Women with pre-pregnancy cardiovascular and/or metabolic conditions, like renal insufficiency, pre-existent hypertension or diabetes mellitus were excluded. Cases of fetal growth restriction due to intra-uterine infection, congenital anomalies or abnormal fetal karyotype were also excluded.

At the Erasmus University Medical Center in Rotterdam (tertiary care hospital) and three secondary care hospitals (Sint Franciscus Hospital, Rotterdam, Maasstad Hospital, Rotterdam and Sint Elisabeth Hospital, Tilburg) women were screened for eligibility and asked to participate in the lifestyle intervention program. At the Amphia Hospital, Breda (secondary care hospital) women were screened for eligibility and subsequently served as the control group. At 5 months postpartum all eligible women were given or sent information about the study together with a letter of invitation to participate. If no response was received within two weeks, women were called on different weekdays. If twice unanswered, women were registered as unable-to-contact. Interested women were invited for a first visit six months postpartum. If during this visit informed consent was obtained, they were registered as participants.

Figure 3.5.1. Time-schedule of study in months after delivery



**Lifestyle counselling, evaluation questionnaires and semi-structured interviews are only applicable to the intervention group but not to the controls*

Study planning

The time-schedule of the study is shown in figure 3.5.1. The first visit was scheduled at six months postpartum, because we aimed for minimal changes in the measured variables due to ongoing recovery after pregnancy[202], and to minimize the chance that the women were going to be pregnant again during the study period. During the first visit, participants were extensively screened for cardiometabolic risk factors. Anthropometric measures included weight, height, waist- and hip circumference, blood pressure and heart rate. Weight was measured on a digital weighting scale in tenths of kilograms. Blood pressure and heart rate were measured according to the guideline of the British Hypertension Society (2004-BHS IV)[270]. Biochemical measures included high density lipoprotein (HDL) (HDL_Cholesterol plus 3rd generation (HDLC3), Cobas®, Roche Diagnostics), low density lipoprotein (LDL) (LDL-Cholesterol plus 2nd generation (LDL_C), Cobas®, Roche Diagnostics) and total cholesterol (Cholesterol Gen.2 (CHOL2), Cobas®, Roche Diagnostics), HDL/total cholesterol ratio, triglycerides (Triglycerides (TRIGL), Cobas®, Roche Diagnostics), fasting glucose (Glucose HK

Gen.3 (GLUC3), Cobas®, Roche Diagnostics), fasting insulin (Insulin, Cobas®, Roche Diagnostics), the Homeostasis Model Assessment (HOMA)2-score[271] as measure of insulin sensitivity and high-sensitive C-reactive protein (CRP) (C-Reactive Protein Gen.3 (CRPL3), Cobas®, Roche Diagnostics). Lifestyle was evaluated by three questionnaires, i.e. for saturated fat-intake the Maastricht Fatlist[272], for physical activity the International Physical Activity Questionnaire (IPAQ)[273] and for smoking habits the short version of the questionnaire of STIVORO (the Dutch anti-smoking association, www.stivoro.nl).

Three subsequent sessions with a trained lifestyle counsellor (MH) were scheduled between 7 and 10 months postpartum. The intervention consisted of a combination of individual counselling sessions based on the technique of motivational interviewing[193] and the use of a computer-tailored Dutch health education program (www.gezondlevencheck.nl of the Dutch Heart Association). The counselling sessions were preferably face-to-face, but could be taken by telephone if the woman wanted. The computer-tailored health education program and the three questionnaires were completed by the participants before each counselling session. The program provided feedback on the individual scores on the questionnaires. Based on these scores, Individual tailored lifestyle advice was discussed during the sessions and used to set personal lifestyle goals. Progress on the individual goals was discussed, and if applicable adjusted, at each subsequent session.

During the visit at 10 months postpartum the complete screening for cardiometabolic risk factors was repeated with exclusion of the lifestyle questionnaires. Women were encouraged to maintain their lifestyle program.

The final visit of the study was scheduled 13 months postpartum. The complete screening for cardiometabolic risk factors was repeated again, including the lifestyle questionnaires. In addition, women who participated in

the lifestyle intervention program received questionnaires to evaluate the intervention program (tables 3.5.3-3.5.5), including the Patient Satisfaction Questionnaire (PSQ-18)[274]. The questions were based on the motivators and barriers reported in previous focus group studies [186] [206]. Additionally, a qualitative semi-structured interview was conducted among women in the intervention group (table 3.5.6).

Statistical analysis

Primary outcome of feasibility was the proportion of eligible women who completed the intervention. This best represents how many women who could receive lifestyle intervention were actually motivated to complete the intervention. The higher this proportion, the more feasible it would be to plan larger-scale studies to test effect of postpartum lifestyle intervention after complicated pregnancy and to offer lifestyle intervention – if effective - as usual care. The proportion of eligible women who completed the intervention was defined as:

$$\frac{\mathrm{n}_{\text{Completed study}}}{\mathrm{n}_{\text{Eligible}}} = Rate_{Participation} * Rate_{Adherence} = Rate_{Participation} * \left(1 - Rate_{Dropout}\right)$$

Participation rate was defined by the number of women who agreed to participate in the study divided by the total of women who were eligible for participation. Based on other studies in primary lifestyle interventions[275] [276], a participation rate of 15% was expected. Adherence was defined by the number of women who attended the 13-months visit divided by the number of women who agreed to participate in the study. Based on other studies in primary lifestyle interventions in fertile women[60] an adherence of 75% was expected. Based on these numbers, the lifestyle intervention was found to be feasible if the

proportion of eligible women that completed the intervention was at least 11%.

The primary outcome measure for effectiveness was change in weight before and after the intervention. If the lifestyle intervention would be effective in improving diet and exercise, it would result in weight loss. Weight, as part of Body Mass Index (BMI) is a major risk factor of cardiometabolic disease. A weight loss of 2.7 kg, corresponding with a risk reduction of 50% for diabetes mellitus after 4 years, was considered clinically relevant [58 277]. With mean weight loss in the intervention group of 3.5 kg (SD 5.5), mean weight loss in the control group of 0.8 kg (SD 4.4)[277], α 0.05 (2-sided), β 0.80 and a cases-to-control ratio of 2:1 and an expected drop-out rate of 30% we calculated a sample size of 108 cases and 54 controls. Secondary outcome measures included the other anthropometrical, biochemical and lifestyle measurements.

Based on the intention-to-treat principle, women who became pregnant during the study period were considered as drop-out. Their pregnancy would have had considerable influence on the outcome measures. Women who dropped out for other reasons were approached for the final visit at 13 months postpartum.

Statistical analyses were performed using IBM SPSS Statistics, version 20, International Business Machines Corp©. The weight change between six months postpartum and the end of the study at 13 months postpartum was calculated for each participant in the intervention and control group. Using a linear regression model with weight change as outcome variable, we used the regression coefficient of the case group as effect of the intervention and thus adjusted for normal or 'background' change in the control group that would supposedly have occurred if lifestyle intervention had not been conducted (model 1). We also adjusted for known confounders (baseline weight measure at start at 6 months postpartum, duration of breastfeeding), and significantly

different demographic variables between the case and control group (model 2). This analysis was repeated for all secondary outcome measures, where the baseline weight measure was replaced by the baseline measure of the dependent variable. Results are presented as mean change and 95% confidence interval.

During the study we experienced lower adherence in the control group than expected. To compensate, we multiple imputed the 13-month measures for participants who had attended the visits at 6 and 10 months postpartum. The imputation model was based on the mean and standard deviation of participants who attended all visits, with a random generated z-score. Sensitivity analysis was performed by comparing the findings with the analysis without imputation. Three random iterations of imputation were done. Significant findings were only reported, if all 3 iterations showed significant results.

The study was funded by a research grant of ZonMw (61200024). Ethical approval was granted by the institutional review board of the Erasmus University Medical Centre (2006-164) and the participating secondary care hospitals.

RESULTS

Table 3.5.1 summarizes the demographics and baseline measures at enrolment. Significant differences between the intervention and control group were observed for ethnicity, marital status, birth weight, frequency of preeclampsia and severe preeclampsia and gestational age at delivery. Furthermore, the groups significantly differed in weight, systolic blood pressure and diastolic blood pressure at baseline measurement.

Table 3.5.1. Baseline characteristics of the study participants (n=206)

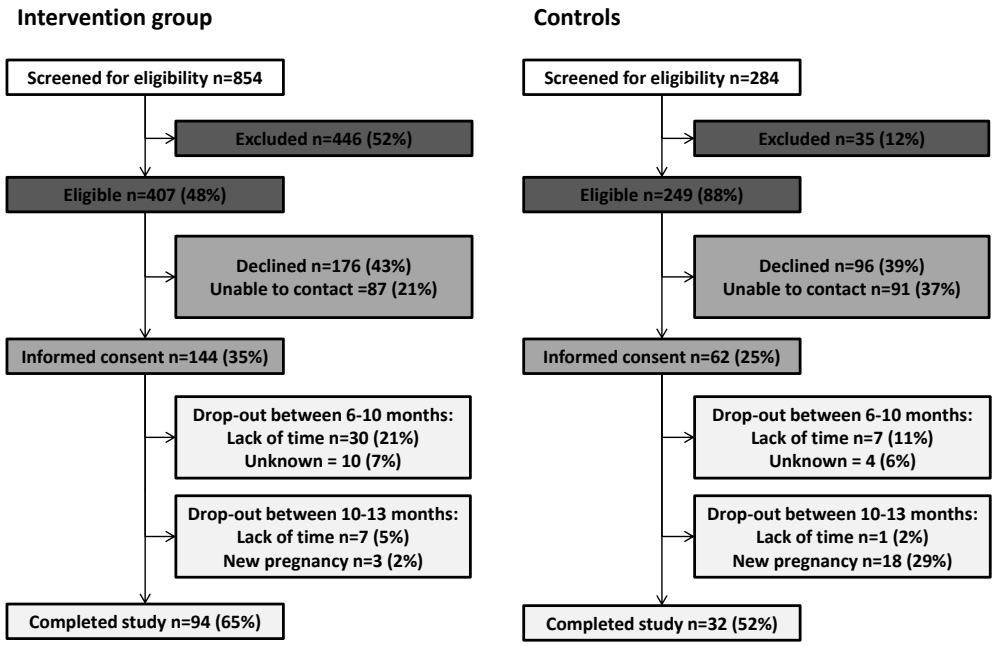
	Cases (n=144)	**Controls (n=62)**	**p-value**
Age (years)	31.6±4.2	30.7±8.8	0.31
Ethnicity			0.03
Dutch	94%(134)	97%(60)	
Turkish	3%(5)	-	
Moroccan	3%(5)	3%(2)	
Education			0.05
Primary school	8%(12)	2%(1)	
Secondary school	44%(63)	45%(28)	
Higher education	44%(64)	48%(30)	
Unknown	3%(5)	5%(3)	
Married	58%(84)	42%(26)	0.03
Primiparous	70%(101)	71%(44)	>0.99
Twin pregnancy	8%(12)	5%(3)	0.56
Birth weight (grams)	2209±1137	2947±868	<0.001
Breastfeeding (days)	42(0-421)	33(0-465)	0.88
Pregnancy complication			
Preeclampsia	83%(120)	68%(42)	0.02
Severe (% of preeclampsia)	76%(91)	57%(24)	0.03
IUGR	24%(35)	24%(15)	>0.99
Gestation diabetes mellitus	15%(21)	26%(16)	0.07
Insulin-dependent (% of gestational diabetes mellitus)	52%(11)	31%(5)	0.32
Gestational age at delivery (days)	242±31	263±20	<0.001
Baseline measures at start of study			
Weight (kg)	81±20	75±16	0.02
BMI (kg/m2)	28.3±6.6	26.4±5.4	0.05
WHR (cm/cm)	0.83±0.06	0.82±0.06	0.14
Systolic blood pressure (mmHg)	120±12	112±13	<0.001
Diastolic blood pressure (mmHg)	77±10	71±9	0.001
Blood pressure medication	9%(13)	6%(4)	0.78

Numbers in Mean ± SD, Median(Range) or %(n), significance is calculated with ANOVA (means), Mann-Whitney-U(medians) or Chi-Square(%).

Feasibility

The proportion of eligible women that completed the intervention was 94/407 (23%). Figure 3.5.2 shows the inclusion, participation and adherence to the study. Of the eligible women 41% declined participation (43% in the

Figure 3.5.2. Flowchart of inclusion, participation and compliance



intervention group, 39% in the control group). The main reported reason for declining participation was lack of time. An additional 27% of the eligible women could not be contacted (21% in the intervention group, 37% in the controls).

Of the 144 women who participated in the intervention group, 28% dropped out between 6 and 10 months postpartum, compared to 18% in the controls. The main reason was again lack of time. An additional 7% drop-out in the intervention group was observed between 10 and 13 months postpartum compared to 31% in the controls. The main reason for drop-out at this time was a next pregnancy.

Evaluation questionnaires were completed by 99% of the women who completed the intervention, but by none of the women who dropped out. Reported values are percentages of the responders. The questionnaires and their scores are shown in tables 3.5.3 to 3.5.5.

A strong motivator to participate in the lifestyle intervention was the experienced morbidity in the pregnancy (85%). Other motivators were the perceived increased risk of future disease (60%), risk of recurrence in a next pregnancy (58%) and the possibility to improve personal health (60%). A majority of the responders reported that feedback on their risk profile made them aware of their risk of future disease (80%) and empowered them to improve their lifestyle (84%).

Satisfaction with the lifestyle intervention was high (86%). A majority of the responders was satisfied with the counselling sessions (89%) and use of the computer-tailored health education program (61%). Perceived barriers to participate in the lifestyle intervention were travel distance (33%) and travel time (35%) to the hospital, although 76% thought the hospital to be a good setting for the counselling sessions. A total of 65% agreed that counselling sessions conducted by telephone were a good alternative for face-to-face counselling.

Preferred time between counselling sessions was eight weeks (range 4-16) and preferred average duration of the intervention program was 12 months (range 2-72). Preferred time to start with lifestyle intervention was at three months postpartum (range 0-26).

Effectiveness

Based on the differences in demographic and baseline measurements in table 3.5.1, we introduced prevalence of preeclampsia and severe preeclampsia, as well as gestational age at delivery into the adjustment model for the effect analysis.

Table 3.5.2 shows the changes in the intervention group after lifestyle intervention. Weight was significantly decreased by 4 kg in the intervention

Table 3.5.2. Effect of lifestyle intervention program

Parameter	Unit	Intervention group (n=144)		
		6 months	13 months	p-value
Weight	kg	81±20	77±19	<0.001
BMI	kg/m^2	28±7	27±6	<0.001
Waist-to-hip ratio	cm/cm	0.83±0.06	0.81±0.07	<0.001
Systolic blood pressure	mm Hg	120±12	117±12	0.09
Diastolic blood pressure	mm Hg	77±10	75±8	0.10
Blood pressure medication	%	9%	16%	0.02
Heart rate	bpm	75±11	71±8	<0.01
Total cholesterol	mmol/L	5.0±0.9	4.6±0.8	<0.001
LDL-cholesterol	mmol/L	3.1±0.8	2.9±0.7	<0.001
HDL-cholesterol	mmol/L	1.4±0.3	1.3±0.4	0.50
HDL/total cholesterol ratio	mol/mol	3.9±1.2	3.7±1.2	0.08
Triglycerides	mmol/L	1.3±0.9	1.2±1.0	0.07
Fasting glucose	mmol/L	4.9±0.6	4.9±0.9	0.31
75 gr-OGTT 2-hour value	mmol/L	5.2±1.2	5.0±1.7	0.54
Abnormal glucose (DM-2)	%	14%	12%	0.45
HOMA2-score	%S	130±106	144±111	0.57
CRP	mmol/L	5.7±9.4	5.7±8.1	0.76
Urinary protein/creatinine ratio	g/mol	12±23	12±23	0.40
Total protein in 24-hour urine	g/24h	113±207	116±159	0.58
Smoking	%	15%	14%	0.74
Physical activity	MET	3672±6554	3830±4240	0.07
Physical activity	steps/day	8290±2508	8658±2099	0.47
Fat intake total	g/day	17.0±5.1	15.1±5.1	<0.001
Fat intake snacks	g/day	6.2±3.0	5.5±3.0	<0.01

group. After adjustment for the change in controls, baseline weight, duration of breastfeeding, preeclampsia and severity of preeclampsia and gestational age at delivery, a significant decrease of 1.9 kg (0.3 to 3.4) could still be attributed to the lifestyle intervention. BMI and waist-to-hip ratio also significantly decreased, which remained after adjustment. Total and LDL-cholesterol changed significantly in the intervention group. However, after adjustment for the mentioned confounders this change was no longer significant. The change in HOMA2-score in the intervention group became significant after adjustment for the mentioned confounders. Lifestyle habits all showed favourable trends in the

Effect lifestyle intervention program at 13 months postpartum (95% CI)	
Model 1*	**Model 2#**
-1.8 (-3.2 to -0.3)	-1.9 (-3.4 to -0.3)
-0.8 (-1.3 to -0.3)	-0.9 (-1.4 to -0.3)
-0.04 (-0.06 to -0.03)	-0.04 (-0.06 to -0.03)
1.4 (-2.2 to 4.9)	0.7 (-3.1 to 4.4)
1.2 (-1.4 to 3.8)	0.8 (-1.9 to 3.6)
15% (4% to 25%)	19% (9% to 28%)
-2.9 (-5.6 to 0.6)	-0.7(-4.1 to 2.7)
-0.2 (-0.4 to 0.1)	-0.2 (-0.4 to 0.1)
-0.1 (-0.3 to 0.1)	-0.1 (-0.3 to 0.2)
0.1 (-0.02 to 0.2)	0.1 (-0.02 to 0.2)
-0.1 (-0.3 to 0.1)	0.1 (-0.3 to 0.2)
-0.04 (-0.2 to 0.1)	-0.02 (-0.2 to 0.2)
0.1 (-0.2 to 0.3)	0.01 (-0.3 to 0.4)
0.1 (-0.7 to 0.9)	0.1 (-0.9 to 1.0)
-13% (-39% to 12%)	-22% (-45% to 1%)
71 (-12 to 154)	59 (18 to 99)
0.2 (-2.6 to 2.9)	0.9 (-2.2 to 4.1)
2 (1 to 4)	2 (0.1 to 4)
27 (-12 to 66)	29 (-3 to 60)
-5% (-17% to 7%)	-5% (-16% to 7%)
2251 (329 to 4174)	844 (-945 to 2634)
452 (-695 to 1599)	302 (-1373 to 770)
-2.9 (-4.8 to -1.0)	-2.9 (-4.6 to -1.2)
-0.8 (-2 to -0.4)	-1.0 (-2.0 to 0.04)

intervention group after adjustment for the mentioned confounders except for total fat score, which decrease was significant.

Figures 3.5.3a-c shows the unadjusted change over time in the intervention and the control groups. All anthropometrical measures (figure 3.5.3b) show a rebound effect in the intervention group between the 10 and 13 months visit after counselling visits were discontinued. An increase in the use of blood pressure medication was observed in the intervention group, compared to a decrease in the control group.

Figure 3.5.3a. Lifestyle changes during the study period

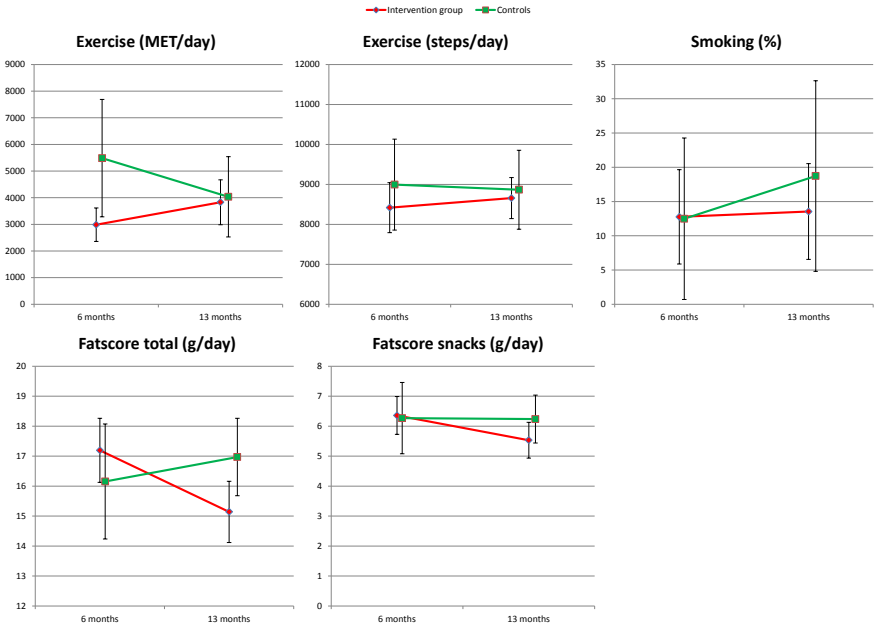


Figure 3.5.3b. Anthropometric changes during the study period

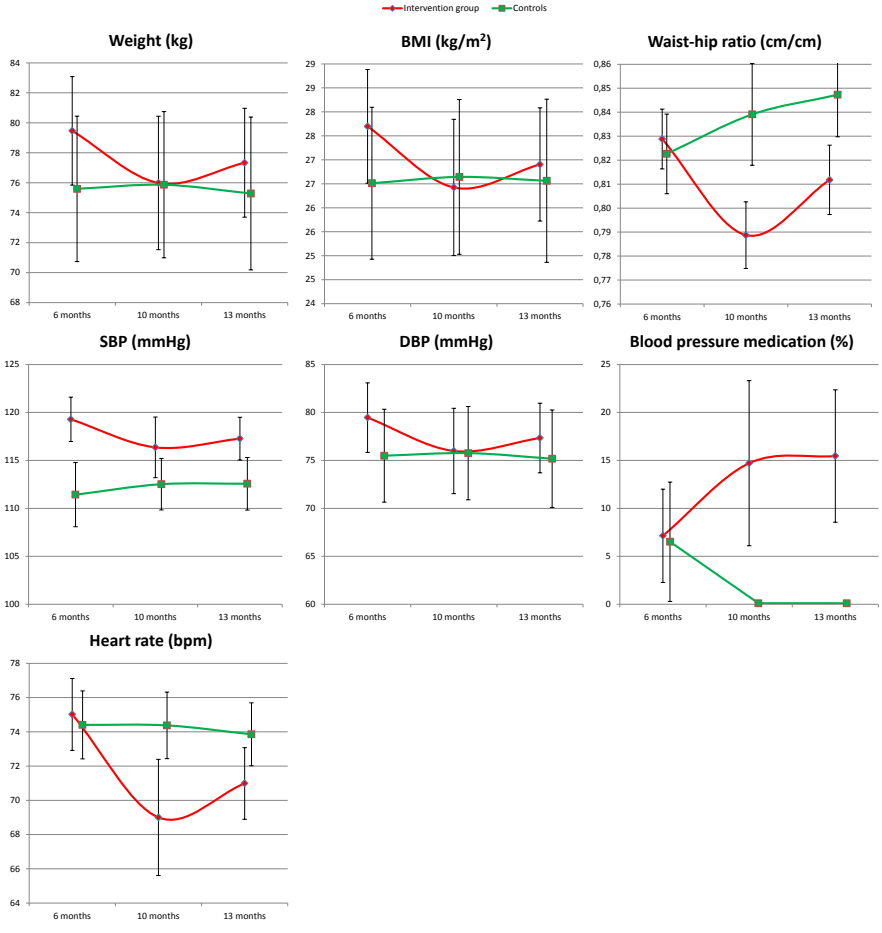
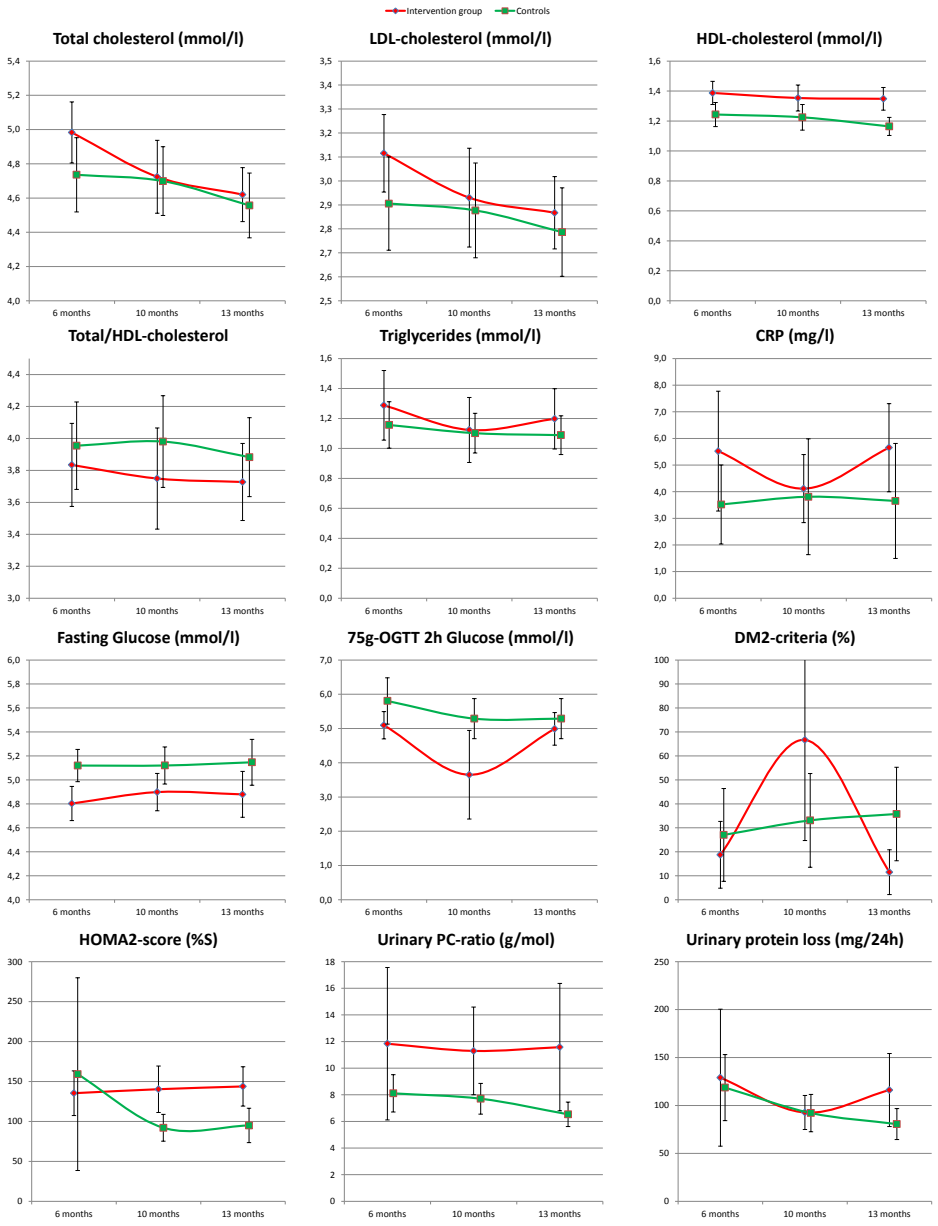


Figure 3.5.3c. Biochemical changes during the study period



DISCUSSION

We found a high proportion of eligible women who complied with the intervention, and women had a significant weight loss after the intervention, supporting feasibility and effectiveness of lifestyle intervention to improve maternal cardiometabolic risk factors.

Feasibility

The proportion of eligible women who complied with the intervention was 23%, twice the percentage we assumed (11%). Participation rate in the intervention group was 35%, which was higher than the expected 15%. On the other hand, adherence in the intervention group was 65%, which was lower than the expected 75%.

Participation rate in our study was twice as high as in other primary lifestyle interventions[275 276]. We showed that the pregnancy complication, the perceived increased risk of future disease and the risk of recurrence in a next pregnancy were strong motivators to comply with the study. This supports the idea that a complicated pregnancy opens a window of opportunity for lifestyle intervention. Adherence to the intervention (65%) was lower than expected. The main reason for drop-out was lack of time and was 4 times higher in the first half of the follow-up compared to the second half. Prior research showed that women generally prefer the location of the counselling close to home[186], suggesting that offering the lifestyle intervention in a primary health care setting might increase participation and adherence.

Only two recent studies on lifestyle interventions after metabolic complicated pregnancy reported participation and adherence rates. Both studies aimed to reduce the risk of type 2 diabetes mellitus in women with a history of

gestational diabetes mellitus. The proportions of eligible women that completed the intervention were 43%[278] (intervention was initiated at seven to eight weeks postpartum with a follow-up of 12 months) and 24% respectively (women were recruited within one to three years after their pregnancy with a follow-up of two years)[279]. This might indicate that the window of opportunity for lifestyle intervention after a complicated pregnancy is most present shortly after delivery and disappears over time. Offering lifestyle intervention six weeks after delivery might lead to a higher proportion of women complying to lifestyle intervention.

Of all eligible women in the intervention group, 21% could not be traced. Other postpartum lifestyle studies report similar percentages up to 35%[279]. Traceability might be improved shortly after delivery, when women are still in contact with their gynaecologist or midwife.

We used a health education program with tailored advice, already on-line available by the Dutch Heart Foundation. The women in our study liked the possibility to complete the computer-tailored health education online in their own time and found its advice easy to understand. It was, however, not specifically tailored to postpartum women and therefore the advice was not always readily applicable. During the counselling sessions, we tailored the advice to the personal situation. New developments like web-based tailored advice for postpartum women[278] as well as the use of new media like smartphones[280 281] are promising new ways to challenge low participation and adherence in postpartum lifestyle interventions.

Tailoring the start of the intervention to the woman's need might increase participation and adherence rates. Some women who completed the study would in retrospect have preferred to start with the intervention several weeks postpartum. In our study, women were informed at a fixed moment (five months postpartum).

We used the proportion of eligible women who complied with the intervention as measure of feasibility. Other studies focus on dropout rate[60]. However, dropout rate is biased by the motivation of participants and thus by the process of inclusion. By comparing studies by the proportion of eligible women who complied with the intervention, this bias is eliminated.

Effectiveness

Women in the intervention group had a significant weight loss that could be attributed to the lifestyle intervention. Also, the secondary outcomes BMI, waste-to-hip ratio, HOMA2-score and total fat score significantly improved.

Blood pressure medication was significantly more prescribed in the intervention group than in the control group. An explanation might be that the intervention group more often had preeclampsia and severe preeclampsia, leading to a longer recovery time and a longer need for blood pressure medication up to two years[202]. This was also expressed in a significantly higher baseline blood pressure in the intervention group. However, after adjustment for these variables the difference remained significant.

The effect of improved cardiometabolic risk factors was achieved between 6 and 10 months. Between 10 and 13 months a loss of effect was observed. Similar rebound effects were observed in other lifestyle intervention studies[154]. There are currently no strategies that effectively address the challenge of promoting sustained long-term behavioural change[282]. Studies with longer follow-up and on-going counselling with promising new strategies[280 281] must show if and how the improved cardiometabolic risk status by postpartum lifestyle intervention can be sustained.

The potential reduction in risk of recurrence of the sustained pregnancy complication was an important motivator for the women participating in the

intervention. Lifestyle interventions before or during pregnancy are known to be effective in improving obstetrical outcome[283] [284]. If started shortly after a complicated pregnancy, lifestyle intervention might give a larger reduction of the risk of recurrence in the next pregnancy than starting at a next pregnancy or when a next pregnancy is intended. Further studies are needed to evaluate this hypothesis.

We used weight loss as proving effectiveness of lifestyle intervention. Although used as primary outcome variable to test effectiveness by many other intervention studies, recently the Look AHEAD study showed that during the years after intervention weight was regained[285]. However, weight remained slightly but significantly lower, even years after the intervention, compared to women who did not have had intervention.

Strengths and weaknesses of the study

A major strength of this study is that it addresses a topic that is frequently being mentioned in preeclampsia research, but has never been studied before.

Another strength of this study is that we used validated questionnaires to evaluate lifestyle habits and tailored them to individual goals in the counselling sessions to make them easily applicable. Finally, we had a high participation rate as compared to other primary lifestyle studies, adding to the generalisability of our results. Although selection bias can never be totally eradicated in primary lifestyle intervention studies, our non-randomized study design and still low participation and adherence rates contributed to this bias.

Some other factors limit generalisability of our results. First we did not have information about the women who declined participation or could not be traced. Whether our results are applicable to these women, is unclear. Second, the majority of the women in the study were Dutch. Whether our results are

applicable to other than Dutch women, is unclear. Third, a major part of the women had received tertiary care. Whether our results are applicable to all women with complicated pregnancies, is unclear.

The criteria we used for gestational diabetes mellitus were based on the 2003 report of the expert committee on the diagnosis and classification of diabetes mellitus[243]. In 2010 new criteria for gestational diabetes mellitus were presented after completion of the HAPO-study[286]. Compared to the inclusion criteria of our study, the fasting glucose threshold is lower (5.1 mmol/l) and the 2-h glucose threshold after a 75-grams oral glucose tolerance test is higher (8.4 mmol/l). This might limit generalizability of our results to women who have been diagnosed with gestational diabetes mellitus based on other criteria than the ones we used.

Meaning of the study: possible explanations and implications for clinicians and policymakers

This study supports the feasibility and effectiveness of a lifestyle intervention after complicated pregnancies. We suggest that clinicians should discuss the possible beneficial effects of lifestyle intervention with women who experienced a cardiometabolic complicated pregnancy at the regular visit 6 weeks postpartum. If women are willing to comply, lifestyle intervention programs should be made available, preferably close to home in a primary health care setting.

Current guidelines recommend lifestyle modification and early evaluation for the most high-risk women[287], the provision of information to patients and primary care clinicians about increased risks in later life[288], assessment of traditional risk factors and to pursue a healthy lifestyle[289], counselling about beneficial effects of a healthy lifestyle and regular (1-5 yearly) cardiovascular

assessments[290] or counselling for a healthy lifestyle and cardiovascular assessment at menopause[291]. Our study provides support to recommend the availability of postpartum lifestyle intervention in these guidelines.

Unanswered questions and future research

We suggest randomized controlled trials, to decrease selection bias, in varied populations with a follow-up period of several years to confirm efficacy and durability of postpartum lifestyle intervention after complicated pregnancies. Varied populations will help to increase generalisability of the results. A longer follow-up is needed to evaluate the durability of the effects on cardiometabolic risk factors. The ideal primary outcome of these studies would be cardiometabolic events, although the low prevalence of these events needs large cohorts. To further decrease selection bias, more research is needed on motivators and barriers of women to increase participation and adherence to lifestyle intervention.

Table 3.5.3. Response to process evaluation at 13 months postpartum, questionnaire A: General Questions (response 93/144=65%)

		Totally Agree				**Absolutely Not Agree**
1	The intervention program was well adapted to women with a history of preeclampsia, foetal growth restriction of gestational diabetes mellitus	13%	56%	24%	8%	-
2	The intervention program was difficult to integrate into daily life	2%	7%	25%	47%	18%
3	The increased risk of recurrence in a next pregnancy was an important motivator to participate in the study	23%	35%	21%	16%	4%
4	The increased risk of future disease was an important motivator to participate in the study	23%	47%	11%	15%	3%
5	An important motivator to participate with the study was to improve my health	13%	47%	14%	22%	3%
6	The course of my pregnancy was an important motivator to participate in the study	25%	60%	4%	11%	1%

Table 3.5.3. *Continued*

		Totally Agree				Absolutely Not Agree
7	It was my own choice to improve my lifestyle, I did not feel forces by the counsellor	39%	45%	9%	7%	-
8	The counselling sessions helped me to improve my lifestyle	11%	39%	30%	20%	-
9	The counselling sessions were a valuable addition to the computer-tailored health education program	10%	54%	23%	13%	-
10	offsetting behavioural goals helped me to improve my lifestyle	7%	35%	40%	12%	1%
11	Feedback on my personal risk profile for future disease provided me with new information	2%	30%	35%	30%	4%
12	Feedback on my personal risk profile was an important motivator to change my lifestyle	2%	37%	35%	22%	3%
13	Feedback on my personal risk profile made me realise my risks of future disease	20%	60%	22%	8%	
14	Travel distance to the location of the counselling sessions was a barrier to comply with the intervention program	3%	14%	16%	45%	22%
15	Time to travel to the location of the counselling sessions was a barrier to comply with the intervention program	3%	16%	16%	41%	24%
16	The hospital is a good setting for counselling sessions	17%	59%	18%	3%	2%
17	Counselling sessions could be done by phone	11%	34%	20%	31%	4%
18	The recurrent counselling sessions helped me to comply with a healthier lifestyle	4%	48%	32%	14%	2%
		Too Short				**Too Long**
19	The use of the registration form to register my progress helped me to achieve my personal goals	2%	28%	47%	22%	2%
20	The time between the counselling sessions (6 weeks) was	-	4%	84%	12%	-
21	The total time of the intervention program (3 months) was	2%	13%	66%	17%	2%
22	The total time I spent to the intervention program was	-	5%	71%	23%	1%
23	The duration of each counselling session was	-	2%	90%	7%	1%
		Too Low				**Too High**
24	The frequency of the counselling was		11%	72%	17%	-

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Table 3.5.3. *Continued*

		Too Early				Too Late
25	I found the time the intervention program started after my delivery	4%	11%	77%	9%	-
26	For me the optimal time between the counselling sessions would be	8 weeks (4-16)				
27	For me the optimal total of counselling sessions would be	4 (2-12)				
28	For me the optimal time after delivery to offer an intervention program would be	3 months (0-26)				
29	For me the optimal duration of an intervention program would be	12 months (2-72)				

Table 3.5.4. Response to process evaluation at 13 months postpartum, questionnaire B: Computer-tailored health education program (response 93/144=65%)

		Totally Agree				Absolutely Not Agree
1	Completing the computer-tailored health education program took too much time	4%	25%	25%	41%	4%
2	Completing the computer-tailored health education program was easy	13%	70%	9%	7%	2%
3	The tailored advice provided by the computer-tailored health education program easy to understand	17%	71%	8%	3%	1%
4	I liked completing the computer-tailored health education program on-line	20%	57%	13%	6%	4%
5	Completing the computer-tailored health education program was a good way to be informed about my lifestyle	12%	59%	20%	8%	1%
6	Completing the computer-tailored health education program was a good way to get personal advice	10%	57%	23%	10%	1%
7	Log-in to the computer-tailored health education program was difficult	7%	9%	13%	53%	19%
8	I liked the fact that my personal lifestyle data could be viewed by the counsellor	11%	64%	24%	1%	
9	The provided tailored advice was applicable to my personal situation	6%	42%	33%	17%	3%
10	The provided tailored advice was complete	3%	37%	33%	20%	6%
11	The provided tailored advice was applicable to women like me	7%	45%	34%	11%	3%
12	The provided tailored advice was important to me	5%	33%	34%	25%	3%

Continues on next page

Table 3.5.4. *Continued*

		Totally Agree				Absolutely Not Agree
13	The provided tailored advice provided me with new information	1%	24%	35%	32%	9%
14	The provided tailored advice was applicable to women with a history of preeclampsia, IUGR or gestational diabetes mellitus	4%	30%	40%	21%	6%
15	The provided tailored advice was applicable to women 7 to 10 months after delivery	-	30%	47%	22%	1%
16	Repeatedly completing the computer-tailored health education program helped me to improve my lifestyle	2%	31%	39%	25%	3%
17	I liked the fact that I could complete the computer-tailored health education program when it suited me	20%	75%	3%	2%	-
18	The direct feedback on my lifestyle scores made me more aware of my lifestyle	7%	59%	23%	10%	2%
19	Completing the registration form of the computer-tailored health education program helped me to absorb the information	3%	37%	37%	20%	3%
20	The direct feedback of my lifestyle scores was a motivator to improve my lifestyle	4%	41%	40%	12%	2%
21	Completing the registration form of the computer-tailored health education program took too much time	1%	17%	29%	39%	14%

Table **3.5.5.** Response to process evaluation at 13 months postpartum, questionnaire C: Satisfaction (questions 5-22 are the PSQ-18) (response 93/144=65%)

		Very unsatisfied				Very satisfied
1	How satisfied are you with the intervention program?	-	3%	11%	57%	29%
2	How satisfied are you with the result of the intervention program?	-	1%	34%	46%	18%
3	How satisfied are you with the counselling sessions?	-	1%	10%	41%	48%
4	How satisfied are you with using the computer-tailored health education program?	2%	14%	23%	44%	17%

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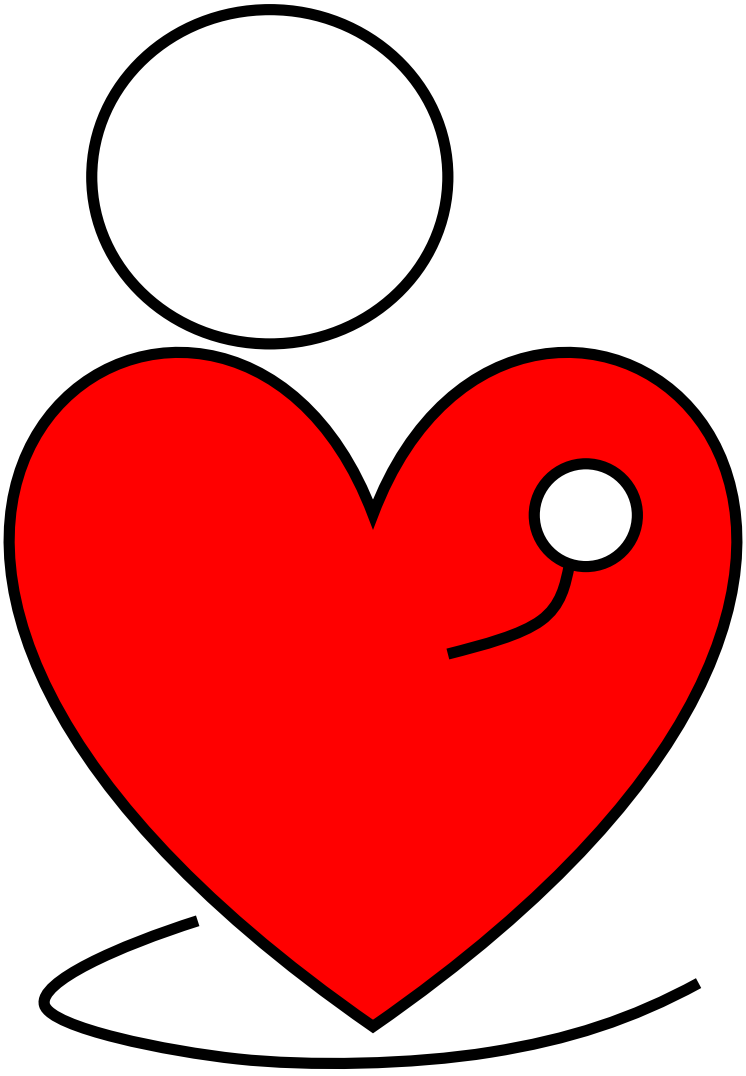
Table **3.5.5.** *Continued*

		Totally Agree				**Absolutely Not Agree**
5	The counsellor gave good information about the need of the counselling sessions	18%	72%	5%	2%	2%
6	Everything needed for a complete intervention program was available	14%	63%	14%	7%	2%
7	The provided counselling could not have been better	9%	45%	32%	14%	-
8	Sometimes I question myself if I got the appropriate counselling	-	7%	18%	59%	16%
9	I am confident that the counselling I needed was provided to me without getting me into financial problems	28%	51%	18%	1%	2%
10	The counsellor was well prepared to the counselling sessions	10%	46%	37%	5%	1%
11	The counselling sessions costed met more than I could afford	-	4%	20%	47%	29%
12	If needed, I could easily get in contact with my counsellor	14%	37%	38%	9%	2%
13	If urgently needed, It was difficult to get in contact with my counsellor	-	4%	46%	29%	21%
14	The counsellor was too impersonal	1%		5%	48%	45%
15	The counsellor was friendly and polite	29%	38%	1%	2%	-
16	The counsellor sometimes was in a haste	-	-	7%	46%	47%
17	Sometimes I doubted the competence of the counsellor	2%	3%	10%	39%	46%
18	I sometimes felt that the counsellor did not listen to me	1%	-	5%	43%	51%
19	The counsellor spend enough time to the visits	53%	43%	2%	-	2%
20	It was difficult to make an appointment on a short notice	1%	4%	33%	29%	31%
21	I am dissatisfied about certain aspects of the counselling sessions	1%	9%	8%	42%	40%
22	If needed, counselling could be provided to me	23%	31%	39%	4%	3%

Part Four

Discussion



This thesis should make us rethink on how cardiometabolic complications of pregnancy should be interpreted. It shows that cardiovascular recovery after preeclampsia could take as long as 2 years after delivery. It also presents preeclampsia not only as a marker, but as an independent risk factor of future cardiovascular disease. Finally, it describes a complicated pregnancy as a unique opportunity by using pregnancy as a stress-test to identify women at increased risk of future cardiometabolic disease. Women with a complicated pregnancy often struggle with their newly acquired motherhood, physical and psychological complaints and feelings of guilt, anxiety and worry for the health of their newborn and their own. This thesis proves lifestyle intervention as a feasible and probably effective way to offer these women a chance of a healthier future.

Postpartum recovery after preeclampsia

Recovery of hypertension and proteinuria can last until 2 years after preeclampsia. Severity and duration of preeclampsia affect postpartum recovery. The more severe the preeclampsia is and the longer it is prolonged, the longer it takes to recover which can take up to 2 years after delivery. At the regular check-up at 6 weeks postpartum, the gynecologist and midwife have a unique opportunity to identify women who are not fully recovered and need close cardiometabolic follow-up.

If hypertension or proteinuria persist at 6 to 12 weeks postpartum, the chance of resolving is still 50-85%. The chance of persistent hypertension after 2 years is 18%. And although persistent proteinuria at 2 years postpartum is rare (2%), identification of persistent disease could initiate proper treatment and limit progression of cardiometabolic disease over time. Moreover, persistent hypertension or proteinuria should initiate broad cardiometabolic screening for other traits, like dyslipidemia or impaired glucose intolerance.

The NICE guideline (2011)[288] does not address postpartum cardiometabolic screening yet. However, more recent developed guidelines do address this need of postpartum cardiometabolic screening after preeclampsia, but in various ways due to low-level evidence on screening strategies (cohorts or case-control studies or expert opinions). The variations are explicated in table 4.1. Explicit follow-up on hypertension and proteinuria are mostly not mentioned. Only one guideline (SGOC[289]) mentions a timeframe when to screen or act and one other guideline (ACOG[287]) takes severity of preeclampsia into account.

The Dutch guideline is most conservative regarding cardiometabolic screening, recommending only to start at the age of 50[291]. In case hypertension and proteinuria resolve within 2 years postpartum, this is a good recommendation, given the lack of evidence on the effect on future cardiometabolic events of routine postpartum extensive cardiometabolic screening.

More evidence is needed to uniform best practice of postpartum follow-up and screening after preeclampsia. Studies should focus on the chance of finding (1) modifiable risk factors, (2) treatable risk factors and (3) on the reduction of cardiovascular risk. Screening should not start before 2 years postpartum to reduce the risk of over-treatment when spontaneous recovery is still at hand.

Preeclampsia as risk factor of future cardiovascular disease

This thesis shows that preeclampsia is not just a marker, but an independent risk factor for future cardiovascular risk. Modelled odds-ratios for cardiovascular risk, based on differences in cardiometabolic health between formerly preeclamptic women and women with an uncomplicated pregnancy,

Table 4.1. International guidelines on postpartum follow-up and lifestyle intervention after preeclampsia

Guideline	Year	Follow-up hypertension	Follow-up proteinuria	Cardiometabolic screening	Advice on lifestyle
NICE[288] (England)	2011	None	None	None	Inform women about increased risk, intervention not mentioned
ACOG[287] (USA)	2013	None	None	Yearly extensive screening if delivery <37 weeks	Recommend lifestyle modification
SGOC[289] (Canada)	2014	Until well controlled, if difficult to control: referral to internal medicine	If persistent at 3-6 months postpartum: referral to nephrology	Once at least 6 weeks postpartum extensive screening	Women should pursue a healthy lifestyle
SOMANZ[290] (Australia, New-Sealand)	2014	None	None	Yearly blood pressure 5-yearly extensive screening	Counsel women that they will benefit from a healthy lifestyle
DSOG[291] (Netherlands)	2014	Until normotensive	None	Extensive screening at the age of 50 years	Counsel women to maintain a healthy lifestyle

NICE = The National Institute for Health and Care Excellence
ACOG = American Congress of Obstetricians and Gynecologists
SGOC = The Society of Obstetricians and Gynecologists of Canada
SOMANZ = Society of Obstetric Medicine of Australia and New Zealand
DSOG = Dutch Society of Obstetrics and Gynecology

still leave a significant gap with observed odds-ratios.

The model we used to estimate the independent risk of preeclampsia for future cardiovascular disease had limitations that could have overestimated the

independent effect of preeclampsia. However, another study that support the conclusion that preeclampsia is an independent risk factor is the HUNT-trial. It is a longitudinal prospective follow-up program in Norway, measuring cardiometabolic risk factors in women every decade[207]. A cohort was defined that had given birth between the 1985 and 1995 check-up. Compared to women with a non-hypertensive pregnancy, women after hypertensive disorder in pregnancy (including preeclampsia) had a 0.8 kg/m^2 increase in BMI, 6.2 mmHg increase in systolic blood pressure and 3.5 mmHg increase in diastolic blood pressure, adjusted for age at follow-up and pre-pregnancy values of BMI, systolic and diastolic blood pressure. While parity in general decreases risk of cardiovascular disease[292], this confirms our finding that preeclampsia independently and irreversibly decreases cardiovascular health and thus increases the risk of future cardiovascular disease.

Lifestyle intervention after complicated pregnancy

Lifestyle intervention after complicated pregnancy is feasible and effective in improving cardiometabolic health. Participation rate in our study was twice as high as in other primary lifestyle interventions[275 276]. Compliance was fair with a drop-out rate of 29%[60], but could be improved by offering lifestyle intervention closer to home or by phone.

Informing women of their risk profile made them more aware of their risk of future cardiometabolic disease. This was a good motivator to improve cardiometabolic health. However, women after a complicated pregnancy are having difficulties in finding time to invest in their own recovery. Caring duties for their, sometimes, prematurely or growth-restricted newborn take a lot of time. They perform worse on physical and psychological tests compared to women after an uncomplicated pregnancy[149]. Major determinants are NICU-

admission or death of their newborn[293-295]. Other determinants were a younger age, severity of preeclampsia, cesarean section and low gestation age[293].

When they need to go back to work at 10-12 weeks after delivery, they generally do not feel fully recovered. We started our intervention program at 6 months postpartum. Some women expressed their wish to participate, but had lack of time. Tailoring the moment to start with lifestyle intervention after complicated pregnancy can improve participation rates.

Gynecologists, midwifes and primary health care physicians should identify women at risk of future cardiometabolic disease at 6 weeks postpartum and inform them about their risk profile and risk of future cardiometabolic disease. They should initiate a lifestyle intervention program in combination with psychological counselling. The latter especially for those who have risk factors for post-traumatic stress, like younger maternal age and previous severe preeclampsia, cesarean section, fetal death, extreme prematurity and NICU-admission.

A strong recommendation based on this thesis is that gynecologists and midwifes should be responsible for the identification of these 'high risk' women and that primary health care physicians should be responsible for initiating a lifestyle intervention program and psychological counselling. The physician should refer to a trained lifestyle coach/counsellor, who has the time to listen and could help the women to set and reach their lifestyle goals. The coach/counsellor should guide these women at least 5 to 10 years, but probably lifelong.

However, more knowledge is still needed on the effects of lifestyle intervention after complicated pregnancy. Future research should include (1) randomization between different intervention strategies and (2) long-term maternal cardiometabolic follow- up.

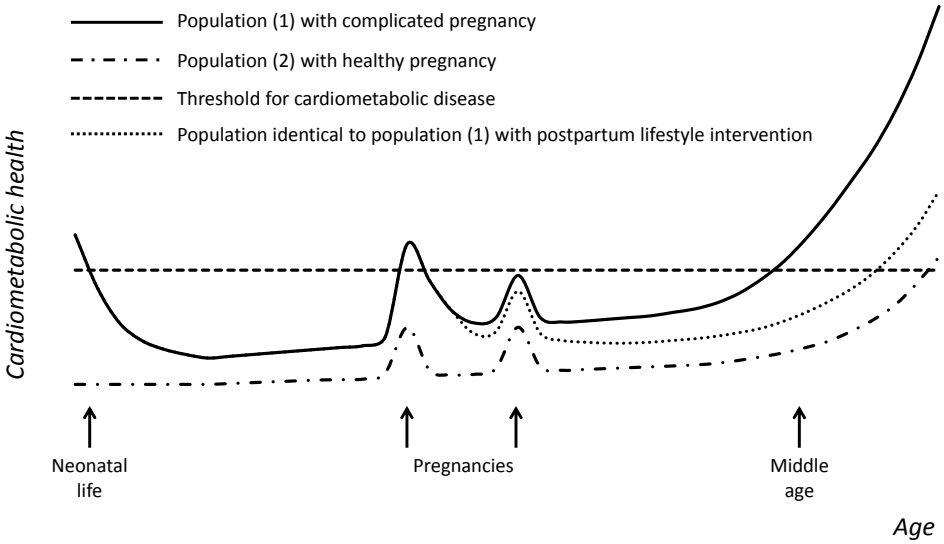
Scientific implications

The way this thesis changes our view on cardiometabolic complications of pregnancy is summarized in figure 4.1. The finding that cardiovascular recovery after preeclampsia could take as long as 2 years after delivery is presented in a less steep slope of the curve toward cardiometabolic recovery after a cardiometabolic complicated pregnancy. The finding that cardiometabolic complicated pregnancy is an independent risk factor of future disease is displayed by cardiometabolic health not returning to the 'base curve' after complicated pregnancy. Finally, the finding that lifestyle intervention is a feasible and might be an effective way to offer a chance of a healthier future is presented in the dotted line after cardiometabolic complicated pregnancy.

More knowledge is needed on the costs and benefits of postpartum screening strategies for cardiovascular traits.

Our study was not designed to prove the effect of lifestyle intervention, nor to do a cost-benefit analysis. Our findings on the effect of lifestyle intervention after cardiometabolic complicated pregnancy need to be confirmed in randomized controlled trials, comparing different intervention strategies. Inclusion criteria can be the same as in our Pro-Active study. More ethnicities should be included, offering them written material, questionnaires and counselling session in their native language. Lifestyle intervention could be initiated as early as 6 weeks postpartum, but start of the program must be tailored to the individual needs of the woman. Lifestyle intervention should be organized close to home by involving gynecologists and midwifes (responsible for the identification of women) primary health care physicians (responsible for organizing the initiation of lifestyle intervention) and trained

Figure 4.1. Possible effect of lifestyle intervention after complicated pregnancy on cardiometabolic health and future disease (adapted from Sattar and Greer, 2002[1])



coaches/counsellors. Follow-up should be at least 5 years, but preferably up to 10 years or longer and could be combined with a study on cardiometabolic screening strategies, e.g. yearly versus 5-yearly screening.

Primary outcome should ideally be the prevalence of cardiometabolic disease. However, intermediate cardiometabolic risk factors could be used, like weight, blood pressure, cholesterol and triglyceride-levels and exercise and fat intake.

Another interesting secondary outcome to study would be the risk of recurrent disease in a subsequent pregnancy. Preconceptionally initiated lifestyle intervention for weight reduction to reduce the risk of recurrent preeclampsia has not been studied yet[296], but is suggested by a risk reduction if initiated during pregnancy[284]. Lifestyle intervention to increase physical activity has no effect on risk of preeclampsia if initiated during or before pregnancy[297].

This might be a power-problem, since pre-pregnancy lifestyle interventions are scarce. It might be hypothesized that lifestyle intervention might be more effective if offered for a longer period, starting shortly after complicated pregnancy.

Another interesting secondary outcome would be psychological well-being during lifestyle intervention. Psychological burden might be an undervalued but important independent risk factor for cardiometabolic disease in women[52], and might offer a new terrain of prevention of cardiometabolic disease in women's health.

Clinical implications and current guidelines

Current guidelines differ in their advice what to do after a complicated pregnancy like preeclampsia (table 4.1). The newest guidelines recommend counselling of women that they will benefit from a healthy lifestyle. The somewhat older NICE guideline[288] does not mention lifestyle intervention, but advises to inform women about their increased risk of future disease. However, guidelines do not guide in the organization of lifestyle interventions.

Caution must be taken to advise for routine extensive cardiometabolic screening without proper studies on best practice. Benefits might be low, since risk profiles might be too low to start treatment. Although positive effects of lifestyle intervention could be observed, they might be small and therefore might have discouraging effects on compliance. Also the absence of classical risk factors for future disease could falsely reassure women that they already have a healthy lifestyle, leaving a risk for drop out of lifestyle coaching.

Recommendations for current practice

Gynecologist and midwife:

1. At the 6-weeks postpartum check-up after preeclampsia measure blood pressure and proteinuria. If still present, inform the primary health care physician by writing to take over follow-up. Advice to refer to a nephrologist if proteinuria is still present after 2 years or progresses. Advice for an extensive cardiometabolic screening if hypertension is still present after 2 years.
2. At the 6-weeks postpartum check-up after cardiometabolic complicated pregnancy, inform the woman about their increased future risk and the beneficial effect of a healthy lifestyle. Refer to primary health care physician (by writing) for lifestyle intervention.
3. Emphasis the need for a pre-conception consultation in case the woman wants to become pregnant again in the future. During pre-conception consultation focus on lifestyle and modifiable and treatable cardiometabolic risk factors. If applicable, counsel the woman that she will benefit from a healthier lifestyle.

Primary health care physician:

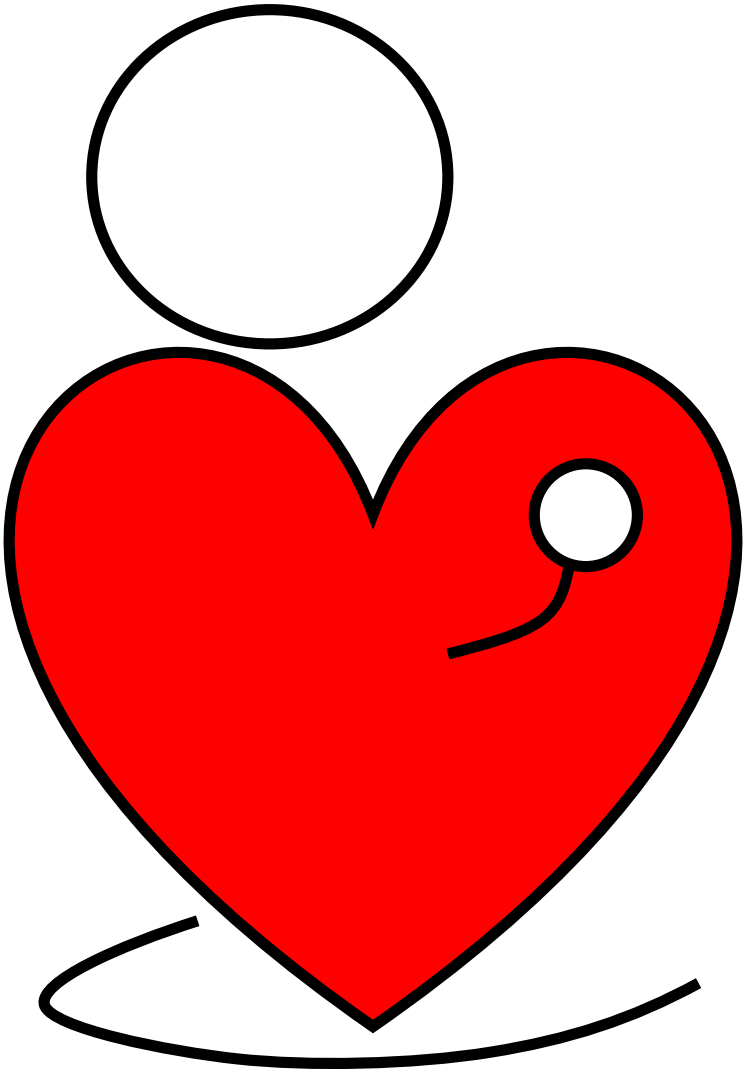
4. During follow-up after preeclampsia refer to a nephrologist if proteinuria is still present and perform an extensive cardiometabolic screening if hypertension is still present after 2 years.
5. Counsel a woman after cardiometabolic complicated pregnancy that she will benefit from a healthier lifestyle. If she wants to, refer her to a lifestyle coach/counsellor. The latter especially if she has risk factors for post-traumatic stress, like younger age, severe preeclampsia, cesarean section, fetal death, extreme prematurity and NICU-admission.
6. If a woman expresses the wish for a new pregnancy, refer her to a gynecologist for a pre-conception consultation.

Gynecologist, midwife and primary health care physician:

7. Write a local protocol describing (the organization of) follow-up, cardiometabolic screening and lifestyle intervention after complicated pregnancies.

Part Five

Summary



SUMMARY

Women with a history of cardiometabolic complicated pregnancy are at increased risk for future disease. The metabolic syndrome may represent a pathophysiological link between a complicated pregnancy and future cardiometabolic risk. However, since studies focus on women after their pregnancy, it remains unclear whether pregnancy complications themselves (irreversibly) affects cardiometabolic health. The answer to this question does not alter the fact that a complicated pregnancy uniquely identifies these women at a young age as high risk for future disease. This represents a unique possibility for primary lifestyle intervention. However, although it is difficult to reach and motivate the eligible people to change their lifestyle, the experience of having had a complicated pregnancy might open up a window of opportunity to guide these women to a healthier future.

The introduction and outline of this thesis are presented in **part 1**. The general aim of this thesis is to develop and evaluate a postpartum program appraising cardiovascular health and offering lifestyle intervention after complicated pregnancy to reduce future cardiometabolic risks.

Lot of research is being performed on cardiovascular health after preeclampsia. **Part 2** describes our findings that contribute to the appraisal of cardiovascular health after complicated pregnancy. In **chapter 2.1** a historical prospective cohort is used to test how time to resolution correlate with the levels of blood pressure and proteinuria during preeclampsia and the prolongation of pregnancy after the development of preeclampsia. We showed that maximal blood pressure and prolongation of pregnancy were significantly correlated with time of postpartum recovery of hypertension. Every day that preeclampsia was prolonged added 4% more time to recovery of hypertension. This suggests that

preeclampsia exhibits a direct effect on postpartum cardiovascular health. In **chapter 2.2** we used a retrospective cohort to test the hypothesis that different phenotypes of preeclampsia are associated with thrombophilia factors. We also provide an overview of the literature. We conclude that only anti-phospholipid antibodies are associated with (severe) preeclampsia.

The development and evaluation of a lifestyle intervention program after cardiometabolic complicated pregnancy is described in **part 3**. In **Chapter 3.1** we provide a review of the literature (until May 2010) to identify potential intervention strategies. We found no studies on postpartum lifestyle interventions after cardiometabolic complicated pregnancies. We included 21 studies on postpartum lifestyle intervention on unselected women on the basis of pregnancy complications. Six of 8 weight loss interventions, 4 of 5 smoking cessation interventions, and 4 of 8 smoking relapse prevention interventions were shown to be effective. In **chapter 3.2** we estimate the effects of lifestyle intervention after preeclampsia on the risk of cardiovascular disease. First, the differences in cardiovascular risk factors after preeclampsia compared to an uncomplicated pregnancy were estimated. Second, the effects of lifestyle interventions on cardiovascular risk factors were estimated. Validated risk prediction models were used to translate these results into an effect on cardiovascular risk. We estimated the odds-ratio of cardiovascular disease after lifestyle interventions on a combination of exercise, dietary habits and smoking cessation to be 0.91 (0.87-0.96). Since lifestyle intervention in this model does not completely ameliorate the risk of cardiovascular disease, we also conclude that preeclampsia may represent an independent risk factor for cardiovascular disease.

In **chapter 3.3** and **chapter 3.4** we describe our focus group studies on women after complicated pregnancies. With regard to women's preferences for

postpartum lifestyle counseling (**chapter 3.3**) we found that all women expressed a need for participation in postpartum lifestyle counseling. They preferred participation to be tailored to individual preferences. A combination of face-to-face counseling supported by computer-tailored lifestyle advice appealed to them. With regard to motivators and barriers to the adoption of a healthy postpartum lifestyle (**chapter 3.4**) we found that although women expressed that they intended to live a healthy postpartum lifestyle, it was generally not achieved. Motivators included improving their own current health condition as well as modeling a healthy lifestyle for their children. Important barriers were reported to be lack of knowledge, poor post-pregnancy recovery and lack of professional support after delivery.

Chapter 3.5 describes the Pro-Active study: a specific pre-post controlled designed study to evaluate the feasibility and effectiveness of a postpartum lifestyle intervention after complicated pregnancies to improve maternal risk factors for future cardiometabolic disease. Our results support feasibility and effectiveness of a lifestyle intervention after complicated pregnancies to improve maternal cardiometabolic risk factors. The proportion of eligible women who complied with the intervention was twice as high as in other primary lifestyle intervention studies, supporting the window of opportunity for lifestyle intervention after a complicated pregnancy. We also conclude that further randomized controlled studies are needed with longer follow-up to confirm our findings and evaluate durability. In the meantime, we suggest health care professionals to offer lifestyle interventions to women after complicated pregnancies.

Part 4 provides the general discussion on how the results of this thesis should make us rethink the interpretation of cardiometabolic complications of pregnancy. It presents preeclampsia as an independent risk factor of future

cardiovascular disease. It also proves lifestyle intervention as a feasible and probably effective way to offer these women a chance of a healthier future. It gives an overview of scientific implications by describing further research to better test the effects of lifestyle interventions. Regarding clinical implications, it reflects on the current international guidelines and gives recommendations for current practice.

SAMENVATTING

Vrouwen met in de voorgeschiedenis een cardiometabool gecompliceerde zwangerschap hebben in de toekomst een verhoogd risico op vergelijkbare ziekten. Het metabool syndroom kan dienen als pathofysiologische link tussen een gecompliceerde zwangerschap en toekomstige cardiometabool risico. Doordat studies zich richten op vrouwen na hun zwangerschap, blijft het echter de vraag of de gecompliceerde zwangerschap zelf (irreversibel) effect heeft op cardiometabole gezondheid. Het antwoord op deze vraag laat echter onverlet dat een gecompliceerde zwangerschap vrouwen op jonge leeftijd identificeert meteen verhoogd risico op toekomstige ziekte. Dat betekent een unieke kans voor primaire leefstijl interventie. Terwijl het lastig is om deze groep mensen in het algemeen te bereiken en te motiveren hun leefstijl aan te passen, zou het doormaken van de gecompliceerde zwangerschap een 'window of opportunity' kunnen zijn, waarin deze vrouwen open staan voor leefstijlaanpassingen.

De introductie en uiteenzetting van dit proefschrift worden beschreven in **deel 1**. Het belangrijkste doel van dit proefschrift is het ontwikkelen en evalueren van een postpartum programma voor het beoordelen van cardiovasculaire gezondheid en begeleiden van leefstijl aanpassingen om te komen tot verlaging van het risico op toekomstige cardiometabole ziekte.

Er is veel onderzoek verricht naar cardiovasculaire gezondheid na pre-eclampsie. **Deel 2** beschrijft onze bevindingen die bijdragen aan het inschatten van de cardiovasculaire gezondheid na een gecompliceerde zwangerschap. In **hoofdstuk 2.1** wordt aan de hand van een historisch prospectief cohort getest hoe het postpartum herstel van bloeddruk en proteïnurie correleert met de bloeddruk en proteïnurie tijdens de pre-eclampsie en de tijdspanne tussen het stellen van de diagnose pre-eclampsie en de bevaldatum. We laten zien dat

zowel de maximale bloeddruk als het tijdsbestek tussen de diagnose pre-eclampsie en bevalling beide significant gecorreleerd zijn met het postpartum herstel van de hypertensie. Elke dag dat de vrouw met pre-eclampsie langer zwanger blijft, voegt 4% toe aan de tijd die nodig was voor herstel van de hypertensie. Deze bevinding suggereert dat pre-eclampsie een direct effect heeft op postpartum cardiovasculaire gezondheid. In **hoofdstuk 2.2** gebruiken we een retrospectief cohort waarin we de hypothese testen dat verschillende fenotypes van pre-eclampsie geassocieerd zijn met trombofilie factoren. We geven ook een literatuuroverzicht. We concluderen dat alleen antifosfolipide antistoffen geassocieerd zijn met (ernstige) pre-eclampsie.

De ontwikkeling en evaluatie van een leefstijl interventie programma na cardiometabool gecompliceerde zwangerschap wordt beschreven in **deel 3**. In **hoofdstuk 3.1** geven we een overzicht van de literatuur (tot mei 2010) om potentiele strategieën te identificeren. Studies over leefstijl interventie programma's na cardiometabool gecompliceerde zwangerschap konden we echter niet vinden. Om toch een idee te krijgen van de effectiviteit van leefstijl interventie programma's includeerden wij 21 studies over leefstijl interventie na zwangerschap van een groep ongeselecteerde vrouwen. Zes van de 8 interventies op gewichtsverlies, 4 van de 5 op stoppen-met-roken en 4 van de 8 voorkomen-opnieuw-te-gaan-roken laten een significant effect zien. In **hoofdstuk 3.2** maken wij een schatting van het effect van leefstijl interventie na pre-eclampsie op het risico op hart- en vaatziekten. Eerst schatten wij de verschillen in risicofactoren voor hart- en vaatziekten tussen vrouwen na pre-eclampsie in vergelijking met vrouwen na een ongecompliceerde zwangerschap. Vervolgens schatten wij het effect van leefstijl interventies op de risicofactoren voor hart- en vaatziekten. Tot slot gebruikten wij gevalideerde predictie modellen om deze bevindingen te vertalen naar een verschil in het risico op hart-

en vaatziekten. Dit resulteerde in een odds-ratio voor hart- en vaatziekten na leefstijl interventie op een combinatie van bewegen, eetgewoonten en stoppen-met-roken van 0,91 (0,87-0,96). Aangezien leefstijl interventie het toegenomen risico op hart- en vaatziekten na pre-eclampsie niet volledig doet verdwijnen, concluderen wij tevens dat pre-eclampsie kan worden beschouwd als een onafhankelijke risicofactor voor hart- en vaatziekten.

In **hoofdstuk 3.3** en **hoofdstuk 3.4** beschrijven we 2 focusgroep studies met vrouwen na een gecompliceerde zwangerschap. Met betrekking tot hun voorkeur voor postpartum counseling over leefstijl (**hoofdstuk 3.3**) zien wij dat alle deelnemende vrouwen de behoefte hadden om postpartum te worden geïnformeerd over het belang van een goede leefstijl. Ze gaven de voorkeur aan informatie die specifiek op hen van toepassing was. Een combinatie van face-to-face counseling, ondersteund door computergestuurde, specifieke leefstijl adviezen vonden ze een aantrekkelijke strategie. Met betrekking tot motiverende en remmende factoren voor het postpartum aannemen van een gezonde leefstijl (**hoofdstuk 3.4**) zien wij dat ondanks dat vrouwen zich dat wel voornamen, het hen over het algemeen niet lukte om dat te bereiken. Motiverende factoren waren onder andere het verbeteren van hun gezondheid en een rolmodel zijn voor hun kinderen. Belangrijke remmende factoren waren gebrek aan kennis, langzaam herstel postpartum en gebrek aan professionele ondersteuning.

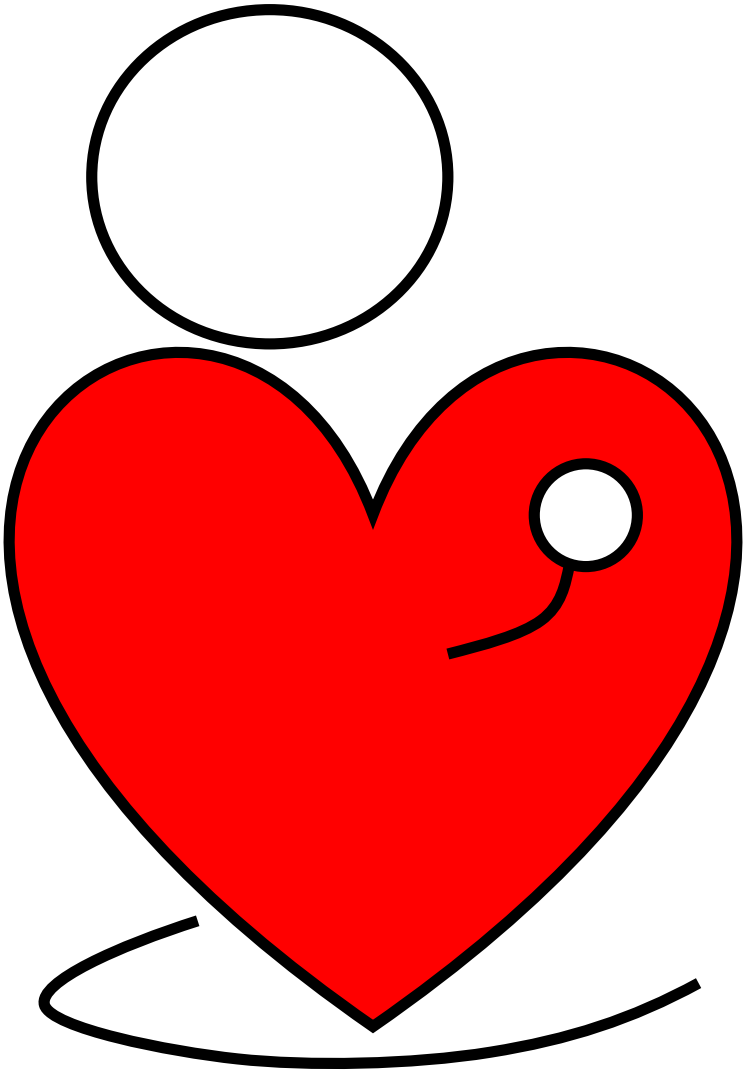
Hoofdstuk 3.5 beschrijft de Pro-Active studie: een specifiek pre-post gecontroleerde studie voor het testen van de haalbaarheid en effectiviteit van een postpartum leefstijl interventie na gecompliceerde zwangerschap op het verbeteren van risicofactoren van toekomstige cardiometabole ziekten. Onze resultaten ondersteunen de haalbaarheid en effectiviteit van een postpartum leefstijl interventie op het verbeteren van risicofactoren. Het aantal vrouwen dat

tot het einde bij de interventie betrokken bleef, was 2 keer zo hoog in vergelijking met andere primaire leefstijl interventie programma's. Daarmee wordt de 'window of opportunity' na een gecompliceerde zwangerschap onderschreven. We concluderen eveneens dat gerandomiseerde, gecontroleerde studies, met een langere follow-up dan onze studie, nodig zijn om onze bevindingen te bevestigen, met name ook de houdbaarheid van het effect van leefstijl interventie. Voor de tussenliggende tijd suggereren we dat zorgverleners aan vrouwen na een gecompliceerde zwangerschap leefstijl interventies aanbieden.

Deel 4 betreft de algemene discussie over hoe dit proefschrift ons de interpretatie van cardiometabole complicaties van de zwangerschap doet heroverwegen. Pre-eclampsie wordt gepresenteerd als onafhankelijk risicofactor voor toekomstige hart- en vaatziekten. Leefstijl interventie wordt als een haalbare en waarschijnlijk effectieve manier gezien om vrouwen de kans te geven op een gezondere toekomst. Het geeft een overzicht over de wetenschappelijke implicaties, waarbij toekomstig onderzoek wordt beschreven waarin het effect van leefstijl interventie kan worden getoetst. Met betrekking tot klinische implicaties wordt een reflectie gegeven op de huidige internationale richtlijnen en worden aanbevelingen gedaan voor de praktijk.

Part Six

Addenda



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Research skills

- Course English writing 2008
- NIHES course (introduction to data-analysis, regression analysis, survival analysis) 2009

Oral Presentations

- Symposium Circle of Life, Rotterdam, Netherlands 2006
  Future maternal cardiovascular disease after complicated pregnancy
- ISSHP congress, Reykjavik, Iceland 2007
  Duration of proteinuria after preeclamptic pregnancy
- Doelen-congress, Rotterdam, Netherlands 2009
  Lifestyle intervention after preeclampsia
- Regional minisymposium, Rotterdam, Netherlands 2010
  Preeclampsia as independent risk factor of future cardiovascular disease
- ISSHP-congress, Melbourne, Australia 2010
  Preeclampsia is probably an independent risk factor for cardiovascular disease

- ISSHP-congress, Melbourne, Australia 2010
  Postpartum lifestyle intervention after complicated pregnancy proves feasible
- ISSHP-congress, Melbourne Australia 2010
  What effect can we expect of postpartum lifestyle intervention after preeclampsia?
- CHIPS-minisymposium, Amsterdam, Netherlands 2011
  Lifestyle intervention studies after severe hypertensive disorders of pregnancy: efficacy and feasibility
- Minisymposium Preeclampsia, Groningen, Netherlands 2011
  Lifestyle intervention studies after severe hypertensive disorders of pregnancy: efficacy and feasibility
- ISSHP-congress Geneva, Switzerland 2012
  Lifestyle intervention after complicated pregnancy successfully improves cardiovascular and metabolic health: Results of the Pro-Active Study
- ISSHP-congress Geneva, Switzerland 2012
  Lifestyle intervention after complicated pregnancy successfully improves saturated fat-intake, but not exercise and smoking habits: Results of the Pro-Active Study
- Minisymposium HELLP-foundation, Amersfoort, Netherlands 2013
  Lifestyle intervention after complicated pregnancy: is it feasible?

- ISSHP-congress New Orleans, USA 2014
  Thrombophilia and the origin of preeclampsia: rumors of the past?
- ISSHP-congress New Orleans, USA 2014
  Effects of lifestyle intervention after complicated pregnancy: Results of the Pro-Active study

Poster Presentations

- ISSHP-congress, Washington, USA 2008
  Does severity of preeclampsia influence postpartum normalization of proteinuria and hypertension?
- ISSHP-congress, Washington, USA 2008
  Normalization of blood pressure after preeclampsia
- Gynae-congress, Utrecht, Netherlands 2009
  Resolution of hypertension after preeclampsia
- SGI-congress, Orlando, USA 2010
  To screen for proteinuria after preeclampsia: the protein:creatinine ratio in a single spot urine sample can reliably replace a 24-hour urine collection
- ISOM-congress, Melbourne, Australia 2010
  Postpartum lifestyle intervention after complicated pregnancy proves feasible
- SGI-congress, Miami, USA 2011
  Postpartum lifestyle intervention after complicated pregnancy proves feasible
- ISSHP-congress, Rome, Italy 2011
  Associations between thrombophilia and preeclampsia

Awards

- ISOM-congress, Melbourne, Australia 2010
  Investigator's Travel Award
- ISSHP-congress, Melbourne, Australia 2010
  Young investigator's Travel Award
- SGI-congress, Miami, USA 2011
  Award for Best New Investigator Poster Presentation
- ISSHP-congress, Geneva, Switzerland 2012
  Best Abstract Award by Preeclampsia Foundation

Publications

- D. Berks, E.A.P. Steegers, M. Molas, W. Visser 2009
  Resolution of Hypertension and Proteinuria after preeclampsia
  Obstet Gynecol, 2009 Dec;114(6):1307-14
- M. Hoedjes, D. Berks, I. Vogel, A. Franx, W. Visser, J.J. Duvekot, J.D.F. Habbema, E.A.P. Steegers, H. Raat 2010
  The effect of postpartum lifestyle intervention on weight loss, smoking cessation, and prevention of smoking relapse: a systematic review
  Obstet Gynecol Survey, 2010, Oct;65(10):631-52
- M. Hoedjes, D. Berks, I. Vogel, J.J. Duvekot, A. Oenema, A. Franx, E.A.P. Steegers, H. Raat 2011
  Preferences for postpartum lifestyle counselling among women sharing an increased cardiovascular and metabolic risk: A focus group study
  Hypertens Pregnancy, 2011;30(1):83-92

- M. Hoedjes, D. Berks, I. Vogel, J.J. Duvekot, W. Visser, A. Franx, E.A.P. Steegers, H. Raat 2011

  Motivators and barriers to a healthy postpartum lifestyle in women at increased cardiovascular and metabolic risk: A focus group study

  Hypertens Pregnancy, 2012;31(1):147-55

- M. Hoedjes, D. Berks, I. Vogel, J.J. Duvekot, W. Visser, A. Franx, E.A.P. Steegers, H. Raat 2011

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  Birth, 2011 Sep;38(3):246-255

- M. Hoedjes, D. Berks, I. Vogel, J.J. Duvekot, W. Visser, A. Franx, E.A.P. Steegers, H. Raat 2011

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  J Womens Health, 2011 Oct;20(10):1535-42

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International conferences

- SGI-congress, Toronto, Canada 2006
- SGI-congress, Reno, USA 2007
- ISSHP-congress, Reykjavik, Iceland 2007
- ISSHP-congress, Washington, USA 2008
- SGI-congress, Glascow, United Kindom 2009
- Doelen-congress, Rotterdam, Netherlands 2009
- ISOM-congress, Melbourne, Australia 2010
- ISSHP-congress, Melbourne, Australia 2010
- SGI-congress, Miami, USA 2011
- ISSHP-congress, Rome, Italy 2011
- ISSHP-congress, Geneva, Switzerland 2012
- ISSHP-congress, Tromsø, Norway 2013
- ISSHP-congress, New Orleans, USA 2014

Other activities

- Resident Obstetrics and Gynecology 2003-2012
- Gynecologist, Westfriesgasthuis Hoorn 2012-

DANKWOORD

Wat zit het leven steeds weer vol verassingen. Het is mei 2005 als ik begin als 3de-jaars AIOS gynaecologie in het Erasmus MC. Net droog achter de oren van alle liters vruchtwater van 2 jaar werken in een drukke periferie is overmoed mij niet vreemd. Wat valt er nog te leren? Alle verloskundige instinkers zijn immers bekend, geen probleem te groot of het is oplosbaar, geen dienst te druk of je ontmoet als vanzelf de eerste zonnestraal van een nieuwe dag – soms de voorbode van een lekker glaasje whiskey. En ja, soms gebeurt er iets 'onverklaarbaars' of 'onvermijdelijks', maar zeg toch zelf, daar weet toch niemand een antwoord op?

Na amper 2 maanden academie zit ik in mijn steilste leercurve ooit. Het is oktober 2005 als Hans Duvekot, Chef de Clinique van de afdeling verloskunde, mij vraagt op zijn kamer te komen om 'iets te bespreken'. Oh nee, wat heb ik gemist? Het ging toch juist zo lekker? Waarom doet hij zo vriendelijk? Het moet vast iets héél ernstigs zijn. Op weg naar zijn kamer denk ik snel aan de afgelopen weken op zoek naar een aanwijzing waar dit gesprek over zou kunnen gaan. Niets schiet me te binnen en plots zitten we daar. Een plek die toen nog als onwennig aanvoelde. Raar eigenlijk om daaraan terug te denken. Nu is het vaak de eerste kamer waar ik naar toe loop, als ik op bezoek ben in het Erasmus MC. En ben ik teleurgesteld als de deur op slot blijkt.

'Wat zou je ervan vinden om promotieonderzoek te gaan doen naast je opleiding?' Ik moet wel héél schaapachtig hebben gekeken, want na een korte pauze voegt hij eraan toe: 'Eric en ik hebben het erover gehad dat jij echt iemand bent voor dit onderzoek.' 2 Weken later ben ik AGIKO en 1 maand later begin ik aan mijn eerste jaar fulltime onderzoek.

Beste Hans en Eric, het was geen gemakkelijk onderzoek: veel werd ons pas gaandeweg duidelijk. En daarmee ontdekten we een schat aan waardevolle informatie en weer nieuwe vragen. Ik was geen gemakkelijke promovendus. Met mijn eigen wijs zocht ik mijn weg in dit onderzoek. En dat ging niet altijd even snel als dat we hadden gewild. Gaandeweg werd het onderzoek een deel van mijzelf en van ons. *Pro-Active* verwerd van een acroniem tot een entiteit. Een entiteit die garant stond voor nieuwsgierigheid, passie, vernieuwing en verbinding. Daarom dat dit proefschrift, naast de bekroning op een geweldig project dat we met elkaar hebben neergezet, ook een –zachte – ondertoon heeft van verdriet. Het confronteert met de eindigheid van mooie dingen. Mijn lijntje met de bruisende en verslavende Academie, waar altijd iets gebeurt en mensen zitten die van zich verwonderen hun vak hebben gemaakt, houdt hier op. Maar ja, alsof ik tijd heb om daarbij stil te staan. De nieuwe uitdagingen struikelen al over elkaar heen, wachtend om opgepakt te worden. Enthousiasme en Passie, en vooral ook het doorzettingsvermogen om te blijven verwonderen en te zoeken naar wat mogelijk is, heb ik van jullie beiden af mogen kijken. Ik heb daar diep bewondering voor, jullie zijn daarin mijn grote voorbeeld. Ik ben jullie onmetelijk dankbaar voor het vertrouwen dat jullie mij destijds in 2005 en alle jaren daarna hebben gegeven en de passie en toewijding waarmee jullie mij hebben besmet.

Beste Hein, wat hebben ook wij samen gezocht naar de weg in dit project. Jij was voor mij iets meer op afstand, maar jouw deur stond altijd open. Altijd bereid om mee te denken in weer eens een moeilijk dilemma. En wat heb ik daarin veel van je geleerd. Jij hielp mij en destijds ook Meeke zelf zoeken naar oplossingen, maar had altijd een slim idee als het écht even niet ging. Iemand in zijn kracht zetten kan jij als geen ander. Heel hartelijk dank daarvoor!

Beste Arie, eigenlijk voel ik me naar jou altijd een beetje schuldig. Jij hebt destijds het onderzoeksproject geschreven, samen met Hein, maar toen ging je weg en moest je dit onderzoek achterlaten in het Erasmus MC. Gelukkig bleef er contact bestaan via deelname van het St. Elizabeth ziekenhuis in Tilburg aan het project. Ik voel me dan ook zeer vereerd dat je vandaag in de commissie zit.

Beste overige commissieleden en in het bijzonder Joline, Eric en Christianne, ik wil jullie hartelijk danken voor jullie interesse in het proefschrift en de bereidheid deze kritisch te lezen. Ik voel me vereert dat ik dit proefschrift aan jullie mag voorleggen.

Beste Meeke, eindelijk heb ik die eindstreep ook gehaald! Jij begon iets later en was veel eerder klaar. Wat had ik je toen graag nagedaan. Hoe jij dat destijds voor elkaar hebt gekregen met een klein kind en heen en weer reizend tussen Tilburg en Rotterdam, is me nog altijd een raadsel. Ondanks dat we ons soms ingegraven voelden door allemaal papieren die allemaal ongeveer even belangrijk waren, vonden we toch altijd weer onze weg. En die weg ging altijd vóóruit. Ik ben ongelofelijk trots dat wij dit project samen hebben neergezet en ben je heel dankbaar voor de tijd waarin we samen weg van de Pro-active hebben bewandeld.

En natuurlijk zijn er nog velen anderen die ik dank verschuldigd ben. Allereerst natuurlijk alle vrouwen die aan de studie hebben deelgenomen. Zonder hen was dit project nooit geslaagd. Dat geldt ook voor Mirjam, Robbert, Sarah, en Meike. Dank jullie hartelijk voor het meedraaien in de poli-spreekuren. Mark, dank voor de ondersteuning in Access. Wie had gedacht dat ik daar ook een passie in zou vinden. Een passie die zijn vruchten af heeft geworpen en ook

nu nog afwerpt. Joke, Wilma en Titia, dank voor het verwerken van de labsamples en natuurlijk de gezelligheid. Collega's in het Erasmus MC, Sint Franciscus Gasthuis en het Westfriesgasthuis voor de ruimte en tijd. Vrienden en familie voor de nooit aflatende interesse in de voortgang van het project.

Een bijzondere vermelding voor jou Hajo. Hartelijk dank voor je continue interesse en betrokkenheid. Niet alleen bij dit project, maar vooral ook op het persoonlijk vlak en niet te vergeten, mijn carrière. Ik weet nog heel goed, volgens mij was het september 2011, dat jij me een keer uitnodigde in het Westfriesgasthuis te Hoorn. Nadat ik je al ettelijke malen voor gek had verklaard – de afstand met Rotterdam was immers veel te groot – heb ik een dag meegelopen. Ik was direct verkocht en 's avonds heb je bij een hapje eten aan de haven geholpen de logistieke oplossing te vinden. Jij zag dat ik in het team gynaecologen paste en het team bij mij. Dat is jouw kracht: jij ziet dingen die anderen (nog) niet zien. En in plaats van je te vervreemden, maak je anderen deelgenoot van jouw visie, juist door interesse te tonen in de ander. Daarmee heb je dingen kunnen bereiken die anderen nooit voor mogelijk hielden. Ik bewonder dat in je en hoop tegen het einde van mijn carrière nog net zo jong van geest te zijn als jij.

En natuurlijk De Sjôtelsplek: Marco, Marieke, Guy, Marion, Hèlen, Dankert, Arjan, Mirjam, Marcel, Daniëlle, Nettie en Kees. Ooit in 1994 klein begonnen in een vakantiehuisje in Schoorl en al snel uitgegroeid tot de vriendclub die we nu zijn. Lief en leed hebben we gedeeld en verwerkt. Wie kan nu zeggen dat hij met zijn studievrienden na 23 jaar nog elk jaar 2 keer een weekend feestviert? Zonder jullie zou ik niet de persoon zijn die ik nu ben. Jullie zijn mijn beste vrienden voor altijd.

Beste Lyanne, ik ben zo blij dat jij samen met Alike mijn paranimf wilt zijn. Jij kan als geen ander een situatie zó ontregelen dat er een geheel nieuw perspectief ontstaat. Noem het humor, noem het je-kunnen-verwonderen. Beide kernkwaliteiten die je doen realiseren dat het leven continue in beweging is en vol verassingen zit. Met die basis voel ik me op 17 januari niet alleen staan, maar staan we daar echt met z'n drieën en dat voelt bijzonder goed.

Tot slot is het doen van promotieonderzoek niet alleen iets wat je tijdens werktijd doet. De soms lange dagen, de uren achter de computer, de weken weg op congres zijn daar maar enkele voorbeelden van die anderen om je heen ervan merken. Maar ook de minder tastbare dingen, zoals in gedachten zijn, omdat er creatieve input nodig is voor een artikel. Of heel enthousiast vertellen dat het nu écht bijna klaar is (de eerste keer was geloof ik zo'n 5 jaar geleden). Promoveren doe je niet alleen, zeggen ze, en ze hebben gelijk. Maar het is iets waar je als bijstander je soms onmachtig kan voelen. Kinderen beleven het anders dan volwassenen. Die weten ook niet altijd beter. Ze hebben er ontzag voor dat hun vader een eigen boek heeft geschreven, maar vinden het eigenlijk maar stom dat het allemaal in het Engels is. Dan begrijpt toch niemand er iets van. Volwassenen zien de offers die je soms moet brengen om het project in beweging te houden. Wat dat betreft is het eigenlijk maar oneerlijk dat alleen mijn naam op het boekje staat. Daarom hier de eer die jou toekomt. Dank je vanuit het diepst van mijn hart voor alle tijd, geduld en ruimte die je me hebt gegeven om dit project waar te maken. Alike, ik houd van je.

CURRICULUM VITAE

Durk Berks was born at home on the 3rd of May 1974 in Amsterdam, The Netherlands. He went to primary school on de Antonia Kleuterschool, following on the Dr Rijk Kramerschool in Amsterdam, continuing on De Scheepskameel after moving to Almere. He started his secondary school on Het Baken in Almere, The Netherlands. After moving to Nuenen, The Netherlands, he continued on het Eckhart College, where he graduated in 1992. Shortly after, he attended Medical School at the Rijksuniversiteit Limburg in Maastricht, The Netherlands, (now called Maastricht University) in 1992, from which he graduated in July 1999. From august 1999 until December 2000 he worked as a junior resident at the Department of Obstetrics and Gynecology at the Maaslandziekenhuis Sittard, The Netherlands (now called Orbis). In December 2000, he moved to Rotterdam, working as a fertility doctor in het Zuiderziekenhuis in Rotterdam, The Netherlands (now called Maasstad ziekenhuis) until May 2003, where he met his beautiful wife. In May 2003, he started his training in Obstetrics and Gynecology at the Sint Franciscus Gasthuis, Rotterdam, The Netherlands (now called Franciscus Gasthuis & Vlietland) and the Erasmus Medical Center, Rotterdam, The Netherlands. During his training, he started his PhD in December 2005. He worked as PhD-student from December 2005 until May 2007 and November 2008 until November 2009. He graduated as Gynecologist in February 2012. He works as gynecologist in het Westfriesgasthuis Hoorn, The Netherland, with obstetrics and fertility as mean areas of expertise. He is member of the hospital's Lean core-team and member of the Steering committee on integrated obstetric care. He lives in Rotterdam with Alike and their 3 beautiful daughters: Meike, Sophie and Jasmijn.