



**Karolinska  
Institutet**

**Division of Obstetrics and Gynecology, Department of  
Clinical Sciences, Danderyd Hospital**

# CLINICAL AND EPIDEMIOLOGICAL ASPECTS OF OBESITY DURING PREGNANCY AND THE PUERPERIUM

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska  
Institutet offentligen försvaras i Aulan/Danderyds sjukhus.

**Fredagen den 6 december, 2013, kl 09.00**

av

**Elisabeth Storck Lindholm**

Leg. Läkare

*Huvudhandledare:*

Docent Daniel Altman  
Institutionen för kliniska vetenskaper  
Karolinska institutet Danderyds sjukhus

*Bihandledare:*

Med. Dr. Margareta Norman  
Institutionen för kliniska vetenskaper  
Karolinska institutet Danderyds sjukhus

Med. Dr. Charlotte Palme Kilander  
Institutionen för kvinnor och barns hälsa  
Karolinska sjukhuset, KI

*Fakultetsopponent:*

Docent Ulf Hanson  
Institutionen för kvinnor och barns hälsa  
UAS

*Betygsnämnd:*

Professor Marie Bixo  
Institutionen för klinisk forskning och  
utbildning KI SÖS

Docent Lennart Nordström  
Inst. för Kvinnor och barns hälsa  
Karolinska sjukhuset, KI

Docent Masoumeh Rezapour  
Institutionen för kvinnor och barns hälsa  
UAS

**Stockholm 2013**



From the Division of Obstetrics and Gynecology, Department of  
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Karolinska Institutet, Stockholm, Sweden

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Elisabeth Storck Lindholm, MD



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Stockholm 2013

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ISBN 978-91-7549-384-8

Printed by



[www.reproprint.se](http://www.reproprint.se)

Gårdsvägen 4, 169 70 Solna

## Abstract

**Objective:** To study different aspects of obesity during pregnancy, birth and the puerperium. Paper I is an intervention study of obese pregnant women. Paper II compares fatty acid (FA) patterns in breast milk and neonates' plasma phospholipids in normal-weight mothers and an intervention group of obese mothers. Paper III reports the risk of obstetric anal sphincter lacerations in relation to maternal obesity among primiparas. Paper IV compares health care consumption and sick-listing among obese and normal-weight pregnant women.

**Methods:** *Paper I* is a pilot clinical study of women with BMI  $\geq 30$ , included during a first-trimester prenatal visit. Twenty-five pregnant women were included in the intervention program, comprising visits to midwife, obstetrician and dietician, as well as weekly water gymnastics.

*Paper II* is a randomized observational study of 41 obese and 41 normal-weight pregnant women. Twenty-nine obese women participating in a weight reduction program were included for comparison. FA were analyzed with capillary gas chromatography of lipids in breast milk collected at three and 10 days and one and two months postnatally, as well as in infants' plasma sampled three days after birth.

*Paper III* is a nationwide register-based study including 210,678 primiparas who gave vaginal birth to a singleton, identified from the Swedish Medical Birth Register between January 1, 2003 and December 31, 2008. Body Mass Index (BMI) was categorized into four classes, according to World Health Organization (WHO) guidelines.

*Paper IV* is a nationwide register-based study of 108,103 pregnant women, identified from the Swedish Medical Birth Register, the Maternal Health Care Register and the Swedish National Inpatient Register between January 1, 2003 and December 31, 2008. The women were categorized into four BMI classes, according to WHO guidelines.

**Results:** *Paper I:* Fourteen (56%) of the women had a gestational weight gain of  $\leq 6$  kg (study goal). There were no cases of gestational diabetes. Three (12%) women had mild hypertension. Three women (12%) were delivered by emergency cesarean section. All babies were healthy and had normal birth weights.

*Paper II:* The concentrations of omega-3 FA were lower and the omega-6/omega-3 ratio was higher in neonates and in consecutive samples of breast milk from obese mothers, compared to normal-weight mothers. FA patterns were more similar to those in normal-weight mothers when obese mothers participated in an intervention program with dietary advice and physical activity.

*Paper III:* In multivariate analyses, increasing BMI showed a nearly dose-response-type protective effect against grade III-IV sphincter lacerations.

*Paper IV:* Obese women made more visits to midwives, doctors and the specialized antenatal care unit. They also complained of fear of childbirth more often. They had longer in-hospital stays and were sick-listed more often during pregnancy.

**Conclusions:** Obese pregnant women use more healthcare recourses during pregnancy. During delivery the risk for anal sphincter lacerations decreases with higher BMI. There might be an effect at eating and exercise habits with intervention and the results suggest the importance of health promoting guidance of obese pregnant women also influencing the early fatty acids pattern of their infants.

**Keywords:** Anal sphincter tears, Health care consumption, Obesity, Omega-3, Omega-6, Physical activity, Pregnancy, Weight reduction program.

## List of publications

This thesis is based on the following papers, referred to in the text by their roman numerals:

- I. Weight control program for obese pregnant women  
**Storck Lindholm E**, Norman M, Palme Kilander C, Altman D  
Acta obstetricia et gynecologica Scandinavica 2009;89(6):840-3
- II. Different fatty acid pattern in breastmilk of obese compared to normal-weight mothers  
**Storck Lindholm E**, Strandvik B, Altman D, Möller A, Palme Kilander C  
Prostaglandins, leukotrienes, and essential fatty acids 2013;88(3):211-7
- III. Risk of obstetric anal sphincter lacerations among obese women  
**Storck Lindholm E**, Altman D.  
BJOG; DOI: 10.1111/1471-0528.12228.
- IV. Obesity, health care consumption and sick leave during pregnancy  
**Storck Lindholm E**, Blomberg M, Norman M, Altman D.  
In manuscript

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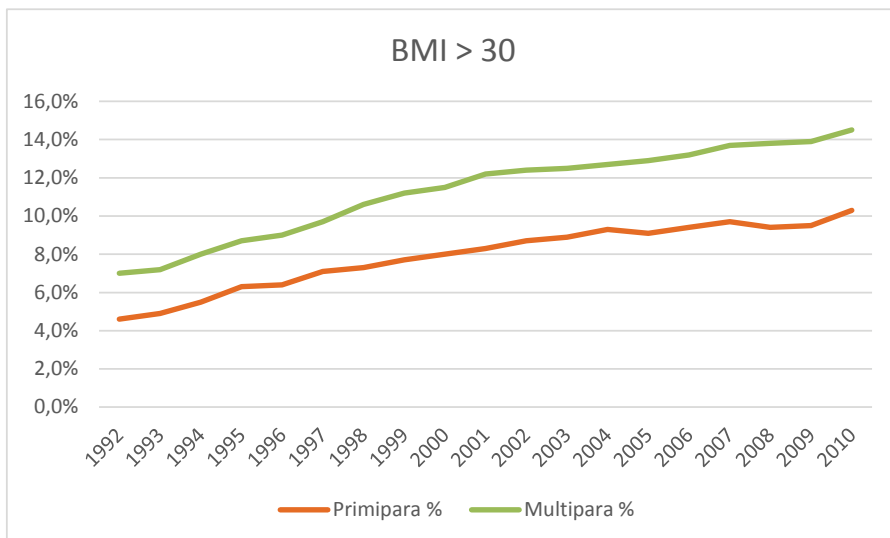
## List of abbreviations

AA	Arachidonic acid
ALA	Alpha-linoleic acid
BMI	Body Mass Index
CI	Confidence interval
DHA	Docosahexaenoic acid
DVT	Deep vein thrombosis
EPA	Eicosapentaenoic acid
EFA	Essential fatty acids
EPDS	The Edinburgh Postnatal Depression Scale
FA	Fatty acid
fT4	Free thyroxin
GWG	Gestational weight gain
Hb	Hemoglobin
HbA1c	Glycosylated hemoglobin A1cS
HDL	High-density lipoprotein
HR	Hazard ratio
ICD	International Classification of Diseases
IPR	The Swedish National Inpatient Register
ITT	Intention to treat
IUGR	Intrauterine growth retardation
LA	Linoleic acid
LCPUFA	Long-chain polyunsaturated fatty acids
LDL	Low- density lipoprotein
LGA	Large for gestational age
LNA	$\alpha$ -Linoleic acid
MBR	Medical Birth Register
MI	Motivational interviewing
MUFA	Monounsaturated fatty acids
n-3	Omega-3 fatty acids
n-6	Omega-6 fatty acids
NNR	Nordic Nutrition Recommendations
NS	Not statistically significant
OGTT	Oral glucose tolerance test
OR	Odds ratio
PA	Physical activity
PCOS	Polycystic ovary syndrome
PE	Pulmonary embolism
PTH	Parathyroid hormone
PUFA	Polyunsaturated fatty acids
RR	Relative risk
SD	Standard deviation
sFt	S-ferritin
SFA	Saturated fatty acids
SGA	Small for gestational age
TSH	Thyroid-stimulating hormone
VTE	Venous thromboembolism
WHO	World Health Organisation



## 1. Introduction

Obesity has reached nearly epidemic proportions in the developed world. According to the World Health Organization (WHO), there are more than 300 million obese people worldwide <sup>1</sup>. Australia, Canada, the UK and the USA report obesity rates of 30%, 28%, 30% and 42%, respectively, for individuals aged 30 years and up <sup>2</sup>. Since 1980, people in Sweden have, on average, become 1 cm taller and 5 kg heavier. In 2011, more than 50% of the men and about 40% of the women in Sweden were overweight or obese (obese women: 10.5%; obese men: 11.8%). The same year, 12.6% of Swedish pregnant women were obese. The incidence of obesity has slowly risen since the early 90th (Figure 1) and the incidence of obesity differs in different parts of Sweden and women with a high level of education are less likely to be obese (Figure 2). Overweight and obesity in adulthood are linked to increased risk of mortality and morbidity. The Framingham Heart Study from Massachusetts, with follow-up from 1948 to 1990, showed that obese female smokers lost 7.2 years and obese male smokers lost 6.7 years of life expectancy, compared with normal-weight smokers <sup>3</sup>. Both overweight and obesity are

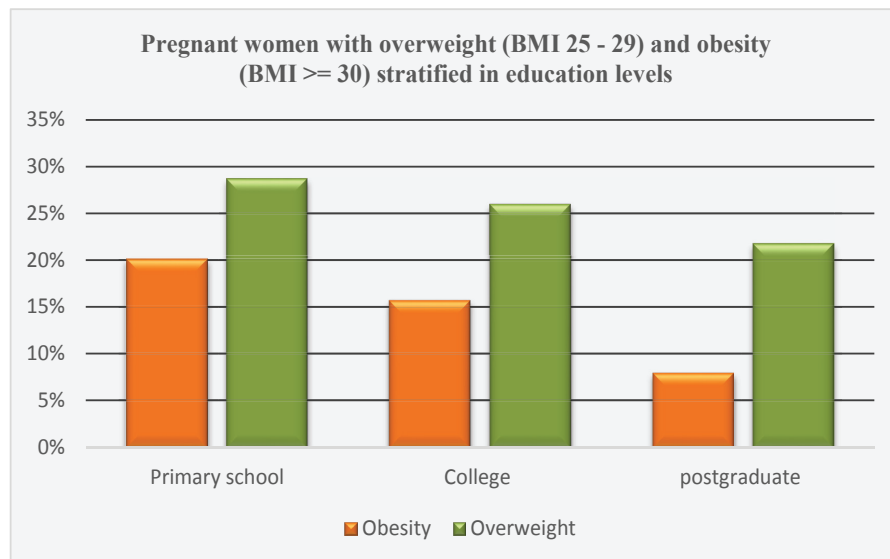


**Figure 1.** Body Mass Index (BMI) > 30 in early pregnancy, registered at antenatal clinic. Modified from Swedish Medical Birth Register, annual report 2013.

major causes of co-morbidities, which can lead to further morbidity and mortality. In a meta-analysis from 2009, Guh et al <sup>4</sup> provide a comprehensive review of the incidence of co-morbidities related to obesity and overweight, presenting evidence of 18 such co-morbidities. Obesity and overweight were associated with type II diabetes, all cancers except esophageal and prostate cancer, all cardiovascular diseases, asthma, gallbladder disease, osteoarthritis and chronic back pain. Obesity, defined by BMI, was most strongly associated with the incidence of type II diabetes in females (relative risk (RR): 12.41; 95% confidence interval (CI): 9.03 - 17.06). The percentage of overweight and obese people has risen over the past 30 years; the increase is higher among men than women. In Sweden, significantly more children and young adults have become overweight during the past 20 years, which will lead to health consequences for many years (Norberg & Danielsson, 2012) <sup>5</sup>.

## 1. 1. Obesity in pregnancy

Maternal obesity is a significant risk factor for adverse outcomes during pregnancy. In women, early onset of obesity is associated with menstrual irregularities, chronic oligo-/anovulation and infertility. These adverse effects of obesity are specifically evident in polycystic ovary syndrome (PCOS) <sup>6</sup>. Women with a BMI of >35 are 26-49% less likely to conceive, compared to those with a BMI of 21-29 <sup>7</sup>.



**Figure 2.** Modified from Swedish Medical Birth Register, annual report 2013

### 1. 1. 1. Miscarriage

A pooled analysis in a review from 2011 revealed a higher miscarriage rate (13.6%) in 3 800 obese women than the corresponding rate (10.7%) in 17 146 normal-weight women (odds ratio (OR) 1.31; 95% CI: 1.18-1.46). They also found a higher prevalence of recurrent early miscarriage in obese than in normal-weight women (0.4% versus 0.1%; OR: 3.51; 95% CI: 1.03-12.01) <sup>8</sup>. The exact reason for this obesity-related increased risk of miscarriage is unknown, but the higher rates of PCOS and insulin resistance among obese women <sup>9</sup> have been discussed as part of the explanation.

### 1. 1. 2. Congenital malformations

Paternal pre-pregnancy obesity is associated with congenital malformations, particularly anomalies of the central nervous system and heart <sup>10-12</sup>. Maternal obesity is associated with a 1.7-fold increased risk of neural tube defects, and severe obesity is associated with a risk increased more than 3-fold <sup>13</sup>. The biological mechanisms behind this association between maternal obesity and birth defects are unknown. Altered glucose metabolism and poor maternal diet are potential explanations. Lower maternal folate levels, well-known to be implicated in the etiology of neural tube defects, may be a factor. Hyperinsulinemia is strongly associated with neural tube defects and may represent the physiological pathway responsible for the increased risk of this particular malformation in both the diabetic and obese populations <sup>14</sup>.

### **1. 1. 3. Stillbirth and neonatal death**

Stillbirth remains a serious reproductive complication, with a frequency of 2-5 per 1 000 births, and constitutes more than half of all perinatal deaths <sup>15</sup>.

Women with pre-pregnancy obesity have more than twice the risk of stillbirth and neonatal death <sup>16-18</sup>, compared to normal-weight women <sup>19</sup>. A meta-analysis by Flenady et al <sup>20</sup> showed that maternal overweight and obesity was the highest-ranking modifiable risk factor for antenatal death, contributing to around 8 000 stillbirths ( $\geq 22$  weeks' gestation) annually, across all high-income countries. The pregnancy disorders associated with the highest risk of stillbirth were small for gestational age (SGA) and placental abruption, which highlights the role of placental pathology in stillbirth.

The mechanism underlying the increased risk of stillbirth associated with higher BMI is a matter of speculation. It has been suggested that infants are often discretely SGA in unexplained stillbirths <sup>21</sup>. Kristensen et al found that the birth weights of babies born, at term or post-term, to obese women were lower among the stillborn, compared with live-born neonates <sup>17</sup>.

Gestational diabetes, preeclampsia and eclampsia are more common among overweight and obese women, but even after these groups are excluded from studies, the increased stillbirth risk remains. Obesity is known to be associated with disturbances in lipid metabolism. Hyperlipidemia may, directly or indirectly through lipid peroxidases, damage endothelial cells and promote vasoconstriction and platelet aggregation, which may in turn contribute to the preeclampsia process <sup>22</sup>. The risk might increase with hyperlipidemia and insulin resistance, in cases of which fibrinolytic activity is known to be markedly decreased <sup>23</sup>. This has been suggested to increase the risk of placental thrombosis and decrease placental perfusion <sup>17</sup>.

### **1. 1. 4. Gestational diabetes**

Since obesity predisposes to type II diabetes, obese pregnant women's risk of gestational diabetes increases with rising BMI. The OR increased from 3.56 [95% CI: 3.05-4.21] in obese women to 8.56 [95% CI: 5.07-16.04] in severely obese women, compared to normal-weight controls, in a meta-analysis by Chu et al <sup>24</sup>.

### **1. 1. 5. Preeclampsia and gestational hypertension**

Preeclampsia is a hypertensive disorder of pregnancy, defined as hypertension (blood pressure  $\geq 140/90$  mmHg) and proteinuria (urinary protein  $\geq 300$  mg/24 h). It occurs in 5-7% of all pregnancies and is a leading cause of maternal and fetal morbidity and mortality <sup>25</sup>. Elevated pre-pregnancy BMI is a strong independent risk factor for preeclampsia and the degree of obesity is related to the severity of preeclampsia. A study by Bodnar et al <sup>26</sup> showed that the ORs for preeclampsia were 1.7 for overweight white women, 3.4 for obese white women, 2.1 for overweight black women and 3.2 for obese black women. The ORs for severe hypertension of pregnancy in white women with BMI 25 and 30 were 3.6 and 8.8, respectively, while the corresponding respective figures in black women were 3.0 and 4.9. Both weight gain during adulthood and weight gain between pregnancies increase the risk of preeclampsia. Suggested explanations for this higher risk in obese women are systemic inflammation, hyperlipidemia, oxidative stress, insulin resistance, endothelial dysfunction, reduced immune function and lifestyle factors such as poor antenatal diet and antenatal physical inactivity <sup>22,27</sup>.

### **1. 1. 6. Preterm delivery**

A recent study in the Journal of the American Medical Association showed that preterm deliveries increased with elevated BMI and that the overweight- and obesity-related risks were the highest for extremely preterm delivery. Among normal-weight women, the rate of extremely preterm delivery was 0.17%, while the rate for obese women was 0.27%. The association between high BMI and the risk of moderately preterm delivery was stronger in short women than in taller women. The risk of medically indicated preterm delivery also increased with higher BMI. Maternal obesity is associated with inflammatory up-regulation through increased production of adipokines in adipose tissue and enhanced systemic secretion of pro-inflammatory cytokines<sup>28</sup>. In spontaneous preterm delivery, there are elevated levels of inflammatory proteins (cytokines), which are associated with cervical ripening and may also cause both weakening of the membranes and preterm myometrial contractions. Additional mechanisms that may contribute to preterm delivery in obese women include endothelial dysfunction, insulin resistance, oxidative stress, and lipotoxicity<sup>28</sup>. Obese women have also increased risks of genital<sup>29</sup> and urinary tract<sup>30</sup> infections, which are recognized risk factors for chorioamnionitis and preterm delivery<sup>31</sup>.

### **1. 1. 7. Small for gestational age and macrosomia**

A study by Beaten et al showed that obese, overweight, and normal-weight women were each slightly less likely to deliver a SGA (< 10th percentile) baby as well as each more likely to deliver a macrosomic infant ( $\geq 4,000$  g)<sup>32</sup>. Other studies have shown that obesity is an independent risk factor for SGA (OR 1.24). Maternal age  $\geq 35$  years (OR 1.16), nulliparity (OR 1.13), cigarette smoking (OR 2.01), gestational hypertension (1.46), preeclampsia (OR 2.94), chronic hypertension (OR 1.68) and placental abruption (OR 2.57) are other risk factors. Gestational diabetes (OR 0.80) and type I diabetes (OR 0.26) are, on the other hand, associated with reduced risk<sup>33,34</sup>. Women with a prior history of bariatric surgery, regardless of obesity status, were more likely to have anemia, chronic hypertension, endocrine disorders and SGA infants<sup>35</sup>.

There are associations between paternal obesity and birth weight as well. In the SCOPE study in Australia, men who fathered an SGA infant were more likely to be obese (OR 1.50) and to have central adiposity (OR 1.53), compared with men who fathered a non-SGA infant. Elevated paternal blood pressure was, however, not associated with SGA<sup>36,34</sup>.

### **1. 1. 8. Venous thromboembolism**

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs at a rate of more than 1 per 1 000 adults in western countries. The majority of cases occur in those aged over 45 years<sup>37</sup>. A systematic literature review by Ageno et al<sup>38</sup> found that obesity (BMI > 30) more than doubled the risk of VTE (OR 2.33; 95% CI: 1.68-2.34). Pregnant women are 4 - 5 times more likely to develop VTE than non-pregnant women<sup>39</sup>. VTE remains one of the most common causes of maternal mortality in the developed world<sup>40</sup>. The risk of DVT is 1.36 per 1,000 deliveries and the risk of pulmonary embolism (PE) is 0.36 per 1 000 deliveries. Half of pregnancy-related VTE occurs postpartum<sup>41</sup>. James et al found that obesity significantly increased the risk of VTE during pregnancy (OR 4.4; 95% CI: 3.4-5.7)<sup>41</sup>. A normal pregnancy is accompanied by changes in the coagulation and fibrinolytic systems. Levels of clotting Factors I, II, VII, VIII, IX and XII increase, while protein S levels decline and fibrinolysis is inhibited. There is also a significant decrease in the activity of activated protein C, an important anticoagulant, as gestation progresses.

These physiological changes may be important for minimizing intrapartum blood loss but they entail an increased risk of VTE during pregnancy and the postpartum period <sup>42</sup>.

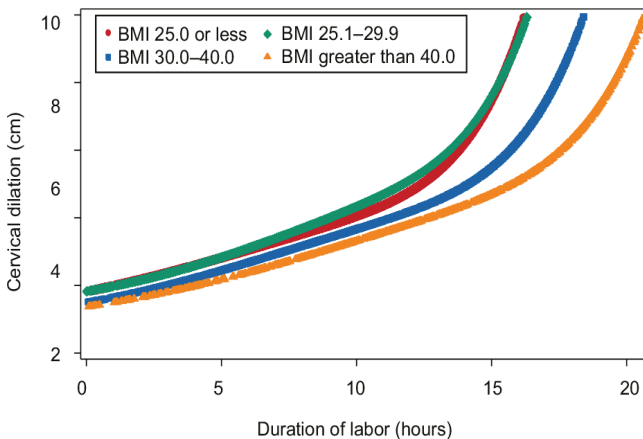
There are several possible explanations for obese individuals' higher risk of VTE. More body fat, especially abdominal fat, might limit venous return; obesity is associated with chronically elevated intra-abdominal pressure and decreased blood velocity in the femoral vein. Furthermore, there may be increased inflammation, oxidative stress, and endothelial dysfunction <sup>43</sup>. Visceral adipose tissue is metabolically active, producing adipokines such as leptin, important in the regulation of body weight. Leptin levels are elevated in obese individuals since the central nervous system appears to gradually become resistant to its effects. Leptin is associated with adenosine diphosphate-induced platelet aggregation <sup>44</sup> and correlated with tissue plasminogen activator (tPA) antigen. Higher concentrations of plasminogen activator inhibitor-1 (PAI-1) inhibit fibrinolysis, thereby maintaining a thrombotic state.

BMI has also been shown to positively correlate with Factor VII, Factor VIIIc, fibrinogen and von Willebrand Factor levels. The chronic inflammation of obesity or hyperinsulinemia may be responsible for these observed elevations <sup>45</sup>. Factor VIII concentrations are strongly associated with increased risk of VTE, as is hyperfibrinogenemia <sup>46</sup>.

There are also several lifestyle factors that might influence the relationship between obesity and VTE. Epidemiological evidence is inconclusive about the effects of physical activity (PA) in overweight and obese people. A 2009 study from Sweden showed that non-smoking women who were physically active and consumed alcohol in moderation were at lower risk of VTE <sup>47</sup>. The LITE study showed that a diet with more plant foods and fish and less meat and processed meat reduced the incidence of VTE in middle-aged women <sup>48</sup>.

### 1. 1. 9. Labor

Monitoring labor progress may be more difficult in obese women due to the greater depth required for ultrasound penetration to the level of the fetus and increased difficulty in tracing contractions. Obesity significantly increases the incidence of cesarean delivery. In a study of nulliparas, Weiss et al <sup>49</sup> found a cesarean delivery rate of 20.7% in the control group, compared with 33.8% in the obese group and 47.4% in the morbidly



**Figure 3.** Labor curve for nulliparous women stratified by body mass index (BMI) Norman. Effect on Obesity on the labor Curve. *Obstet. and Gynecol.* 2012

obese group. In a study by Baeten et al <sup>31</sup>, the cesarean delivery rate was nearly doubled in women with BMI > 30. Obesity is associated with an increase in operative complications such as excessive blood loss, increased duration of surgery and increased incidence of post-operative wound infection and endometritis <sup>49,50</sup>.

General anesthesia for cesarean delivery is associated with a much

higher risk of maternal mortality, compared with regional anesthesia<sup>51</sup>. Obesity was found to be a major risk factor for maternal mortality in several studies<sup>51,52</sup>, with failed intubation and aspiration representing the cause of death in the majority of cases. The incidence of failed intubation in the morbidly obese parturient has been reported to be as high as 33%. The duration of the first stage of labor among both nulliparous and multiparous women with BMI  $\geq 30$  is longer and cervical dilation is slower (4.7 vs. 4.1 hours, from 4 to 10 cm). The difference in the progression of dilation from 4 cm to 6 cm was the most pronounced (2.2 vs. 1.9 hours)<sup>53</sup>. The difference in labor progress is related exclusively to the latent phase and is thus not related to the active phase of labor. Fyfe et al found that obese women who reached the second stage of labor had a higher rate of spontaneous vaginal birth and fewer operative vaginal births, compared with women with normal BMI<sup>54</sup>. In our study from 2013, we found that increasing BMI had a nearly dose-response-type protective effect against grade III and IV perineal tears, in comparison with normal-weight women<sup>55</sup>.

It is important to monitor the second stage of labor carefully when the parturient is obese, since the risks of low Apgar score, meconium aspiration and shoulder dystocia are increased. In a study from 2004, Cedergren et al showed that morbidly obese patients (BMI > 40) had a 3-fold increase in shoulder dystocia and close to a 3-fold increased risk of meconium aspiration and fetal distress. The associations were similar, but less strong, for women with BMI between 35.1 and 40. Interestingly, the incidence of placenta previa decreased among obese and morbidly obese women<sup>56</sup>.

### 1. 1. 10. *The pelvic floor and risk factors for perineal tears*

The pelvic organs are suspended by the pelvic ligaments and supported by the levator ani muscles, which play a critical role in supporting the pelvic visceral organs and a major role in urinary, defecatory and sexual function. The levator ani muscle has a three-dimensional structure; its anterior portion (pubococcygeal and puborectal) is oriented vertically as a sling around the mid-urethra, vagina, and ano-rectum (Figure 4). The opening in the levator ani muscle through which the urethra and vagina pass is called the urogenital hiatus, limited ventrally by the pubic bones, laterally by the levator ani muscles, and dorsally by the perineal body and the external anal sphincter<sup>57</sup>. The posterior portion of the levator ani, the iliococcygeal muscle, has a horizontal upwardly biconvex shape; it serves as a supportive diaphragm while the anterior portion closes the urogenital hiatus, pulling the urethra, vagina, perineum, and ano-rectum toward the pubic bone. When the fetus emerges through the birth canal, the widest part of the fetal head stretches the pelvic floor muscles, fascia and nerves and may cause reversible

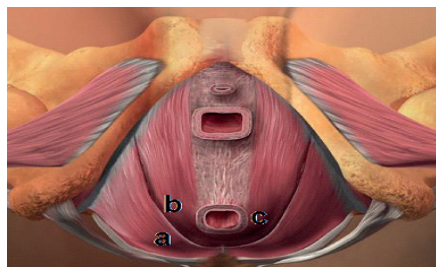


Figure 4. The levator ani muscles of the female pelvic floor a) Iliococcygeus, b) Pubococcygeus, c) Puborectalis

or permanent damage by direct laceration or ischemia<sup>58</sup>. Pudendal nerve denervation, which occurs primarily during the second stage of labor, has been demonstrated in 80% of women following their first vaginal delivery. Pelvic floor denervation has been implicated in the etiology of urinary incontinence, pelvic organ prolapse, chronic constipation and defecatory difficulty. Stretching and disruption of the pelvic floor muscles, as well as fascial tears, can heal but the resulting connective tissue may not be of the same tensile strength as the original<sup>59</sup>



### **1. 1. 11. Perineal tears**

Ruptures of the pelvic floor during childbirth are divided into four categories, based on morphological severity according to the International Classification of Diseases (ICD) 10th revision:

**Grade I:** a tear in the vaginal mucosa or superficial perineal skin but not in the underlying tissue

**Grade II:** a tear extending beyond the perineal skin and vaginal mucosa to perineal muscles and fascia

**Grade III:** a tear involving the muscles of the anal sphincter complex

**Grade IV:** a complete rupture of the anal sphincter muscles, including the anal or rectal mucosa

Risk factors for grade III-IV ruptures of the pelvic floor are: nulliparity, fundal pressure, midline episiotomy, birth weight > 4.5 kg, instrumental delivery, perineal edema, poor ocular surveillance of the perineum, deficient perineal protection during delivery and protracted final phase of the second stage<sup>60,61</sup>. The reasons for the above-mentioned, intriguing protective effect of increasing BMI against severe perineal tears are as yet unclear.

## **1. 2. Nutrition during pregnancy and breastfeeding**

### **1. 2. 1. The Barker hypothesis**

Nutrition plays a key role in many aspects of health. Excessive caloric intake is a major determinant of complex chronic diseases, such as obesity, type II diabetes, cardiovascular disease and even cancer. In poor countries, malnutrition and under-nutrition, especially during the perinatal period, increase not only neonatal mortality and perinatal morbidities but also the risk of chronic disease during adulthood<sup>62</sup>. There is extensive epidemiologic and experimental data showing that early sub-optimal nutrition can have health consequences several decades later. This association has been conceptualized into the Developmental Origins of Health and Disease Hypothesis, first described by David Barker<sup>63,64</sup>.

Epigenetics is defined as the study of heritable changes in gene expression that do not involve alterations in the DNA sequence<sup>65</sup>. Epigenetic marks include DNA methylation, histone modifications and a variety of non-coding RNAs<sup>66</sup>. The gene expressions are plastic and seem to respond to different environmental signals, including diet.

### **1. 2. 2. Obesity among children**

Also among children, overweight and obesity are a rising problem in the Western world. Decreased PA and more junk food intake are contributing factors. A study by Whitaker et al showed that children from low-income families with obese mothers had a more than doubled risk of obesity at two to four years of age<sup>67</sup>. Other risk factors are high weight gain between birth and 5 months, maternal smoking during pregnancy, parental overweight or obesity, decreasing duration of breastfeeding and earlier introduction of complementary food<sup>68,69</sup>.

### 1. 2. 3. *Nutrition during pregnancy*

The supply of substrates to the developing fetus and placenta is essential for normal growth and development. Availability of nutrients for the fetus is dependent on maternal nutritional status and maternal diet.

During pregnancy, plasma volume expands, which affects absorption. Urinary excretion and metabolism of different nutrients change nutrient levels and availability. Placental size, function and metabolism determine the extent of nutrient transfer to the fetus and how it utilizes available substrates, which in turn influences its growth and endocrine status <sup>70-72</sup>.

In developing countries, low pre-pregnancy weight and low caloric intake or weight gain during pregnancy are major contributors to the incidence of intrauterine growth retardation (IUGR) <sup>73</sup>. Poor nutrition is also common under deprived socio-economic conditions in developed countries. On the other hand, pregnant women with eating disorders in high-income countries risk adverse neonatal outcomes associated with IUGR and microcephaly <sup>74</sup>. Fetal nutrition during critical periods of development can thus have specific effects on fetal structure and function, contributing to an increased susceptibility to adult disease <sup>63</sup>.

Epidemiological studies of the Dutch famine, in 1944-1945 at the end of the Second World War, revealed that the timing of malnutrition is important for subsequent health outcome. For months during the winter between 1944 and 1945, people in the German-occupied part of the Netherlands were only given two pieces of bread, two potatoes and a piece of sugar beet per day. Exclusive exposure to this diet with extremely low fat content, during the last trimester of pregnancy and the first months of life, resulted in a decreased rate of obesity during adult life, whereas exposure to the famine during the first half of fetal life was associated with an increased rate of obesity <sup>75</sup>. In another study, famine exposure during the third trimester of pregnancy reduced birth weight by around 10% but early pregnancy, mid-pregnancy or periconceptual exposure did not affect birth weight in one cohort <sup>76</sup>. Recent studies provide evidence that everyday maternal dietary composition during pregnancy can influence birth size in developed countries. A study by Moore et al in Australia showed that the proportion of energy derived from protein in early pregnancy was positively associated with birth weight and placental weight. They also found that the baby's ponderal index was negatively related with the proportion of energy from carbohydrates in early and late pregnancy. The association was independent of the mothers' BMI and weight gain during pregnancy <sup>77</sup>. Godfrey et al <sup>78</sup> obtained similar findings, while no effect of maternal nutrition on birth size was observed in a study by Mathews et al <sup>79</sup>.

Maternal obesity is due, at least in part, to poor dietary habits <sup>80</sup>. Micronutrients are essential for cell processes, including protein translation, enzymatic reactions and gene expression regulation. Animal studies demonstrate teratogenic effects of deficiencies in micronutrients such as folate or zinc <sup>81</sup>. In humans, inadequate folic acid intake increases the risk of neural tube defects while periconceptual folate supplementation has a strong protective effect <sup>82</sup>. A study from India showed that adequate maternal folate status, accompanied by low maternal vitamin B12, predicts increased risk of insulin resistance in children <sup>83</sup>. This also provides evidence that maternal micronutrient balance can influence the offspring's health.

The knowledge of energy requirements during pregnancy, which differ among individual women, is incomplete. The 2004 WHO recommendations suggest that the respective daily energy requirements are 0.35 MJ in the first trimester, 1.2 MJ in the second trimester and 2.0 MJ in the third trimester.

## **1. 2. 4. *Especially important nutrients during pregnancy***

### **1. 2. 4. 1. *Iodine***

The fetal thyroid gland does not become active until after the first trimester, prior to which the fetus is totally dependent on a maternal source of thyroid hormones, especially for normal brain development. An adequate dietary intake of iodine is essential during pregnancy in order to maintain maternal thyroid function, and later in pregnancy for fetal thyroid function<sup>84</sup>. The iodine requirement is increased during pregnancy, both in order to provide for the fetus's needs and to compensate for the increased renal clearance of iodine<sup>85</sup>. Inadequate maternal iodine intake can lead to neurodevelopmental delays, neurological abnormalities and impaired cognitive and motor development in the child<sup>86</sup>. Iodine deficiency is likely to be the most common preventable cause of mental retardation and brain damage in the world. "Endemic cretinism", a grave and irreversible form of mental retardation, is closely identified with iodine deficiency. A study by Vermiglio et al found associations between iodine deficiency in mothers and increased risk of attention deficit and hyperactivity disorder (ADHD) in their children<sup>87</sup>. Iodine deficiency has also been associated with spontaneous abortion, stillbirth, low birth weight, high neonatal mortality and delayed growth<sup>88,89</sup>. According to the 2004 Nordic Nutrition Recommendations (NNR), the daily iodine requirement is 175 µg during pregnancy and 200 µg during lactation<sup>90</sup>.

### **1. 2. 4. 2. *Iron***

The iron requirement is increased during pregnancy in order to meet the needs of the developing fetus, as well as the need for additional maternal tissue. Iron plays an important role in the body, both in transporting oxygen from the lungs to the tissues via hemoglobin (Hb), and related to the oxygen-binding function of myoglobin in muscle tissue. Iron homeostasis is tightly controlled and regulated by intestinal absorption of dietary iron, which increases when iron stores are low<sup>91</sup>. There are two types of iron in the diet: heme iron, mostly found in meat, and non-heme iron, found in plant-derived food products such as grains and vegetables<sup>92</sup>. Fourteen percent of the iron in a typical Swedish diet is absorbed<sup>92</sup>.

No relationship between maternal and cord serum ferritin (sFt) has been observed, but infants born to women with anemia or with iron deficiency without anemia have been shown to have lower iron stores<sup>93,94</sup>. A maternal sFt < 12 µg/L at delivery has been proposed as a threshold, below which fetal iron stores are at risk of being deficient. Haider et al showed that an improvement in prenatal mean Hb concentration linearly increased birth weight<sup>95</sup>.

A considerable proportion of pregnant women develop iron deficiency and anemia during pregnancy<sup>96</sup>. A study from Denmark showed that 10% of Danish women had iron deficiency and 2-4% had anemia. Only 18% had iron stores of at least 500 mg (sFt > 70 µg/L), the estimated level to cover the net iron requirement of a pregnancy<sup>97</sup>. The current Swedish recommendation is early sFt screening (before week 15). Iron supplementation should either start immediately (if sFt < 20 µg/L) or in week 20 (if sFt 20 - 60 µg/L), and women with an initial sFt > 60 µg/L should not take iron supplements.

### **1. 2. 4. 3. *Calcium***

It has been frequently reported that women of childbearing age do not consume the dietary reference intake of calcium. Fetal calcium deposition has been shown to peak at 350 mg/day in the third trimester, and maternal calcium absorption increases to meet

that demand, with greater increases in absorption reported among women with low intakes<sup>98</sup>. Maternal calcium absorption increases significantly during the second and third trimesters, as does maternal bone turnover<sup>99,100</sup>.

Low calcium intake during pregnancy may stimulate parathyroid hormone (PTH) secretion, increasing intracellular calcium and smooth muscle contractibility, and/or releasing renin from the kidney, leading to vasoconstriction and retention of sodium and fluid. These physiological changes can lead to the development of pregnancy-induced hypertension and preeclampsia<sup>101</sup>. A Cochrane report from 2010 concluded that the average risk of preeclampsia was reduced in women taking calcium supplements (RR 0.45) and that the effect was greatest in women with low baseline calcium intakes (RR 0.36). They found that calcium supplements reduced the rare occurrence of the composite outcome ‘death or serious morbidity’ in women<sup>102</sup>. However, the same review reported no overall association between calcium intake and the risk of preterm birth or stillbirth<sup>102</sup>.

It has been reported that parity influences bone loss during gestation, with greater losses reported in primiparas than in multiparas<sup>103</sup>. The number of childbirths does not appear to increase later fracture risk in women, with studies showing either a negative<sup>104,105</sup> or a neutral<sup>106</sup> relationship between parity and the risk of fracture. Women who begin pregnancy with adequate intake of at least 1 000 mg of calcium/day may not need additional calcium, but women with suboptimal intake (<500 mg) may need additional amounts of calcium to meet both maternal and fetal bone requirements.

#### 1. 2. 4. 4. *Vitamin D*

Vitamin D is a fat-soluble vitamin, crucial for skeletal development. It is predominantly found in foods of animal origin (fatty fish, to some extent in eggs and meat) and fortified products (milk with  $\leq 1.5\%$  fat and margarine in Sweden). However, the primary source of vitamin D is synthesis in the skin following exposure to ultraviolet light, where 7-dehydroxycholesterol is converted to pre-vitamin D<sub>3</sub>. The NNR define a vitamin D level, measured as serum/plasma concentration of 25-(OH) D<sub>3</sub>, of 50 nmol/L as adequate. The recommended daily intake during pregnancy and lactation is 10  $\mu\text{g}$  (400 IU). With limited sun exposure, the current recommended intake may be inadequate to maintain optimal circulating 25-(OH) D<sub>3</sub> concentrations and to maintain health, especially in pregnant<sup>107</sup> and lactating women<sup>108</sup>.

During pregnancy and lactation, the vitamin D requirement is elevated due to a need for enhanced maternal absorption of calcium in order to supply fetal and neonatal bones<sup>109</sup>. There are considerable changes in maternal vitamin D and calcium metabolism, to ensure the calcium required for fetal bone mineral accretion<sup>110</sup>. An active metabolite of vitamin D, 1,25(OH) 2D, increases the efficiency of intestinal calcium absorption, decreases renal calcium excretion and, in conjunction with PTH, mobilizes calcium from bone<sup>110</sup>. Vitamin D is also important for fetal growth, nervous system development, lung maturation and fetal immune system function<sup>111</sup>. Vitamin D insufficiency during infancy can result in defective mineralization with the development of rickets in children<sup>110</sup>. Maternal vitamin D deficiency might also contribute to low birth weight<sup>112</sup>, impaired fetal growth<sup>110</sup> and impaired fetal bone ossification<sup>113</sup>. Vitamin D-deficient pregnant women can develop secondary hyperparathyroidism, which leads to transitory hypoparathyroidism and hypocalcemia in neonates<sup>114</sup>.

#### 1. 2. 4. 5. *Essential fatty acids in breast milk and during pregnancy*

The omega-3 (n-3) fatty acid alpha-linolenic acid (ALA) and the omega-6 (n-6) FA linoleic acid (18:2n-6, LA) are essential fatty acids (EFAs), as they cannot be produced by the human body. The EFAs are converted into long-chain polyunsaturated fatty acids (LCPUFA); n-6 fatty acid LA to arachidonic acid (20:4n-6, ARA). The n-3 fatty acid ALA is converted to eicosapentaenoic acid (20:5n-3, EPA) and docosahexaenoic acid (22:6n-3, DHA). Conversion from ALA and LA to EPA, DHA and AA is low, 1-10 %<sup>115,116</sup>. Conversion rates are lower in infants (especially premature infants). Since the conversion rate is low, especially of EPA and DHA, there has been discussion concerning whether they are essential in the diet, as are ALA and LA, especially in early life. There are also indications that the balance between n-6 and n-3 fatty acids is important, since there is a metabolic transformation competition between LA and ALA for the same enzymes, both regarding desaturation and elongation to their longer derivatives<sup>117</sup>.

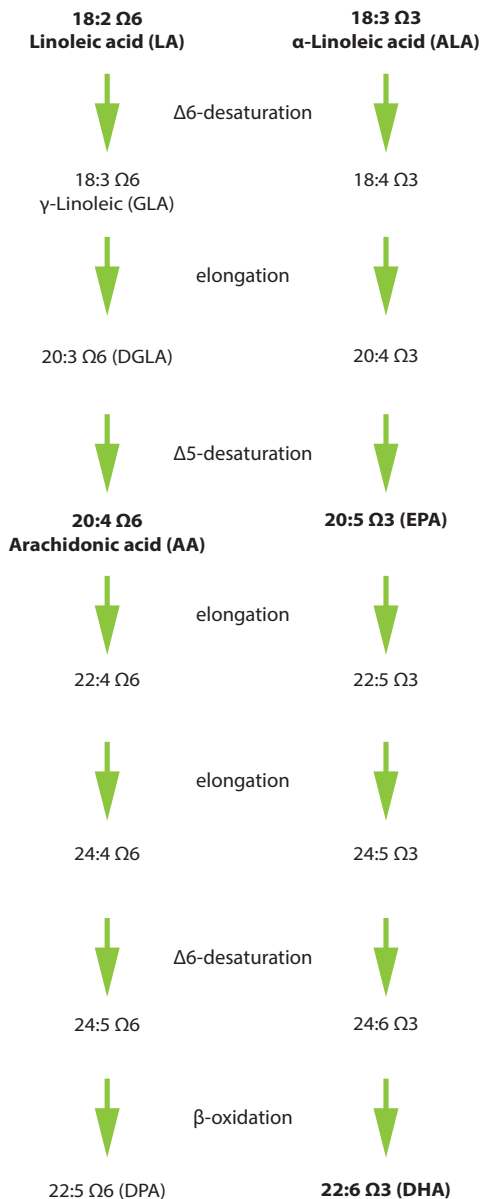
Transfer through the placenta of DHA is an active transport mechanism, resulting in a decrease in maternal DHA, if not compensated for in the diet during pregnancy and breastfeeding<sup>118</sup>. The optimal intake is not known, but it has been suggested that the newborn infant needs about 35 mg DHA and 50-60 mg AA daily<sup>119</sup>.

Concentrations of LA, ALA, DHA and EPA in breast milk depend on the mother's diet and fat stores<sup>120</sup>. The reported mean DHA and AA levels in human milk worldwide are 0.32 % and 0.47 %, respectively, of the total fatty acids. Iron, zinc, vitamin B6 and vitamin E are required for the conversion of ALA and LA to EPA, DHA and AA, due to their functions in elongation enzymes<sup>121</sup>. It has also been shown in a rat model that folic acid intake influences brain DHA levels in adult offspring<sup>122</sup>.

LA and ALA and their long-chain derivatives EPA, DHA and AA are important for numerous physiological and developmental requirements in humans. The brain is composed of large amounts of both DHA and AA. During the third trimester of pregnancy and the first year of life, it grows rapidly and an adequate supply of these FA is thought to be essential for optimal development<sup>123,124</sup>. DHA is also a major component of the retina and thus affects visual acuity<sup>124</sup>. AA and DHA are vital structural elements of cell membranes. LCPUFAs affect growth through their role in the synthesis of prostaglandins and growth hormones and the biosynthesis of membrane components<sup>125,124</sup>. In a cohort study of premature infants, 98 % of the mothers had n-3 FA intakes below recommended levels and a relatively high n-6 FA intake; a negative correlation was found between n-6/n-3 FA ratios and early development up to 18 months of corrected age<sup>126</sup>. Another study showed that the AA/DHA ratio was important for normal motor development in term-born infants at three months of age<sup>127</sup>. A study by Donahue et al found an association between an early high n-6/n-3 FA ratio and obesity in 3-year-olds<sup>128</sup>.

Other possible benefits of n-3 FA during pregnancy have been suggested. A prospective study in India showed that women with preeclampsia had reduced total n-3 FA levels ( $p < 0.05$ ), increased n-6/n-3 ratios ( $p < 0.05$ ), higher oxidative stress ( $p < 0.05$ ) and lower antioxidant ( $p < 0.05$ ) levels. Similar trends were also observed in cord samples after delivery<sup>129</sup>. Observational studies in both developed and developing countries indicate a likely association between low DHA levels (measured in breast milk) and postpartum depression<sup>130</sup>.

Modern diets often provide high amounts of LA and are relatively low in ALA<sup>131</sup>. Fish, in contrast with domesticated animals, are rich in EPA and DHA, due to the synthesis of EPA and DHA in phytoplankton and their transfer up the aquatic food chain. In



**Figure 5.** Metabolic conversion of the essential fatty acids, LA (omega-6 series) and ALA (omega-3 series) to long-chain LCPUFA

the Stone Age, the n-6/n-3 ratio in humans was close to 1<sup>132</sup>. The ratio today varies widely, from less than 5 in Japan to more than 30 in the USA. In most European countries, the n-6/n-3 ratio is between 8 and 20<sup>133</sup>. One reason for reduced intake of seafood could be fear of methyl mercury and dioxin pollution in fish, leading authorities to recommend a reduction, especially in pregnant women. Overfishing with increased prices, and less access to marine food in populations that depend on fishing, are other problems. The increase of fast food and processed food, often made with oils rich in n-6 FA, makes the n-6/n-3 ratio even higher.

Most of our knowledge of the possible importance of LCPUFA for long-term development is obtained from animal studies. Rodents with EFA deficiency during fetal life have reduced growth as neonates and develop obesity and low bone mineral density in adult life<sup>134</sup>. High fasting insulin in the adult offspring was found when dams received a diet with a high n-6/n-3 ratio<sup>135</sup>. Animal studies have also found that an increase in fat mass caused by high insulin can be balanced by an increase in DHA<sup>136</sup>. A study by Palsdottir et al showed that lactating dams that only received saturated fat, resulting in very low levels of EFA and LCPUFA in breast milk, were resistant to obesity when given a high-fat diet as adults. This was associated with changes in the mRNA expression of uncoupling protein 1 in brown fat tissue and in transcription factors in the liver. The results indicate that the FA composition during lactation is

important for body composition and glucose tolerance in the adult offspring<sup>137</sup>. It is known that fat stores are formed during the latter part of the third trimester in humans, and during the second postnatal week in rodents<sup>138</sup>. There might thus be indications that the FA pattern during the perinatal period may have long-term effects. A study from Argentina showed that obese mothers had lower n-6/n-3 ratios in their breast milk than normal-weight mothers<sup>139</sup>.

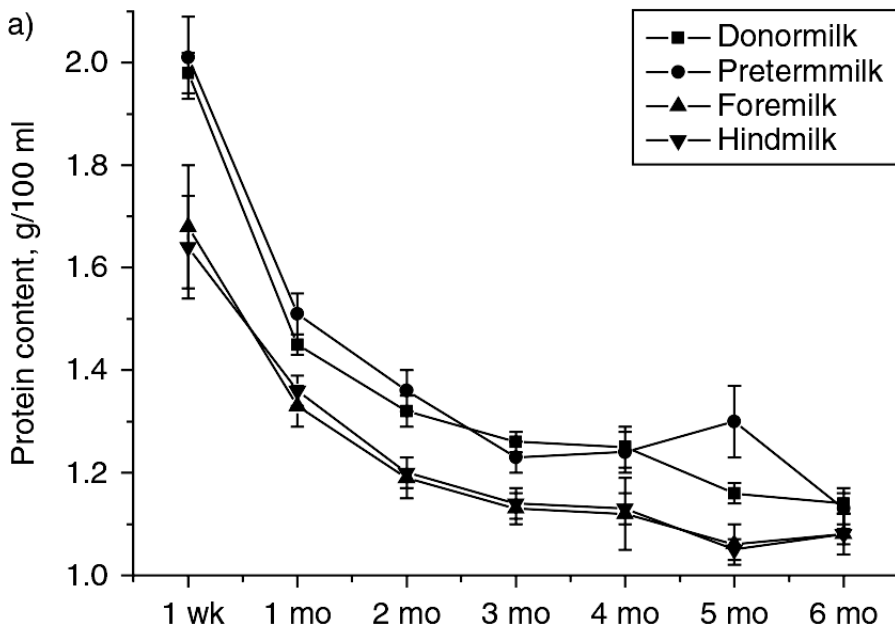
### 1. 3. Human breast milk

Human breast milk is considered to be the best nutrition for the newborn infant because it contains optimal ingredients for healthy growth and development and it is recommended as the exclusive food for the infant from birth to six months of age (WHO, 2002). Breastfeeding protects against gastrointestinal infections, respiratory infections<sup>140</sup> and allergies<sup>141</sup>. Breastfeeding has also been associated with a reduced long-term risk of diseases such as inflammatory bowel disease, obesity and diabetes<sup>142</sup>.

Colostrum is usually present for the first three to five days after birth, followed by transitional milk until about two to three weeks postpartum, after which breast milk is considered to be mature. Breast milk contains high concentrations of factors providing immunological support and protection, such as immunoglobulin, lactoferrin, oligosaccharides and active viable immune cells. It also contains cell proliferation-inducing factors thought to promote development of the neonate's gastrointestinal tract and to stimulate hematopoiesis and maturation of the immune system<sup>143,144</sup>.

#### 1. 3. 1. Proteins in breast milk

The protein content in human breast milk is very low and is not affected by maternal diet; it increases with higher maternal body weight and nursing frequency and decreases in mothers producing higher amounts of milk<sup>145</sup>. The proteins are divided into the whey and casein fractions or complexes, each comprising a remarkable array of specific proteins and peptides<sup>146</sup>. The most abundant proteins are casein,  $\alpha$ -lactalbumin, lactoferrin, secretory IgA, lysozyme and albumin<sup>147</sup>. Non-protein nitrogen-containing



**Figure 6.** The mean protein content of full-term donor and preterm milk and full-term fore- and hindmilk during the first 6 month of lactation. Vertical lines show standard errors of means. (From Saarela, 2005)

compounds, including urea, uric acid, creatine, creatinine, amino acids and nucleotides, comprise approximately 25% of breast milk nitrogen. Compared to bovine milk, human milk contains only one third of the protein (Frank, 1988). Neither lactose nor protein concentrations vary throughout one breastfeeding<sup>148</sup>. Colostrum, however, has a higher protein content (30-70 g/L or 3-7%) than mature breast milk (7-25 g/L or 0.7-2.5%), which may additionally benefit the infant during the first few days after birth<sup>149,148</sup>. The protein content of human breast milk decreases rapidly during the first month and then decreases slowly until six months of lactation. It is well known that the total protein concentration is higher in preterm than full-term milk in the early postpartum period<sup>150</sup>. It has also been found that the protein composition changes rapidly and more markedly in preterm than in full-term milk, so that immunological components (e.g. IgA) decrease and nutritional components, such as lactalbumin, increase<sup>151</sup>.

### **1. 3. 2. Fat in breast milk**

Of the major digestible energy components (fat, lactose and protein) in human breast milk, fat is the most variable. The fat in breast milk provides about 50% of infants' energy intake. Most of the FA are saturated, with a predominance of palmitic acid (16:0). The major fat content consists of triglycerides, while phospholipids and cholesterol are a minor part. The fat content increases during the feeding; fat levels are thus two to three times lower in foremilk than in hindmilk. Hindmilk consequently supplies 25 to 35 kcal/100 ml more energy, on average, than foremilk<sup>148,149</sup>. The fat content is highest in colostrum, decreasing during the transition to mature milk. The LCPUFA and EFA content depends both on the mother's diet and adipose tissue<sup>152</sup>.

### **1. 3. 3. Carbohydrates in breast milk**

The principal carbohydrate in human breast milk is the disaccharide lactose. The concentration of lactose is the least variable of the macronutrient concentrations in breast milk but milk lactose is positively correlated with milk volume<sup>145</sup>. The other significant carbohydrates in breast milk are the oligosaccharides, which comprise approximately 5 - 15 g/L, depending on lactation stage and maternal genetic factors. The oligosaccharides are considered to be non-nutritive and bioactive. They are prebiotic agents that selectively encourage the growth of beneficial (probiotic) organisms. Furthermore, the oligosaccharides and their protein conjugates are recognized as pathogen-binding inhibitors that function as soluble "decoy" receptors for pathogens with an affinity for binding to oligosaccharide receptors expressed on the infant's intestinal surface<sup>144</sup>.

### **1. 3. 4. Micronutrients in breast milk**

Many micronutrients, including vitamins A, B1, B2, B6, B12, D and iodine, vary in human milk, depending on maternal diet and physique. Vitamin K levels are extremely low in human milk and many countries recommend an injection of this vitamin in order to avoid hemorrhagic disease of the newborn. Vitamin D levels are also low in breast milk, particularly with low maternal exposure to sunshine. Current pediatric recommendations prescribe postnatal vitamin D supplementation until at least two years of age<sup>153,154</sup>.

### **1. 3. 5. The breast milk microbiome**

Several studies have demonstrated that breast milk from healthy women contains approximately 103-104 colony-forming units (cfu)/ml, representing a continuous source of potential commensal bacteria for the infant gut<sup>155</sup>. More than 200 different bacterial species have been isolated from human milk. Traditionally, it is believed that the pre-



sence of bacteria in breast milk is a result of contamination from the mother's skin or the infant's oral cavity, but there must also be other pathways to the breast. Bifidobacteria present in breast milk are strict anaerobes; it is thus unlikely that they are transported from the infant's mouth to the skin of the breast<sup>156</sup>. Bacteria can also be isolated from colostrum before the infant is born and live bacteria orally administered to lactating women can be retrieved from breast milk<sup>157,158</sup>. One possible route for microbes to the breast is massive migration from the maternal intestinal tract, with subsequent uptake by different immune cells<sup>159</sup>.

#### 1. 4. Weight gain in pregnancy

Limiting gestational weight gain (GWG) to the recommended level is important in order to optimize maternal and neonatal health outcomes. A retrospective cohort study by Vesco et al, including 2 080 obese women, showed that GWG above that recommended by the American Institute of Medicine in 2009<sup>160</sup> did not significantly decrease the SGA risk but was associated with an increased odds both of macrosomia (OR 3.36; 95% CI 1.74-6.51; 6.0% vs. 2.1%) and large for gestational age (LGA) (OR 1.80; 95% CI 1.36-2.38; 23.8% vs. 16.6%). GWG below that in the recommendations was associated with increased odds of SGA (OR 3.94; 95% CI 2.04-7.61; 8.8% vs. 2.7%) and decreased odds of LGA (OR 0.56; 95% CI 0.37-0.84; 11.2% vs. 16.6%). Table 1 shows the American Institute of Medicine recommendations for GWG in obese women.

A 2007 study from the Swedish Medical Birth Register found that the optimal GWG was 4- 10 kg for women with initial BMI less than 20, 2- 10 kg for BMI 20-24.9, less than 9 kg for BMI 25-29.9 and less than 6 kg for BMI 30 or more, based on significant risk estimates of adverse maternal and fetal outcome<sup>161</sup>.

GWG is strongly associated with postpartum weight retention, i.e. not returning to pre-pregnancy weight within six months after delivery. For some women, GWG is a

**Table 1.** Recommendations for total and rate of weight gain during pregnancy, by prepregnancy BMI

Prepregnant Weight Category	BMI	Recommended Range of total Weight	Recommended Rates of Weight Gain† in the Second and Third Trimesters (kg) (Mean Range [kg/week])
Underweight	Less than 18.5	13 - 18	0.5 (0.45 - 0.59)
Normal Weight	18.5 - 24.9	11 - 16	0.5 (0.36 - 0.45)
Overweight	25 -29.9	7 - 11	0.3 (0.27 - 0.32)
Obese	30 and greater	5 - 9	0.2 (0.18 - 0.27)

\* Calculations assume a 0.5-2 kg weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997)

trigger for developing overweight and obesity<sup>162</sup>.

#### 1. 5. Physical activity in pregnancy

There is strong evidence of health benefits related to PA (Physical Activity) in pregnancy, for example reduced risk of preeclampsia<sup>163</sup>, gestational diabetes<sup>163,164</sup> and preterm birth<sup>165</sup>. The lower rate of prematurity may be related to reduced oxidative stress and

the lower incidence of preeclampsia may be associated with exercise<sup>166</sup>. Regular exercise appears to increase antioxidative enzymes in pregnant women, which in turn reduces oxidative stress and preeclampsia. These may be contributing factors to the reduced prematurity rate reported for exercisers versus non-exercisers.

Decreasing PA and more depressed mood are common during pregnancy<sup>167</sup>. Studies from several different countries suggest that only about 40% of pregnant women exercise. Positive factors for exercising more during pregnancy include higher education and income, not having other children in the home, being white and being more active prior to pregnancy<sup>168</sup>. A randomized study from Sweden showed that a water aerobics program was more effective than a land-based physical exercise program in decreasing pregnancy-related low back pain<sup>169</sup>. Reducing physical discomfort, increasing mobility, improving body image and increasing health-promoting behaviors are other positive effects of similar programs<sup>170</sup>. Several studies have reported positive effects of yoga in pregnant women, including less stress, anxiety and pain during pregnancy<sup>171</sup>. USA exercise guidelines recommend that all healthy women undertake at least 150 min of moderate-intensity aerobic activity a week during pregnancy<sup>172</sup>.

### **1. 6. Interventions aimed at limiting gestational weight gain**

Many interventions have been conducted with the aim of limiting GWG to appropriate levels. A meta-analysis by Thangaratinam et al reported that mean GWG in the combined intervention groups was 1.4 kg lower than in the control groups. Only PA was associated with reduced birth weight (mean difference -60 g). Taken together, the interventions were associated with a reduced risk of preeclampsia (OR 0.74; 95% CI 0.60 to 0.92) and shoulder dystocia (OR 0.39; 95% CI 0.22 to 0.70). No significant effect was found concerning other critically important outcomes. Diet-based interventions were the most effective; they were associated with reductions in GWG and improved obstetric outcomes<sup>173</sup>. A Cochrane review published in 2012 suggested that, analyzed together, the studied interventions had limited effect, as only a small reduction in total GWG had been found<sup>174</sup>.

Hil et al undertook a systematic review evaluating the theories of behavior change informing GWG interventions; 19 studies were identified for inclusion. Eight studies were informed by a behavior change theory. Studies based on theory were as effective as non-theory-based studies at limiting GWG. They showed that the interventions were effective at limiting GWG, with the intervention groups gaining significantly less weight than the control groups (weighted mean difference = -1.54 kg). Seven of the reviewed studies showed significantly less GWG in the intervention group, while the other studies had found non-significant differences. Dietary interventions were significantly more effective at limiting GWG than both PA and mixed interventions. The provision of information, motivational interviewing, behavioral self-monitoring and providing rewards contingent on successful behavior appear to be key strategies in GWG interventions.

### **1. 7. Intervention research**

In the book "*Intervention research*" Frasier et.al states that intervention research is a dynamic process involving researchers, agencies and practitioners: "*As purposeful actions, interventions may operate at the individual, family, organizational, neighborhood, regional, national or other level*".

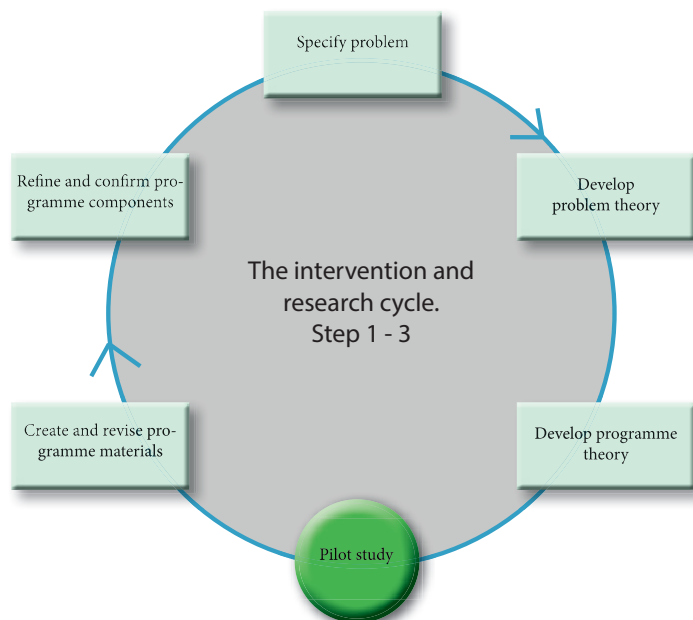
Interventions may be comprised of a single action or a cluster of actions<sup>175</sup>.

Intervention research has different purposes. Through intervention research, programs are developed and refined. It is a systemic process in which research findings, theory and practice knowledge are conjoined to create new programs or to modify existing ones. Intervention research attempts to ascertain whether a program is effective and produce the desired outcomes. Intervention research findings can inform theory, clarify what made the program work and conclude that a program, rather than some other factor, has caused an observed outcome.

According to Frasier, there are five steps in intervention research:

1. Specify the problem and develop a program theory
2. Create and revise program materials
3. Refine and confirm program components
4. Assess effectiveness in a variety of settings and circumstances
5. Disseminate findings and program materials

**Step 1** involves the detailed description of a problem, a target population and a change process. In most cases, the first step in problem specification is to measure its incidence and prevalence. Is the prevalence rising? The demographic characteristics, political and economic cost and social significance of the problem are identified. Prevalence data can demonstrate risk over time and identify high-risk populations. Subsequently, mediating factors and mechanisms are identified, the literature is reviewed and experts



*Figure 7. The intervention and research cycle*

are consulted.

Developing a program theory involves identifying those risk factors and protective factors which are malleable, capable of being influenced. Identifying the intervention level, setting, outcomes and developing a logic model are other components. The program theory includes both proximal and distal outcomes as well as specifying a change model. The program theory is also called the change process or the theory of change. After creating a program theory with targeting factors that are feasibly changed through a series of intervention actions, a pilot study is performed.

In **step 2** program materials are developed and revised, based on critical reviews and findings from the pilot study (or studies). The initial task involves fully specifying the intervention and testing the components for feasibility. Program materials should be rooted in a theory of change or logic model. This step includes assessing the capacity of practitioners to implement and adhere to the proposed treatment plan.

**Step 3** Interventions often involve several components, each designed to address an important risk factor. In step 3, each component is tested, separately and in different combinations. A variety of designs may be used to estimate the effect of each major component or combinations of components <sup>176</sup>. It is important to test each component, because one part of the intervention program may be substantially more effective, substantially more costly or more difficult to implement than the other parts. When step 3 is complete, the key components should be well defined and the differential benefits of each component should be clear.

In **step 4**, effectiveness is tested. Effectiveness trials are design to confirm intervention components in routine practice; the intervention is tested in a setting in which the researchers may have limited control, on a broad heterogeneous sample. Since fidelity is a central part of effectiveness trials, step 4 often entails programs being supervised by on-site staff. The estimates are based on intention-to-treat (ITT) and efficacy subset analyses. ITT is the outcomes of all participants for whom the intervention is intended, regardless of whether they received all, part or none of the intervention. Efficacy subset analyses focus on estimating the treatment effect.

**Step 5** When intervention research is successful, it has a significant impact on social and health problems, if implemented widely. The intervention is only useful if it reaches the at-risk population, works as intended and is maintained over time. Dissemination of findings and materials is aimed at actively helping the intervention to spread. Diffusion, “letting it happen”, occurs more realistically by practice penetration. Programs with a high degree of practice penetration are, according to Rogers et al <sup>177</sup>:

- Superior to services as usual
- Compatible with agency practices
- No more complex than existing services
- Easy to try (and reject if they fail), and
- Likely to produce tangible results recognizable by authorities as important

## 1. 8. Motivational interviewing

Motivational interviewing (MI) is a client-centered, directive therapeutic style to enhance readiness for change by helping clients explore and resolve ambivalence about change <sup>178</sup>. MI is a complex clinical style for eliciting the client’s own values and motivations for change. It is far more about listening than telling, about evoking rather than instilling. MI communicates not, “*I have what you need,*” but instead, “*You have what you need, and together we will find it.*” Like other psychotherapies, MI is a complex

and skillful method that is learned over time.

MI practice rests on four general principles:

- Expressing empathy for the client by accepting the client's situation and recognizing that ambivalence is normal
- Developing discrepancy between present behavior and personal goals or values, thereby encouraging the client to present reasons for change
- Rolling with resistance to counteract presentation of reasons not to change
- Supporting self-efficacy of the possibility of change, and emphasizing client responsibility for choosing and carrying out change

Four processes can often be identified in MI counseling: 1. *Engaging*, creating an alliance and mutual trust between client and counselor; 2. *Focusing*, an agreement on what to keep in focus; 3. *Evoking*, to elicit and support motivation for behavior change; and 4. *Planning*, which is essentially goal-setting and focusing on how goals for behavior change might be reached <sup>179</sup>.

MI has a solid evidence base to support its efficacy, and has consistently been shown to be more effective than no treatment or placebo control conditions <sup>178</sup>. MI is a potentially useful method to increase motivation for behavior change in pregnancy.

## **2. Aims**

The overall aim of this thesis is to study different aspects of obesity and its association with pregnancy, delivery and breastfeeding, applying both clinical and epidemiological methodology and, if possible, to increase our understanding of how to improve the care of obese women during pregnancy, delivery and breastfeeding.

### **2. 1. Aims of the studies**

1. To investigate whether an intervention program was feasible, both for the pregnant women and the health care staff involved in the program, and whether it was safe for mother and child (Paper I).
2. To investigate the FA pattern in obese mothers' breast milk and their neonates' plasma, compared with the corresponding pattern in normal-weight mothers and their neonates (Paper II).
3. To assess the risk of obstetric anal sphincter lacerations in relation to maternal obesity among primiparas. (Paper III).
4. To compare health care consumption and sick-listing among obese and normal-weight pregnant women (Paper IV).

### 3. Methods and subjects

#### 3.1. Ethics

Ethical approval from the Research Ethics Committee at Karolinska Institutet was obtained prior to initiation of all studies: Paper I: dnr: 2006/1100-31/4; Paper II: dnr: 2008/1427-31/3; Papers III and IV: dnr: 2008/1427-31/3. All patients gave their informed consent to participate in the clinical studies (Papers I and II). The analyses in Papers III and IV were performed on the statistical group level; no specific patients could be identified.

#### 3.2. Paper I

This is a prospective pilot study. Twenty-seven pregnant women with BMI > 30 were enrolled in a dietary and PA program during their first trimester. Twenty-five women completed the program. One woman had Sjögren's disease, one had ulcerative colitis and asthma, one had PCOS, two had been treated for hypertension, one had asthma and one had vitamin B12 deficiency. None of the women smoked during pregnancy.

The program included visiting a midwife every fortnight throughout the pregnancy and participating in two group support sessions, where all participants in the program met and discussed their experiences, guided by a midwife. The program also included an individual consultation with a dietician at the beginning of pregnancy. Participants were instructed to eat according to 'the plate model'<sup>180</sup>, aimed at minimizing unneces-

*Table 2. Logic model of intervention study*

Inputs	Activities	Materials	Intermediate outcomes	Distal outcomes
Funding from Stockholm County council	Education of midwives from delivery board and mother healthcare centers.	Manuals to midwives, doctors and dieticians	Increased knowledge in healthy food and physical activity during pregnancy.	Weight gain less than 6 kg during pregnancy
Expert supports	Training in MI Information's to hospital staff and to other Mother Healthcare Centers	MI and weight control, Mother Healthcare Centers	Increased motivation in mothers	Percentage of <ul style="list-style-type: none"> <li>• Cesarean section</li> <li>• Preeclampsia</li> <li>• Hypertension</li> <li>• Macrosomia</li> </ul>
Local resources	Coaching	Meeting with dietician, food diary	Increased confidence in mothers	
	Questioners to patients: confidence, knowledge	Meeting with midwife from delivery ward		
		Water gymnastic Exercise 30 minutes/day		

sary calories, and to eat full meals at regular intervals. The women were recommended to keep a food intake diary, where everything they ate was recorded together with their PA. All patients in the program were offered water gymnastics once a week and they were required to exercise 30 minutes per day the other days of the week. If the pregnancy remained normal, the women consulted an obstetrician three times during pregnancy and at a follow-up visit six to eight weeks after delivery. Maternal BMI was calculated at inclusion and GWG was recorded at every consultation with the midwife. Pregnancy-induced complications were recorded in a separate protocol. Data on delivery outcomes were collected from the hospitals' computerized charts and included mode of delivery, complications and birth weight.

Blood was sampled on inclusion at the beginning of pregnancy and repeated at pregnancy weeks 28-32 and 40. Blood samples were analyzed for Hb, serum total cholesterol, free FA, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, folate, thyroid-stimulating hormone (TSH) and free thyroxin (fT4). Glycosylated hemoglobin A1C (HbA1c) was tested at the beginning of pregnancy. In gestational week 28-30, the participants had an oral glucose tolerance test (OGTT). All pregnancies were dated by ultrasound in gestational week 18-19 and all participants had two additional ultrasounds in gestational weeks 32 and 40. The Edinburgh Postnatal Depression Scale (EPDS) was used as a screening tool for detection of ante- and postnatal depression <sup>181</sup>.

### 3. 3. Paper II

The fatty acids pattern in breast milk and neonatal plasma was analyzed in an observational study of 41 obese and 41 normal-weight pregnant women. Twenty-nine obese women participating in a weight reduction program were included for comparison. In order to randomly include normal-weight and obese controls, they were included after a woman from the intervention study had been delivered. Thus, when a baby was born in the intervention group, the next mother with pre-pregnant BMI > 30 kg/m<sup>2</sup> and with a baby of the same gender was invited to participate. If a woman declined to participate (n=4), the next woman fulfilling the criteria was contacted. The next woman with a BMI < 25 kg/m<sup>2</sup> and a baby of the same gender was also asked to participate. For the last 12 infants born to the women in the intervention group, the number of control infants was doubled.

The intervention was a weight control program, including general dietary advice and increased PA, and was introduced for pregnant obese women with BMI > 30, as previously described (Paper I). FA supplementation or intake was not discussed. The Swedish National Food Agency's general recommendation for all pregnant women, was to eat fish two or three times a week; however, n-3 supplementation was not recommended. FA were analyzed with capillary gas chromatography of lipids in breast milk collected at three and ten days and one and two months postnatally, as well as in the infants' plasma phospholipids, sampled three days after birth. All mothers answered, while still in the neonatal ward, a short food frequency questionnaire concerning the intake of fish, eggs, and vegetables during pregnancy. The questionnaire also included fats used for spread and cooking, sweets and the daily number of full meals. On the third day after birth, simultaneously with the routine general neonatal screening, a blood sample was taken from the baby for the analysis of plasma phospholipid FA. The mothers were asked to collect breast milk after nursing the baby (hindmilk) on days three and ten, and at one and two months after birth. Phospholipids and breast milk lipids were analyzed with capillary gas-liquid chromatography, as previously described <sup>118</sup>.



### 3. 4. Paper III

This is a population-based cohort study, based on Swedish Medical Birth Register data from January 1, 2003 to December 31, 2008, including 210,678 primiparas. Women with multiple gestations and cesarean sections were excluded. BMI was categorized into four classes: <25, 25-<30, 30-<35 and >35. The Swedish Medical Birth Register has recorded data on more than 98% of all deliveries in Sweden since 1973 and has previously been validated and described in detail<sup>182</sup>. Starting with the first antenatal visit, normally at 8-12 weeks' gestation, information on maternal demographic data, reproductive history, pregnancy and previous births is prospectively collected by a midwife. The record also includes maternal weight and height, from which BMI (kg/m<sup>2</sup>) is calculated. The standardized records are identical throughout the country and are forwarded to the Central Birth Register. In accordance with national guidelines, perineal lacerations were diagnosed by the attending midwife who inspected the vagina immediately after childbirth. The diagnosis and classification of perineal lacerations follow the ICD-10: grade I, labial tears (ICD O70.0); grade II, perineal and vaginal laceration, but no anal sphincter involvement (ICD O70.1); grade III, partial or complete anal sphincter laceration (ICD O70.2); grade IV, complete anal sphincter laceration including rectal mucosa (ICD O70.3). In cases in which the midwife suspects a grade III-IV laceration, the attending obstetrician is consulted to confirm or refute the diagnosis. Information on age at delivery, operative delivery, birth weight, head circumference and maternal diabetes mellitus was also obtained from the register.

### 3. 5. Paper IV

This retrospective population-based cohort study included all primiparas with a singleton pregnancy recorded from January 1, 2003 through December 2008 in the Swedish Medical Birth Register<sup>182</sup>. The study population was linked to two other nationwide Swedish registers, the Swedish National Inpatient Register (IPR) and the Maternal Health Care Register. The final study population was required to be recorded both in the Swedish Medical Birth Register and the Maternal Health Care Register and consisted of 108,103 primiparas. Information on sick-listing was only recorded from 2003 and 2006-2008. Data on inpatient care was obtained from the IPR which has complete national coverage from 1987; more than 99% of all somatic and psychiatric hospital discharges are registered. A previous validation of the IPR by the National Board of Health and Welfare showed that 85-95% of all included diagnoses are valid<sup>183</sup>. The Maternal Health Care Register was created in 1997 as a complementary database to the Medical Birth Register in order to measure antenatal health care quality. Between 2003 and 2008, the Maternal Health Care Register contained information on 71-82% of all pregnancies, variations that are due to changes in national coverage. Midwives report data twice to the Maternal Health Care Register, at the beginning of the pregnancy and 16 weeks after delivery.

Health care consumption up until 7 days prior to delivery was studied in relation to BMI at the first antenatal care visit and included the number of visits to an obstetrician, the number of visits to a midwife, the number of visits to cross-disciplinary clinics for treatment of moderate to severe fear of childbirth (referred to as "Aurora clinics" in Sweden), sick-listing during pregnancy (obtained from the Maternal Health Care Register), the number of hospital admissions and the causes of in-patient care (obtained from the IPR).

## 4. Statistical analyses

### 4.1. Paper I

Fisher's exact test was used to compare proportions. Wilcoxon's matched pairs test was used to compare continuous non-parametric numeric data. Outcomes are presented for the entire group, as well as categorized by BMI at inclusion.  $p < 0.05$  was considered significant for all analyses. Statistical analyses were performed using STATISTICA software (StatSoft Inc. Tulsa, OK).

### 4.2. Paper II

To compensate for suspect skewness in the obese population, the Kruskal-Wallis non-parametric test was used to calculate differences in FA concentrations in plasma between infants in the three groups, and multiple comparisons of mean ranks for all groups was used for ad hoc analysis. Maternal and infant characteristics were compared with the chi-squared test and ANOVA. Multiple regression analysis was used to calculate associations between FA compositions and food intake, smoking, n-3 supplementation and other background factors, as well as to study the relationship between BMI at one year of age and FA in breast milk and infants' plasma. ANOVA repeated measures were used to calculate differences in FA concentrations in breast milk and for ad hoc analysis of differences. The Bonferroni's test was used for repeated measures analysis; only mothers who provided at least three samples were included. Statistical significance was set at  $p < 0.05$  for each statistical hypothesis. Statistical analyses were performed using STATISTICA software (StatSoft Inc. Tulsa, OK).

### 4.3. Paper III

Proportions for grade I-IV lacerations are presented as absolute numbers and proportions with 95% CI, according to BMI class. In order to estimate the effect of BMI on obstetric anal sphincter lacerations, with possible confounders accounted for, uni- and multivariate logistic regression analyses were performed. The univariate analysis used all the variables identified a priori as possible risk factors for anal sphincter lacerations, including BMI class, maternal age, instrumental delivery, birth weight, head circumference and diabetes mellitus. Variables showing a significant relationship in the univariate analysis were included in the final multivariate model. ORs were estimated with 95% CIs. All statistical analyses were performed using SAS software (Cary, NC, USA).

### 4.4. Paper IV

Women were grouped into four BMI categories: normal weight (20-<25); overweight (25-<30); obese (30-<35); and morbidly obese (>-35). For numerical variables, means and standard deviations are presented, whereas one-way ANOVA was used for testing the hypothesis of equal means. Pairwise comparisons among groups are obtained post-hoc by the Tukey HSD test. For categorical variables, frequencies and percentages are presented. Where frequencies are presented, the  $p$  overall in the tables is from the R function probability test, a test of equal proportions. Also presented are  $p$ -values for pairwise comparisons among all BMI groups; these are Holm adjusted post-hoc tests by R function pairwise probability tests. All statistics were performed in R, version 2.14.1.

## 5. Results

### 5.1. Paper I

Twenty-five women (92%) completed the study. Their mean age at entry was 31.7 years and their median parity was 1 (range 0-3). Table 3 shows detailed patient characteristics, while clinical outcomes are presented in Table 4. Fifty-six percent (14/25) kept their GWG under the set goal of 6 kg, six (24%) gained 7-11 kg and the remaining five (20%) had a GWG of 12-20 kg. GWG was significantly lower among women with BMI >35, compared to women with BMI 30-35 ( $p < 0.01$ ). Antenatal assessment of fetal weight estimated ordinary growth. Oligohydramnios was observed in one case. All women delivered normal-sized babies with normal Apgar scores (8-10 at one minute). One baby was born with a cleft palate. Three women (12%) were delivered by emergency cesarean section and one had an instrumental delivery, while the other 21 (84%) were delivered vaginally without complications. Three women (12%) were diagnosed with mild hypertension and there were no cases of reduced glucose tolerance. Five women had a TSH > 2.0 and received thyroxin treatment; one had thyroid peroxidase (TPO) antibodies and continued treatment after delivery. There were no significant differences in triglycerides, cholesterol or the HDL/LDL ratio between women with GWG < 6 kg and those with > 6 kg, or between those with BMI  $30 \leq 35$  and those with BMI > 35. EPDS scores changed, from 4.6 ( $\pm 4$  SD) at Maternal Health Care Center registration early in pregnancy, to 4.2 ( $\pm 3.5$  SD) at 28 gestational weeks and to 5.6 ( $\pm 4.7$  SD) after delivery ( $p=0.5$  and  $0.9$ , respectively, in comparison to baseline). Women with a GWG < 6 kg scored lower ( $4.0 \pm 2.6$  SD) than those who gained > 6 kg, but this difference was not significant ( $5.3 \pm 5.2$  SD;  $p = 0.8$ ). The women were also asked to send in a questioner anonymously. 17 of the women answered and they all wrote that they would recommend the project to a friend, 16 patients scored how pleased they were with the project within the range of 9-10 to a 10 grade scale, one patient scored 5.5.

**Table 3.** Descriptive statistics at study entry.

	Entire study group	BMI 30-35	BMI > 35
	n = 25	n = 11	n = 14
Age (years) <sup>a</sup>	31.7 $\pm$ 3.2	32.2 $\pm$ 3.6	31.2 $\pm$ 2.9
BMI <sup>a</sup>	35.4 $\pm$ 4.4	33.4 $\pm$ 1.6	39.7 $\pm$ 4.2
Weight at admittance (kg) <sup>a</sup>	99.8 $\pm$ 15.0	91.5 $\pm$ 9.5	110.1 $\pm$ 14.0
Length (cm) <sup>a</sup>	164.8 $\pm$ 5.4	163.4 $\pm$ 5.7	166.3 $\pm$ 4.5
Parity <sup>b</sup>	1 (0-3)	1 (0-2)	1 (0-3)
Cesarean section (n)	3	1	2
Vaginal deliveries (n)	9	2	7

<sup>a</sup>Mean  $\pm$  SD. <sup>b</sup>Median, range.

**Table 4.** *Clinical outcomes.*

	Entire study	BMI 30-35	BMI > 35	P-value <sup>a</sup>
	group			
	n = 25	n = 11	n = 14	
Gestational weeks <sup>b</sup>	40 (35-41)	39 (35-41)	40 (37-41)	0.04
Pregnancy maternal weight gain <sup>b</sup>	6.9 ± 6.4	8.5 ± 5.3	5.7 ± 7.0	0.001
Fetal ultrasound <sup>b,d</sup>				
Fetal growth week 32	2.6 ± 7.8	1.4 ± 5.3	3.6 ± 9.5	0.8
Fetal growth week 40	5.6 ± 14.4	-3.7 ± 11.4	9.6 ± 14.4	0.2
Oligohydramnios	1	1	0	0.9
Birth weight (g) <sup>b</sup>	3,484 ± 453	3,305 ± 328	3,611 ± 496 0.1	0.1
Preterm delivery <sup>c</sup>	1	1	0	0.2
Mode of delivery <sup>c</sup>				
Vaginal birth (%)	22	8	14	0.04
Emergency cesarean section (%)	3	3	0	0.04
Elective cesarean section (%)	0	0	0	-
Pregnancy induced complications <sup>c</sup>				
Hypertension	3	1	1	0.9
Symphyseolysis	2	1	1	0.9
Preeclampsia	0	0	0	-
Hepatositis	0	0	0	-

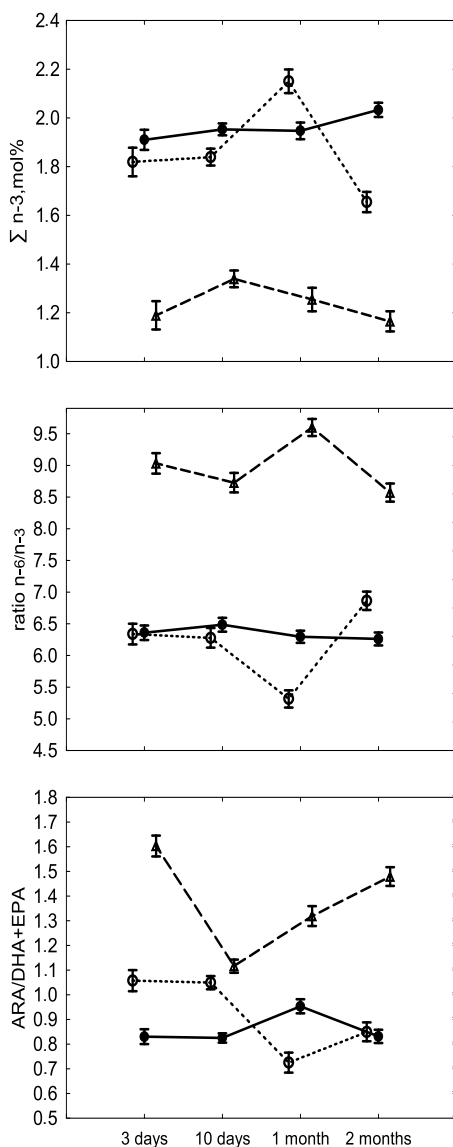
<sup>a</sup>*P-value for comparison between women with BMI 30-35 and women with BMI > 35 using <sup>b</sup>Wilcoxon matched pairs test or <sup>c</sup>Fisher's exact test.*

<sup>d</sup>*Fetal ultrasound presented as % deviation from the normal distribution curve.*

## 5. 2. Paper II

### 5. 2. 1. Mothers

Maternal characteristics are presented in Table 5. The obese mothers had a lower level of education and a higher rate of smoking before pregnancy. None had diabetes mellitus or had developed gestational diabetes. Nine patients in the intervention group and three in the normal-weight group were successfully treated for subclinical hypothyroidism during pregnancy; none of them had thyroid antibodies. Cesarean section was more common in the obese group (n=11) and the intervention group (n=6) than in the normal-weight group (n=3). The obese group ate less fish and seafood than the other groups (p<0.05 for each). Seven obese women, but only two in the normal-weight group and none in the intervention group, reported fish sticks as the main source of fish intake. There was no difference between the groups when it came to fats used for spread or cooking (data not shown). GWG was calculated as increase from pre-pregnancy weight to weight at 36 weeks, and was higher in the normal-weight group than among the obese women. It was not possible to calculate GWG for seven of the obese women, since they declined to be weighed during late pregnancy, suggesting that the GWG in this group was underestimated. The aim of GWG not exceeding 6 kg was almost reached in the intervention group (Table 5).



**Figure 8.** Molar percentage of total *n*-3 FA (upper part), the *n*-6/*n*-3 ratio (central part) and the ARA / DHA+EPA ratio (lower part) in consecutive breast milk samples from mothers in the normal-weight group (closed circles; *n*=17); obese group (triangles; *n*=17) and intervention group (open circles; *n*=10). Only milk from mothers who provided three or more milk samples are included in the figure.

### 5. 2. 2. Neonatal period and growth

Data on the infants are shown in Table 6. Birth weight, birth length, head circumference and ponderal index ( $\text{kg}/\text{m}^3$ ) did not differ between groups. One baby in each group had a birth weight of  $\geq 4.5$  kg, and one baby in the intervention group and four in the obese group were LGA. One baby in the obese group, but none in the normal-weight or intervention groups, was SGA. There were no differences in immediate neonatal outcome in the groups; two infants in the obese group were observed for three days in the neonatal ward, and one baby in the normal-weight group was jaundiced and required short-term daylight therapy. The duration of breastfeeding was similar in the three groups (Table 6), and formula was only occasionally given to some infants during the first days of life. Three women in the normal-weight group, two in the obese group and two in the intervention group breastfed for less than one month. There was no difference in infant weight, length or BMI at 12 months of age and no correlation between BMI at 12 months and duration of breastfeeding, paternal or maternal BMI, FA pattern in breast milk or early plasma phospholipids.

### 5. 2. 3. Plasma phospholipid fatty acid pattern in the infants

There were minor differences between saturated (SFA) and monounsaturated (MUFA) FA levels between groups; SFA were highest and MUFA were lowest in the normal-weight group (Table 7). The plasma concentrations of LA were higher in babies in the intervention group than in the normal-weight and obese groups ( $p < 0.01$  for both differences). Total *n*-3 FA, including EPA and  $\alpha$ -linoleic acid (18:3 *n*-3, LNA), were lowest in the obese group. All ratios between *n*-6 FA and *n*-3 FA were highest in the obese group, with smaller but significant differences between the normal-weight and interven-

**Table 5.** Characteristics of the mothers, group C (BMI < 25 kg/m<sup>2</sup>), Group O (BMI > 30 kg/m<sup>2</sup>), group I (BMI > 30 kg/m<sup>2</sup>) with intervention, see text. Paternal BMI is also given.

	BMI < 25 kg/m <sup>2</sup>	BMI > 30 kg/m <sup>2</sup>	BMI > 30 kg/m <sup>2</sup>	P-value
	Normal weight	No intervention	Intervention	
Age, years, mean ±SD	32.0±4.1	30.5±5.7	32.1±3.7	
Pre-pregnancy BMI, mean±SD	22±1.8	35±3.8	36±5.0	b,e
Weight gain in pregnancy to week 36, kg, mean±SD	13.2±3.8	9.5±5.8	6.6±3.3	b,d
Nullipara, %	61	44	41	
Smoking, n				
Until pregnancy	2	12	1	b,e
During pregnancy	1	3	0	
Education, n				
Elementary school	1	4	2	
University	6	0	5	
Intake of seafood, n				
None	6	21	2	
> 2 times/month	26	15	20	a,c
≤ 2 times/week				
> 2 times/week	9	5	7	
Intake of Omega-3 capsules, n	4	5	2	
Paternal BMI, mean±SD	24±0.4	26±0.4	27±0.4	

a  $p < 0.05$  between C and O groups. b  $p < 0.01$  between C and O groups. c  $p < 0.05$  between O and I groups. d  $p < 0.05$  between C and I groups. e  $p < 0.01$  between C and I groups.

**Table 6.** Infant characteristics including duration of breast feeding. Infants are grouped in relation to maternal BMI. No significant differences between the groups. Mean ±SD

	BMI < 25 kg/m <sup>2</sup>	BMI > 30 kg/m <sup>2</sup>	BMI > 30 kg/m <sup>2</sup>
	Normal weight	No intervention	Intervention
n	41	41	29
Gestational age (weeks)	39.6 ±1.2	38.8 ±1.6	39.5 ±1.6
Birth weight (g)	3490 ±424	3605 ±494	3525 ±465
Birth length (cm)	49.7 ±1.4	49.4 ±1.7	49.5 ±2.0
Head circumference (cm)	35.1 ±1.5	34.8 ±1.6	34.9 ±1.1
Ponderal index at birth (kg/m <sup>3</sup> )	2.9 ±0.2	2.8 ±0.2	2.9 ±0.2
Weight / gestational age > 2 SD (n)	0	4	1
Weight/length > 2 SD (n)	1	7	5
Breast feeding, months	4.1 ±1.9	4 ±0.6	3.9 ±1.9
Any formula fed at day 1-3 (n)	6	11	8
BMI at 12 months (kg/m <sup>2</sup> )	17.6 ±0.8	17.6 ±0.8	17.0 ±1.6

**Table 7.** Major fatty acid pattern in babies' plasma phospholipids at three days after birth. Infants are grouped according to maternal BMI. (Mean  $\pm$  SEM in mol %).

	BMI < 25 kg/m <sup>2</sup>	BMI > 30 kg/m <sup>2</sup>	BMI > 30 kg/m <sup>2</sup>
	Normal weight	No intervention	Intervention
	n = 21	n = 27	n = 11
	Mean + SEM	Mean + SEM	Mean + SEM
$\Sigma$ SFA	54.26 $\pm$ 0.03##	53.84 $\pm$ 0.03	53.20 $\pm$ 0.07**
- 14:0	0.27 $\pm$ 0.01##	0.23 $\pm$ 0.01	0.30 $\pm$ 0.01*
-16:0	36.17 $\pm$ 0.23	36.13 $\pm$ 0.23	35.52 $\pm$ 0.22
-18:0	15.05 $\pm$ 0.14	14.91 $\pm$ 0.21	15.08 $\pm$ 0.14
$\Sigma$ MUFA	13.09 $\pm$ 0.02##	13.37 $\pm$ 0.03	13.30 $\pm$ 0.04
-18:1n9	10.06 $\pm$ 0.02	10.42 $\pm$ 0.02	10.37 $\pm$ 0.03
$\Sigma$ PUFA	32.66 $\pm$ 0.03	32.93 $\pm$ 0.03	33.63 $\pm$ 0.07**§§
-20:3n9	0.26 $\pm$ 0.02	0.29 $\pm$ 0.03	0.18 $\pm$ 0.03*
$\Sigma$ n6	26.52 $\pm$ 0.04##	27.42 $\pm$ 0.04	27.70 $\pm$ 0.07*§§
-18:2n6 (LA)	8.37 $\pm$ 0.07	8.90 $\pm$ 0.06	10.82 $\pm$ 0.14**§§
-20:3n6	2.52 $\pm$ 0.09	2.58 $\pm$ 0.09	2.39 $\pm$ 0.08
-20:4n6 (ARA)	15.37 $\pm$ 0.05##	15.73 $\pm$ 0.03	14.22 $\pm$ 0.01**
$\Sigma$ n3	5.88 $\pm$ 0.02##	5.22 $\pm$ 0.02	5.75 $\pm$ 0.02**
-18:3n3 (LNA)	0.04 $\pm$ 0.00	0.03 $\pm$ 0.01	0.08 $\pm$ 0.00**
-20:5n3 (EPA)	0.68 $\pm$ 0.05##	0.46 $\pm$ 0.05	0.71 $\pm$ 0.04**
-22:6n3 (DHA)	5.15 $\pm$ 0.02##	4.72 $\pm$ 0.02	4.96 $\pm$ 0.02
Ratios			
ARA/DHA+EPA	2.72 $\pm$ 0.01##	3.11 $\pm$ 0.01	2.60 $\pm$ 0.02**
LA/LNA	264.84 $\pm$ 2.60##	308.01 $\pm$ 1.60	251.28 $\pm$ 2.90**§§
ARA/EPA	26.45 $\pm$ 0.21##	39.14 $\pm$ 0.27	27.30 $\pm$ 0.44**
n6/n3	4.71 $\pm$ 0.02##	5.52 $\pm$ 0.03	5.02 $\pm$ 0.03**§§

SFA, saturated fatty acids; MUFA, mono-unsaturated fatty acids; PUFA, poly-unsaturated fatty acids; n6, omega-6 fatty acids; n3, omega-3 fatty acids; ARA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosa-pentaenoic acid; LA, linoleic acid; LNA, Alfa-linoleic acid. Significant differences between normal weight group and obese group are expressed as #  $p < 0.05$ , ##  $p < 0.01$ . Differences between intervention and obese groups are expressed as \*  $p < 0.05$ , \*\*  $p < 0.01$ . Differences between intervention and normal weight group are expressed as §  $p < 0.05$ , §§  $p < 0.01$ .

tion groups (Table 7). Levels of significance are shown, excluding smokers, although smoking did not influence the significance of the differences between groups.

#### 5. 2. 4. Fatty acid pattern in breast milk

The number of mothers providing milk samples was 26/41 in the normal-weight group, 25/41 in the obese group and 25/29 in the intervention group. Three and four milk samples were provided by 17 mothers in the normal-weight and obese groups, respectively, and by 10 in the intervention group. Only results from those mothers providing three samples or more are included in Fig. 8. On day three, SFA concentrations were highest in the milk from the normal-weight group, but levels were highest in the obese group in subsequent samples ( $p < 0.01$ ). MUFA levels were highest in the obese group on day three, but not later on. The concentrations of n-6 FA were highest in the nor-

**Table 8.** Major fatty acid pattern in breast milk at three and 10 days and one and two months after delivery. Mean (SEM)

Time after partus n	BMI < 25 kg/m <sup>2</sup>										BMI > 30 kg/m <sup>2</sup> , no intervention,										BMI > 30 kg/m <sup>2</sup> , intervention group										DfF																																																																																																																																																																																																																								
	3 d					10 d					1 m					2 m					C/O					3 d						10 d					1 m					2 m					C/I																																																																																																																																																																																																								
	16	14	10 d	1 m	2 m	17	17	16	16	17	17	17	17	17	17	17	14	14	14	14	O/I	2 m	2 m	2 m	2 m	8	8	8	8	8		16	16	16	16	16	8	8	8	8	8																																																																																																																																																																																																														
Σ SFA	47.7 (0.13)a	45.5 (0.2)a	45.2 (0.13)a	44.8 (0.12)a	44.8 (0.12)a	45.5 (0.17)b	48.5 (0.25)b	47.5 (0.30)b	48.7 (0.18)b	**	45.7 (0.19)b	45.2 (0.22)a	45.0 (0.29)a	45.9 (0.02)c	7.85 (0.06)a	7.05 (0.09)a	6.92 (0.06)a	7.05 (0.05)a	7.78 (0.12)b	**	6.85 (0.12)b	8.10 (0.12)b	6.97 (0.14)a	7.17 (0.11)a	29.2 (0.09)a	25.7 (0.09)a	26.4 (0.08)a	25.6 (0.08)a	#	29.1 (0.01)a	25.9 (0.09)a	26.9 (0.16)a	26.5 (0.08)b	*	28.7 (0.06)b	24.5 (0.08)b	25.9 (0.03)b	24.7 (0.02)c	6.40 (0.25)a	6.61 (0.03)a	6.36 (0.18)a	6.44 (0.29)a	##	6.15 (0.27)b	5.9 (0.02)b	6.40 (0.20)a	6.80 (0.24)b	*	6.00 (0.39)b	6.09 (0.04)b	6.67 (0.22)	6.45 (0.20)a	##	39.1 (0.09)a	40.1 (0.11)a	41.3 (0.11)a	41.4 (0.11)a	43.0 (0.11)b	38.7 (0.16)b	39.2 (0.12)b	40.2 (0.12)b	**	41.1 (0.14c	41.6 (0.13)c	40.8 (0.16)a	39.8 (0.11)b	##	35.7 (0.02)a	37.3 (0.09)a	37.3 (0.47)a	38.0 (0.76)a	##	39.0 (0.92)b	36.3 (0.10)b	37.0 (0.57)a	38.0 (0.59)a	**	38.5 (1.3)b	40.0 (0.08)c	37.6 (0.49)a	38.0 (0.59)a	##	0.16 (0.01)a	0.08 (0.00)a	0.04 (0.01)a	0.04 (0.01)a	0.18 (0.01)a	0.07 (0.01)a	0.07 (0.01)a	0.07 (0.01)a	0.03 (0.01)a	0.03 (0.01)a	0.13 (0.01)a	0.15 (0.03)b	0.04 (0.01)a	0.03 (0.01)a	##	13.2 (0.12)a	14.4 (0.11)a	13.5 (0.07)a	13.7 (0.07)a	##	11.5 (0.09)b	12.8 (0.11)b	13.3 (0.19)a	11.2 (0.09)b	**	12.2 (0.10)c	13.1 (0.05b)	13.2 (0.12)a	13.4 (0.10)a	##	0.01 (0.00)a	0.20 (0.00)a	0.01 (0.01)a	0	(0.01)a	0.02 (0.01)a	0.02 (0.00)a	0.02 (0.00)a	0.02 (0.00)a	0.02 (0.00)a	0.02 (0.00)a	0.02 (0.00)a	0.02 (0.00)a	0.02 (0.00)a	##	11.3 (0.11)a	12.4 (0.09)a	11.6 (0.06)a	11.8 (0.07)a	##	10.3 (0.07)b	11.5 (0.12)b	12.0 (0.18)b	9.96 (0.09)b	*	10.6 (0.09)b	11.3 (0.05)b	11.2 (0.10)a	11.7 (0.09)a	##	9.99 (0.11)a	11.4 (0.09)a	10.7 (0.06)a	11.0 (0.07)a	##	8.93 (0.08)b	10.3 (0.11)b	11.1 (0.17)a	9.11 (0.08)b	**	9.31 (0.08)b	10.4 (0.05)b	10.3 (0.09)a	10.9 (0.08)a	##	0.39 (0.01)a	0.29 (0.00)a	0.28 (0.01)a	0.22 (0.02)a	##	0.48 (0.47)b	0.33 (0.00)b	0.32 (0.01)a	0.24 (0.02)a	**	0.37 (0.03)a	0.40 (0.01)c	0.27 (0.01)a	0.28 (0.02)a	§	0.49 (0.01)a	0.43 (0.01)a	0.33 (0.02)a	0.32 (0.02)a	##	0.53 (0.01)b	0.46 (0.01)a	0.37 (0.02)b	0.33 (0.02)b	**	0.48 (0.01)a	0.38 (0.01)c	0.39 (0.01)b	0.30 (0.01)a	##	1.91 (0.03)a	1.95 (0.02)a	1.95 (0.02)a	2.03 (0.02)a	##	1.19 (0.02)b	1.34 (0.01)b	1.25 (0.01)b	1.23 (0.02)b	**	1.56 (0.01)c	1.77 (0.01)c	1.98 (0.02)a	1.69 (0.01)c	§	1.25 (0.02)a	1.39 (0.02)a	1.47 (0.02)a	1.49 (0.01)a	##	0.85 (0.02)b	0.89 (0.01)b	0.96 (0.01)b	0.93 (0.01)b	**	1.17 (0.02)a	1.45 (0.01)a	1.37 (0.01)c	1.36 (0.01)c	§	0.1 (0.01)a	0.11 (0.00)a	0.11 (0.01)a	0.13 (0.01)a	##	0.03 (0.00)b	0.07 (0.00)b	0.06 (0.02)b	0.06 (0.00)b	**	0.06 (0.00)a	0.05 (0.00)b	0.13 (0.01)a	0.08 (0.01)c	##	0.56 (0.01)a	0.46 (0.01)a	0.37 (0.01)a	0.41 (0.01)a	##	0.30 (0.00)b	0.38 (0.00)b	0.24 (0.01)b	0.22 (0.01)b	**	0.50 (0.02)c	0.36 (0.01)b	0.59 (0.01)c	0.3 (0.01)c	##

Letters a, b and c denote different ( $p < 0.05$ ) levels of fatty acids at specific time. Significant differences between normal weight group and obese group are expressed as #  $p < 0.05$ , ##  $p < 0.01$ . Differences between intervention and obese groups are expressed as \*  $p < 0.05$ , \*\*  $p < 0.01$ . Differences between intervention and normal weight group are expressed as §  $p < 0.05$ , §§  $p < 0.01$ .

O = Obese; I = Intervention; C = Normal weight mothers



mal-weight group on day three and n-3 FA levels were lowest in the obese group at repeated measurements ( $p < 0.01$ ). This was also true for LNA, EPA and DHA, the latter explained by the low fish intake in the obese group ( $p < 0.01$ ) (Table 8). The n-6/n-3 ratio was highest in the obese group, compared to the two other groups ( $p < 0.01$ ). Furthermore, the ARA/EPA + DHA ratio was significantly higher in the obese group than in the normal-weight group and intervention groups in repeated milk samples ( $p < 0.01$ ) (Fig. 8).

### 5. 3. Paper III

Almost 8% of the study population had a BMI  $> 30$  kg/m<sup>2</sup> and were thus considered to be obese. The distribution according to BMI class is presented in Table 9. The mean age of the study population was 27 years, with only minor differences between the BMI classes. The prevalence of the various perineal lacerations in relation to BMI category

**Table 9.** Distribution of individuals over BMI group

BMI class	Frequency (n)	Percent	Age mean(SD)
<25	148826	70.64	27.1 (4.8)
25-<30	45055	21.39	27.4 (4.9)
30-<35	12352	5.86	27.2 (5.0)
>35	4445	2.11	27.3 (5.0)

is presented in Table 10. In total, 8 958 (4.25%) cases of anal sphincter lacerations, defined as grade III-IV perineal lacerations (see Introduction), occurred. The respective proportions of women with anal sphincter lacerations were 4.25% among those with BMI  $< 25$  kg/m<sup>2</sup>, 4.3% among those with BMI 25 to  $< 30$  kg/m<sup>2</sup>, 4.03% among those with BMI 30 to  $< 35$  kg/m<sup>2</sup> and 3.71% among those with BMI  $> 35$  kg/m<sup>2</sup>. There were very few anal sphincter lacerations involving the rectal mucosa (0.17%). With regard to grade I and II lacerations, there was an almost linear increase in the occurrence of injuries related to increasing BMI. In contrast, the occurrence of anal sphincter lacerations showed an overall inverse correlation with increasing BMI. Univariate logistic regression analyses identified increasing BMI, age, instrumental delivery, birth weight and head circumference as risk factors for both grade I-II and grade III-IV lacerations. Maternal diabetes was not found to have a significant effect on the risk of lacerations, regardless of severity, and was therefore not included in the final multivariate model.

When the independent variables (age, instrumental delivery, fetal weight and head circumference) were included in a multivariate setting (Table 11), increasing BMI showed a nearly dose-response protective effect against grade III-IV lacerations. At the same time, increasing BMI was associated with a dose-response type of increase in the risk of grade I-II lacerations. The greatest risk of anal sphincter laceration was observed among women undergoing an instrumental delivery (OR, 2.92; 95% CI, 2.78-3.06) which, at the same time, decreased the risk of grade I-II lacerations (OR, 0.77; 95% CI, 0.75-0.79). In our study, we found that 15.3% of all women underwent an instrumental delivery, the occurrence of which was nearly identical throughout the BMI classes: BMI  $< 25$  kg/m<sup>2</sup>, 15.1%; BMI 25 to  $< 30$  kg/m<sup>2</sup>, 16.4%; BMI 30 to  $< 35$  kg/m<sup>2</sup>, 14.3%; BMI  $> 35$  kg/m<sup>2</sup>, 15.2%. The significant effect of head circumference which, in the univariate analysis, was associated with both grade I-II (OR, 1.08; 95% CI, 1.07-1.09) and grade III-IV (OR, 1.20; 95% CI, 1.19-1.22) lacerations, was at-

**Table 10.** Delivery damage by BMI. Percentage of obstetric ruptures in different BMI groups

Delivery injury	Percentage	< 25 (N=148826)	25 - < 30 (N=45055)	30 - < 35 (N=12352)	35 - (N=4445)	Total (N=210678)
Ruptures, clitoris (n=65 554)	p (95%CI)	31.7% (31.5%-32.0%)	30.1% (29.7%-30.6%)	28.7% (27.9%-29.5%)	27.6% (26.3%-28.9%)	31.1% (30.9%-31.3%)
Ruptures, vagina (n=116 133)	p (95%CI)	53.5% (53.2%-53.7%)	58.3% (57.8%-58.8%)	60.5% (59.7%-61.4%)	63.9% (62.5%-65.3%)	55.1% (54.9%-55.3%)
Ruptures, perineum (n=79 659)	p (95%CI)	37.0% (36.8%-37.3%)	40.0% (39.5%-40.4%)	39.5% (38.7%-40.4%)	38.0% (36.5%-39.4%)	37.8% (37.6%-38.0%)
Ruptures, sphincter (n=8 884)	p (95%CI)	4.21% (4.11%-4.31%)	4.35% (4.17%-4.55%)	4.00% (3.66%-4.36%)	3.64% (3.12%-4.25%)	4.22% (4.13%-4.30%)
Ruptures, rectum (n=354)	p (95%CI)	0.16% (0.14%-0.18%)	0.19% (0.16%-0.24%)	0.17% (0.11%-0.26%)	0.18% (0.08%-0.37%)	0.17% (0.15%-0.19%)
Ruptures, cervix (n=437)	p (95%CI)	0.21% (0.19%-0.23%)	0.22% (0.18%-0.26%)	0.19% (0.12%-0.28%)	0.18% (0.08%-0.37%)	0.21% (0.19%-0.23%)
Grade I & II ruptures (n=144 513)	p (95%CI)	67.5% (67.3%-67.7%)	70.8% (70.3%-71.2%)	72.0% (71.2%-72.8%)	73.5% (72.2%-74.8%)	68.6% (68.4%-68.8%)
Grade III & IV ruptures (n=8 958)	p (95%CI)	4.25% (4.14%-4.35%)	4.38% (4.20%-4.58%)	4.03% (3.70%-4.40%)	3.71% (3.18%-4.32%)	4.25% (4.17%-4.34%)

Table 11. Univariate and multivariate logistic regression analyses for the association between body mass index (BMI) and perineal lacerations.

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
<b>Grade I-II obstetrical lacerations</b>						
BMI	1.03	1.03-1.03	<0.0001			
< 25	1.00			1		
25 ≤ 30	1.17	1.14-1.19	<0.0001	1.13	1.11-1.16	<0.0001
30 ≤ 35	1.24	1.19-1.29	<0.0001	1.23	1.11-1.16	<0.0001
> 35	1.34	1.25-1.43	<0.0001	1.32	1.23-1.41	<0.0001
Age (years)	1.07	1.07-1.08	<0.0001	1.07	1.07-1.08	<0.0001
Instrumental delivery (yes/no)	0.89	0.87-0.92	<0.0001	0.77	0.75-0.79	<0.0001
Fetal birth weight (g)	1.00	1.00-1.00	<0.0001	1.00	1.00-1.00	<0.0001
Head circumference (cm)	1.08	1.07-1.09	<0.0001	1.06	1.05-1.07	<0.0001
<b>Grade I-IV obstetrical lacerations</b>						
BMI	1.00	0.99-1.00	0.68			
< 25	1			1		
25 ≤ 30	1.03	0.98-1.09	0.25	0.89	0.85-0.95	<0.0001
30 ≤ 35	0.95	0.86-1.04	0.25	0.84	0.76-0.92	<0.0004
> 35	0.87	0.74-1.01	0.08	0.70	0.59-0.82	<0.0001
Age (years)	1.06	1.05-1.06	<0.0001	1.05	1.05-1.06	<0.0001
Instrumental delivery (yes/no)	3.42	1.05-1.06	<0.0001	2.92	2.78-3.06	<0.0001
Fetal birth weight (kg)	3.03	2.90-3.17	<0.0001	2.86	2.70-3.02	<0.0001
Head circumference (cm)	1.20	1.19-1.22	<0.0001	0.99	0.98-1.01	0.82

CI, confidence interval; OR, odds ratio.

Birthweight and head circumference were measured immediately after birth.

tenuated to a non-significant level in the multivariate analysis (Table 11). Increasing birth weight increased the risk of anal sphincter lacerations, and a dichotomized birth weight of 4.5 kg or more (n=4115) was associated with a more than doubled risk, compared to a birth weight of <4.5 kg (OR 2.40; 95% CI, 2.17-2.66).

#### 5. 4. Paper IV

The study population prevalence of overweight (BMI 25 - 29.9) was 25.4%, of obesity (BMI 30 - 34.9) 7.6% and of morbid obesity 3.2% (BMI ≥ 35). Maternal characteristics according to BMI class are presented in Table 12. There were small but statistically significant increases in the number of visits to both obstetrician and midwife with increasing BMI category, compared to normal-weight women (Table 13). The number of women referred to an Aurora clinic (see above) increased with increasing BMI and was significantly more common, compared to 3.6% in normal-weight women (p < 0.001 for all comparisons) (Table 13). The number of sick-listed women during pregnancy

**Table 12.** Background data on study population.

BMI intervals	20 < 25 (n=68,884)	25 < 30 (n=27,461)	30 < 35 (n=8,269)	35 - (n=3,489)	Total (n=108,103)
Distribution	63.7%	25.4%	7.6%	3.2%	100.0%
Age, mean (SD)	28.3 (4.8)	28.4 (5.1)	28.1 (5.2) ***	28.2 (5.2) ***	28.3 (4.9)
Smoking three months before pregnancy n (%)	12,891 (18.7)	6,400 (23.3) **	2,297 (27.8) ***	1,056 (30.3) ****	18,547 (20.6)
Smoking at admission to maternal health care center n (%)	4,196 (6.0)	2,217 (8.1) **	892 (10.8) ***	463 (13.3) ****	7,688 (7.1)
Smoking, during gestational week 30 - 32 n (%)	2,710 (3.9)	1,513 (5.5) **	651 (7.9) ***	348 (10.0) ****	5,222 (4.8)

Legends: \* denotes significant difference between BMI 20-<25 and other groups. † between 25-<30 and † between 30-<35. Single legends denotes significance at level < 0.05, double legends denotes significance at the < 0.01 level.

**Table 13.** Health care consumption during pregnancy

<b>BMI</b>	<b>20 &lt; 25</b>	<b>25 &lt; 30</b>	<b>30 &lt; 35</b>	<b>35 -</b>	<b>Total</b>
n	68,884	27,461	8,296	3,489	108,103
n (year 2003, 2006 - 2008)	42,979	17,155	5,234	2,245	67,613
Mean no. of hospital admission (SD)	0.1 (0.4)	0.1 (0.5) **	0.2 (0.5) ***¶	0.2 (0.6) ***¶††	0.1 (0.5)
Mean no. of days admitted to hospital (SD)	0.5 (2.7)	0.5 (2.8)	0.7 (3.2) ***¶	0.9 (3.3) ***¶†	0.5 (2.8)
Mean no. of visits to physician at maternal health care center (SD). (Year 2003, 2006-2008)	3.1 (1.6)	3.3 (1.8) **	3.4 (1.9) ***¶	3.6 (2.2) ***¶††	3.2 (1.7)
Mean no. of visits to midwife at maternal health care center (SD)	10.9 (2.3)	11.1 (2.5) **	11.4 (2.8) ***¶	11.7 (3.1) ***¶††	11.0 (2.4)
No. of women sick-listed during pregnancy (%). (Year 2003, 2006-2008)	9,003 (22.4%)	4,264 (26.6) **	1,475 (30.1) ***¶	720 (34.6%) ***¶†	15,462 (24.5)
Referred to Aurora clinic n (%)	3,073 (4.5%)	1,920 (4.7)	426 (5.2) *	232 (6.6) ***¶††	5,021 (4.6)

*Legends: \* denotes significant difference between BMI 20 < 25 and other groups. ¶ between 25 < 30 and † between 30 < 35. Single legends denotes significance at level < 0.05, double legends denotes significance at the < 0.01 level.*

*An Aurora clinic is a cross-disciplinary unit for treatment of moderate to severe fear of childbirth.*

**Table 14.** Most common diagnoses for inpatient care hospital admissions in the entire study population.

BMI	20 - <25		25 - <30		30 - <35		35-		Total	
	n	%	n	%	n	%	n	%	n	%
Abdominal pain	459	0.67	198	0.72	77	0.93*	25	0.72	759	0.70
Contractions without cervical ripening before pregnancy week 37	457	0.66	147	0.54	41	0.50	22	0.63	667	0.62
Vaginal bleeding	383	0.56	149	0.54	41	0.50	18	0.52	591	0.55
Threatening premature labor before pregnancy week 37	433	0.63	109	0.40**	27	0.33***	15	0.43	584	0.54
Hyperemesis gravidarum	372	0.54	142	0.52	41	0.50	21	0.60	576	0.53
Preeclampsia easy to moderate	203	0.29	185	0.67**	100	1.21***††	67	1.92***†††	555	0.51
Care due to breech position	231	0.34	91	0.33	27	0.33	13	0.37	362	0.33
Pregnancy induced hypertension	110	0.16	92	0.34**	50	0.60***	40	1.15***†††	292	0.27
Abdominal pain, not pregnancy induced	157	0.23	65	0.24	25	0.30	9	0.26	256	0.24
Other diagnoses that complicates pregnancy	136	0.20	65	0.24	22	0.27	12	0.34	235	0.22
Other specific pregnancy conditions	141	0.20	54	0.20	27	0.33	12	0.34	234	0.22
Pyelonephritis	160	0.23	53	0.19	15	0.18	5	0.14	233	0.22
Gestational diabetes	20	0.03	16	0.06	16	0.19***	15	0.43***	67	0.06

Legends: \* denotes significant difference between BMI 20-<25 and other groups. † between 25-<30 and † between 30-<35. Single legends denotes significance at level <0.05, double legends denotes significance at the <0.01 level.

**Table 15. Most common diagnoses for inpatient care hospital admissions in non-smokers (smokers excluded).**

BMI	20 -< 25		25 -< 30		30 -< 35		35 -		Total	
	n	%	n	%	n	%	n	%	n	%
Abdominal pain	414	0.65	175	0.71	63	0.87	18	0.60	670	0.68
Contractions without cervical ripening before pregnancy week 37	394	0.62	133	0.54	35	0.48	19	0.64	581	0.59
Hyperemesis gravidarum	359	0.56	137	0.55	36	0.50	21	0.70	553	0.5
Vaginal bleeding	342	0.54	132	0.53	32	0.44	17	0.57	523	0.53
Threatening premature labor (< pregnancy week 37)	380	0.60	93	0.37**	24	0.33*	9	0.30	506	0.51
Preeclampsia easy to moderate	191	0.30	164	0.66**	88	1.22***†	56	1.88***†	499	0.51
Care due to breech position	222	0.35	84	0.34	26	0.36	12	0.40	344	0.35
Pregnancy induced hypertension	102	0.16	86	0.35**	47	0.65***†	34	1.14***†	269	0.27
Other diagnoses that complicates pregnancy	138	0.22	55	0.22	21	0.29†	4	0.13	218	0.22
Other specific pregnancy conditions	128	0.20	47	0.19	22	0.30	10	0.34	207	0.21
Pyelonephritis	140	0.22	44	0.18	12	0.17	3	0.10	199	0.20
Abdominal pain, not pregnancy induced	97	0.15	37	0.15	22	0.30	5	0.17	161	0.16
Gestational diabetes	18	0.03	14	0.06	15	0.21***†	14	0.47***†	61	0.06

**Legends:** \* denotes significant difference between BMI 20-<25 and other groups. † between 25-<30 and † between 30-<35. Single legends denotes significance at level <0.05, double legends denotes significance at the <0.01 level.

increased significantly with increasing BMI. Obese women were significantly more often admitted to hospital during pregnancy and had longer average in-hospital stays, compared to normal-weight and overweight women (Table 14). Stratifying for smoking did not change any result in Table 15. In-patient care during pregnancy and related diagnoses, in relation to BMI category, are shown in Table 14. The five most common diagnoses for in-patient care during pregnancy were pregnancy-induced abdominal pain (0.70%); premature contractions without cervical ripening (0.62%); vaginal bleeding (0.55%); imminent premature labor (0.54%); and hyperemesis gravidarum (0.53%). However, none of these diagnoses showed a positive association with increasing BMI. On the contrary, being overweight and obese significantly reduced the occurrence of imminent premature labor ( $p < 0.001$  for both BMI categories), in comparison with normal-weight women.

The prevalence's of pregnancy-induced hypertension, preeclampsia and gestational diabetes increased significantly with increasing BMI, compared to normal-weight women ( $p < 0.001$  for all comparisons). Preeclampsia was more than six times as common, hypertension seven times as common, and gestational diabetes 14 times as common among obese as among normal-weight women ( $p < 0.001$  for all comparisons). Because tobacco smoking was nearly twice as common before and during pregnancy among obese women, compared to normal-weight women, (Table 12), we performed a complementary analysis of the causes of in-hospital care, from which smokers before and during pregnancy were excluded (Table 15). This analysis yielded essentially unaltered patterns in pregnancy-related morbidity as well as in the overall prevalence and proportions of the various diagnoses.



## 6. Discussion

### 6.1. Paper I

Maternal obesity during pregnancy is an established risk factor for a variety of adverse maternal and neonatal outcomes<sup>32</sup>. Almost 60% of the patients participating in our dietary and behavioral intervention program achieved the *á priori* goal of a GWG less than 6 kg. In this context, a weight increase of 6 kg essentially comprises the weight of the fetus, uterus, placenta and amniotic fluid, which means that not only did the majority of patients not gain any weight, but that some even lost weight during pregnancy. The reason that women with BMI > 35 were more successful in their weight control remains unknown but a higher level of motivation might be one explanation.

We find our main results encouraging, considering that the observed 6-kg GWG limit was accompanied by a low rate of complications related to pregnancy and delivery. The food and exercise diaries confirm that the women obtained sufficient nutrients. During pregnancy, obese women are at increased risk of gestational diabetes, hypertension and preeclampsia. In this study, there were two cases of hypertension and one case of preeclampsia, all mild forms not requiring treatment. Two of the women were being treated for hypertension before pregnancy. Furthermore, there were no cases of gestational diabetes and both HbA1c levels and OGTT results were in the normal range for all patients, even those who failed to achieve the GWG goal. This indicates that the dietary and physical changes involved in the program may have beneficial metabolic effects, although they do not necessarily result in optimal weight control.

The most common medical condition necessitating treatment among our patients was hypothyroidism, which also was relatively frequent before pregnancy. There is insufficient evidence to support population-based screening for subclinical hypothyroidism but it is regarded as appropriate in pregnant women and patients at high risk of thyroid dysfunction<sup>184</sup>. The prevalence of subclinical hypothyroidism in obese women is not fully known, but thyroid function, including within the reference range, has been associated with body weight<sup>185</sup> and blood pressure<sup>186</sup> in women. Increasing levels of TSH have also been associated with less favorable lipid concentrations<sup>187</sup>. Our findings of a high rate of hypothyroidism in obese women during pregnancy may have implications for pregnancy outcome, and postpartum maternal obesity, and warrants further investigation. In this study, the upper TSH limit was 2.0 mIE/L in the first trimester. However, there were two patients who had TSH levels above 2.5 mIE/L, the limit stipulated by the American Thyroid Association<sup>184</sup>.

Our weight limitation program was associated with satisfactory perinatal outcomes. There were no cases of IUGR or LGA. All infants had normal birth weights and were delivered at term with normal Apgar scores, except one case of preterm birth in week 35 (this woman had given birth in week 32 in a previous pregnancy). In summary, it seems that weight control, and even intentional weight loss, in obese pregnant women does not generate adverse fetal outcomes.

All patients in the program attempted spontaneous vaginal delivery and our cesarean section rate of 12% is considerably lower than that described by Burstein et al (nearly 33%)<sup>188</sup>. The lower cesarean rate in our patients should probably not be attributed to weight control per se, but rather to the secondary effects of the low rate of gestational complications commonly found among obese women. Also, most patients participating in the study were motivated and received regular support from the midwives in the program. This kind of individual and group support sessions may have contributed to the fact that none of our patients requested elective cesarean section.

During normal pregnancy, levels of plasma lipids, cholesterol and triglycerides increase during the second and third trimesters as a normal physiological response. Compared to non-pregnant levels, cholesterol may rise by 50%, whereas triglyceride levels may increase by as much as 400% in the third trimester<sup>189</sup>. However, very little is known about lipid metabolism in obese pregnant women. We found a lipid pattern in our group of obese pregnant women similar to that in non-obese women, with significant increases in cholesterol and triglyceride levels during the second and third trimesters. The LDL/HDL ratio did not change significantly during pregnancy and it remains to be determined whether increased HDL levels are desirable during pregnancy with regard to cardiovascular effects and the risks of hypertension and preeclampsia<sup>190</sup>.

Obese women are generally at increased risk of depression, compared to normal-weight women<sup>191</sup>. In our group of obese women, overall EPDS scores were stable throughout pregnancy. However, the patients who gained the most weight during pregnancy also scored the highest in the EPDS, showing that there may be an association, albeit non-significant ( $p = 0.8$ ), between depressive symptoms and weight increase among obese women. Although the cause-effect relationship needs to be disentangled, this association provides further ground for monitoring women with excessive weight gain during pregnancy more closely.

The lack of a control group is a drawback of our study; although our clinical data are affirmative, the efficacy of the proposed intervention program, compared to not offering any intervention at all, remains unproven. We also recognize that the relatively small population sample has implications for the statistical strength of our observations and may create limitations primarily involving detection of less common outcomes. The participants' meals and exercise were not evaluated in this study. In the retrospect we could have evaluated the food diary more closely, possibly used food questionnaires, and also for example pedometers, which might have provided additional information, about to which extent the women really changed their eating and exercise habits. The intervention program was demanding in terms of health care resource consumption, particularly concerning the time invested by involved staff. A highly dedicated staff of midwives and obstetricians may have contributed to the advantageous outcomes. This high level of commitment may not be available if the intervention program is undertaken in other settings. Our results may therefore not be generalizable to health care in all contexts until large randomized controlled studies are performed. However, we believe that the study is nonetheless important since it clinically corroborates previous epidemiological research suggesting beneficial effects of minimizing GWG in obese women<sup>161</sup>.

## 6. 2. Paper II

This observational study is one of the first reports showing differences in the concentration of FA in breast milk of obese mothers without diabetes, compared to mothers with normal BMI. Women with diabetes were excluded, since low concentrations of n-3 FA have been found in pregnant diabetics<sup>192</sup>. Only one similar study, from Argentina, has been published previously<sup>139</sup>. All participants in that study had very high concentrations of n-6 FA in breast milk, compared to those in our study, but the difference in the n-6/n-3 FA ratios between obese and normal-weight mothers was similar to that in our study. The significant differences in our study were especially marked for n-3 LCPU-FA, which resulted in a more than 40% higher n-6/n-3 ratio in breast milk from obese mothers, compared with breast milk from normal-weight mothers. In the intervention group, in which the obese pregnant women were given general dietary recommenda-

tions concerning healthy food and regular meals combined with moderately increased PA, the n-6/n-3 FA ratio was more similar to that in the normal-weight group. Similar differences were also found in the infants' early plasma phospholipids. Breast milk mainly reflects maternal diet <sup>133</sup>, but the differences in FA concentrations between obese mothers and mothers with normal body weight may be influenced by several factors besides diet, such as genetic differences in desaturases.

The metabolism of essential FA to LCPUFA is genetically regulated by the FA desaturase <sup>193</sup>, the expression of which was not analyzed in our study. Smoking is known to influence DHA status <sup>194</sup>, and maternal smoking might explain 50% of the decreased plasma n-3 FA concentrations in the obese mothers' neonates found in our study, but the difference remained significant after stratifying for smoking. A recent study showed that EPA could be increased by increased vegetable intake <sup>195</sup>. EPA, but not DHA, differed between the obese groups in our study, suggesting that there was no real difference between the groups regarding the intake of fish and seafood, supporting the theory that the higher EPA concentration might be attributable to vegetable intake. Higher concentrations of n-6 FA, in relation to the n-3 LCPUFA, are seen in Western food, especially in processed and fast food such as fish sticks <sup>196</sup>, and have been associated with future obesity in animal offspring <sup>197</sup>. One observation in our study was that the LA level was high both in the control and intervention groups, reflecting the general recommendations to increase vegetable oil and reduce saturated fat intake. The GWG was significantly lower in the intervention group than in the obese group. To what extent this was due to increased PA or to the dietary intervention cannot be evaluated using this study design and it is unknown how PA affects the FA pattern in breast milk. In animal studies, high n-3 FA concentrations during pregnancy were associated with smaller and fewer adipocytes in the offspring <sup>198</sup>. In this small study, we found no influence on anthropometry or ponderal index at birth or at one year of age in the babies, but the study might have been too small or the ponderal index might have been too crude a parameter to rule out a difference. The infants in our intervention group had the highest LA concentration in plasma on the third day of life, which could be explained by intake of LA-rich food around and after delivery. The obese and normal-weight mothers were included at random and not randomized and the intervention group was voluntarily included, which may have created a selection bias. The mothers were instructed to collect their milk samples directly after breastfeeding but since the FA content differs in breast milk during the day, and especially within feeding portions this might have affected results. It has not been shown that the baby's gender affects breast milk or plasma FA but it is a possibility. We therefore chose a control with the same gender as the case. Higher maternal n-3 polyunsaturated FA (PUFA) intake, higher cord plasma n-3 PUFA and a lower n-6/n-3 ratio were associated with a decreased rate of obesity in children at three years of age <sup>128</sup>. If our results are confirmed, they may also contribute to the understanding of why children of obese mothers have an increased risk of future obesity. A healthy lifestyle is important for both the mother and her baby during pregnancy and breastfeeding and lifestyle interventions may be as important for maternal as for infant health, but long-term follow up is necessary in order to evaluate the effects of such interventions.

### **6. 3. Paper III**

In this nationwide study, we found that maternal overweight and obesity decreased the risk of anal sphincter lacerations in a near-linear fashion. The inverse correlation between increasing BMI and the occurrence of anal sphincter lacerations was clear, but

the highly significant *p*-values were attributed to the very large sample size rather than to major effects. Because obese women are at increased risk of cesarean section as a result of obstetric complications, we restricted the study population to women with vaginal deliveries. The rates of grade III and IV perineal tears decreased with increasing BMI, whereas the opposite was true for grade I and II perineal tears. Previous studies have shown conflicting results regarding the influence of obesity on perineal lacerations<sup>199-201</sup>. We can only speculate as to the reasons for the seemingly protective effect of overweight and obesity on the pelvic floor found in this study. Estrogen and oxytocin receptor efficacy in uterine smooth muscle are modulated by cholesterol which, in turn, is elevated in the serum and myometrial membranes of obese women<sup>202</sup>. This may provide a certain degree of protection against oxytocin overstimulation during the second stage of labor, thereby decreasing the risk of excessive contractions and subsequent pelvic floor injury. On a similar note, uterine smooth muscle has been shown to contract with less force and frequency and to have less Ca<sup>2+</sup> flux in obese than in normal-weight women<sup>203</sup>. Choo et al reported that abdominal skin in morbidly obese women undergoing bariatric surgery exhibited greater tensile strength than skin from normal-weight patients undergoing cosmetic procedures<sup>204</sup>. It is uncertain whether these results can be generalized to pelvic floor connective tissue, but they do provide a possible mechanism through which obese women may contract less obstetric anal sphincter lacerations. The issue of whether maternal birth position influences the risk of anal sphincter laceration remains controversial. Gottvall et al showed that women giving birth in the lithotomy or squatting position had a higher incidence of grade III and IV perineal tears<sup>205</sup>. Overweight and obese women may not be prone to assuming these positions because it may restrict their lung function<sup>206</sup>.

The strengths of our study include the large study population, the nationwide design, the homogeneous classification of important confounders and outcome measures and the categorization of obesity according to international standards. The use of high-quality health care registers, based on standardized records throughout the country and non-selective registration, are major advantages with regard to data ascertainment. At the same time, we recognize that the classification of our primary outcome measure (prevalence of anal sphincter lacerations) has some limitations. First, the diagnosis was not verified by ultrasound, but relied exclusively on subjective clinical assessments. However, anorectal ultrasound is also an investigator-dependent method and diagnosis may thus vary between investigators with this method as well. Midwives' routines for examining perineal lacerations after delivery differ. In some departments, they routinely perform a rectal examination immediately after birth, whereas this is not the case in others. It is unknown whether sphincter lacerations are misclassified in obese women to a higher extent, which might affect results. There may also be regional variations with regard to vigilance and willingness to report the occurrence of anal sphincter lacerations. Consequently, local, regional and sometimes national under-reporting of anal sphincter injuries at delivery may be a limitation of register-based studies. Obese women are at increased risk of both anal and urinary incontinence<sup>207,208</sup>. If the diagnosis of grade III-IV perineal lacerations is considered a proxy for pelvic floor trauma, it may be postulated that the increased risk of stress urinary incontinence among obese and overweight women should be attributed to increased intra-abdominal pressure, resulting in urethral sphincter incompetence, rather than to pelvic floor injury at delivery. It is widely assumed that the first childbirth is associated with the greatest risk of pelvic floor trauma and that subsequent deliveries have less impact on obstetric pelvic floor sequelae<sup>209</sup>. This study was limited to primiparas and we can thus not say whether this is the case for overweight/obese women, although it is biologically plausible. In con-

currence with most previous studies, we found that instrumental delivery (vacuum extraction) significantly increased the risk of anal sphincter lacerations<sup>210</sup>. The near-threefold increase in risk attributed to instrumental delivery also remained after adjustment in multivariate analysis, exhibiting the strongest association with anal sphincter lacerations. Other factors, such as maternal age, diabetes and head circumference, showed no or limited associations with the occurrence of anal sphincter lacerations. Our analysis did not include information on fundal pressure during the final stages of labor (not registered) or episiotomy (not validated). Thus, we cannot account for the effects of these obstetric interventions which may, to some extent, have influenced our results. Macrosomia (birth weight > 4.5 kg) and increasing birth weight increased the risk of anal sphincter lacerations by the same magnitude as instrumental delivery, but did not change the overall inverse correlation between BMI and the risk of anal sphincter lacerations in the adjusted analysis. Our data concur with previous studies, suggesting that increasing birth weight and macrosomia enhance the risk of anal sphincter lacerations at delivery<sup>210,211</sup>, although the longer-term association with anal incontinence remains the subject of debate. In summary, this large-scale, nationwide study provides robust epidemiological evidence that overweight and obesity decrease the risk of obstetric anal sphincter lacerations among primiparas. As a consequence, decisions to perform elective cesarean section in obese women should not be based on concerns for increased risks of grade III or IV perineal lacerations.

#### **6. 4. Paper IV**

Obese women generally consume significantly more health care resources during pregnancy up until seven days prior to delivery, compared to normal-weight women. Obese women are more often admitted for in-patient care, had longer antenatal hospital stays and were more often sick-listed by an obstetrician during their pregnancy, compared to normal-weight women.

Numerous studies have documented the increased risks of adverse outcomes associated with obesity during pregnancy and delivery but few studies have reported on obesity-related consumption of health care services during pregnancy. Two studies from France and one from the US showed that the average costs of in-patient care were significantly higher for overweight and obese women than for normal-weight women. In these studies, most of the increased hospital stay durations among obese women were related to increased rates of cesarean delivery and obesity-related high-risk conditions at delivery<sup>212-214</sup>. This study, however, shows that obesity increases the rate of hospital admissions and length of stay prior to delivery as well. Obesity is thus a source of economic burden for antenatal health care, not only in an outpatient setting, but also involving relatively costly hospital care.

In Sweden, the social welfare system allows for sick-listing by a physician in cases of transient or permanent disability caused by disease, in which case the cost and loss of income are partly reimbursed by the state. In this study, one in three obese women was reported to have been sick-listed during pregnancy. This sick-listing increased in a near-linear fashion with increasing BMI. Sick-listing may have been due to either somatic or mental illness. Given that approximately one in ten pregnant women in Sweden are obese, it is safe to say that society's health care costs for sick-listing attributed to obesity are considerable. Since we had no access to detailed information on sick-listing diagnoses or duration, the extent of inability to work and the association with obesity requires further studies.

In this study, obese women visited both midwives and doctors at Maternal Health Care

Centers significantly more often than normal-weight women. Given that obesity during pregnancy is considered a risk, it is somewhat surprising that the difference was not even greater. Part of the increased number of visits to health care providers was related to somatic pregnancy complications. Obese women had higher rates of hypertension, preeclampsia and diabetes. Whether the greater number of visits to Maternal Health Care Centers was related to worry and anxiety among obese pregnant women is a matter of speculation, albeit indirectly supported by the significantly higher referral rate to Aurora units among obese women, compared to normal-weight women. Obese women are known to experience feelings of anxiety and worry related to the upcoming birth to a higher degree than normal-weight women <sup>215</sup>.

It is well-known that obesity is associated with an increased risk of pregnancy complications, including hypertension, preeclampsia, diabetes and LGA babies<sup>32</sup>. Our study convincingly shows that cardiovascular and metabolic pregnancy complications not only affect antenatal surveillance resources but also have direct implications for in-hospital care consumption during pregnancy. While this finding is of importance for allocating health care resources, it also highlights the need for prevention. It has been shown that rates of preeclampsia, cesarean section, instrumental delivery and LGA can be reduced in obese women with low GWG, compared to those with high GWG <sup>216</sup>. It has also been demonstrated that GWG among obese women can safely be restricted through soft interventional programs including dietary advice and PA, as well as supportive counseling and monitoring by dedicated staff <sup>173,217</sup>. Moreover, Stafne et al showed that the proportion of women sick-listed due to lumbar-pelvic pain was lower in a group of women undertaking aerobic and strengthening exercises during pregnancy, compared to women given standard antenatal care <sup>218</sup>. Another study showed that water aerobics prevented low back or pelvic pain and reduced sick-listing duration during pregnancy<sup>169</sup>. Back pain is more common in obese women than in normal-weight women and increases with age <sup>219</sup>, which may yield additional health care benefits from an interventional program for the former group.

Obesity is a well-established risk factor for premature childbirth and the risk increases with increasing BMI. Premature birth has major impact on the demand for specialized care and hospital resources for both infant and mother. In our study we found that, regardless of smoking, obese women were less likely to be hospitalized for imminent premature labor, i.e. childbirth before gestational week 37. There may be several reasons for this, including misdiagnosis of premature contractions which might be more difficult to diagnose correctly in obese women. It might also be that obese women are less inclined to seek delivery care or that they may perceive contractions differently than do normal-weight women.

Smoking before pregnancy, at the first antenatal visit, and three months into pregnancy increased significantly with increasing BMI. Among the morbidly obese, 10% admitted that they were still smoking in gestational week 30-32, despite mandatory counseling and information by midwives at Maternal Health Care Centers. Smoking does not appear to confound the association between the increased prevalence of hypertension, preeclampsia and gestational diabetes with increasing BMI. Because antenatal health care is free of charge for all Swedish residents, it is unlikely that a socio-economic selection bias would result in underestimation of the effects of smoking. Many studies have showed that smoking during pregnancy reduces the risk of preeclampsia and gestational hypertension by up to 50% <sup>220</sup>. However, the prevalence estimates of these cardiovascular diseases were practically unaffected by the exclusion of smoking women in a separate analysis. There might have been several reasons for this. First, it is possible that the mechanisms underlying the protective effects of smoking on the

risk of preeclampsia among obese women differs from the corresponding mechanisms among normal-weight women. Second, the number of smokers with preeclampsia and hypertension was low and exclusion of these women did thus not have a significant impact on the occurrence of disease. In this case, an even larger study population might have yielded a different result. Third, an unknown confounder may have interfered with the analysis. Further studies are necessary to determine how smoking affects the occurrence of cardiovascular disease during pregnancy among obese women.

The strengths of our study include a very large study population, the use of nationally uniform outcome measures and the availability of high-quality health care registers. Although much attention has been devoted to morbidity and complications surrounding delivery, this is one of the few studies focusing on antenatal health care consumption among obese women. The unique national registration number assigned to all Swedish residents, at birth or immigration, allowed for unambiguous record linkage across the registers, as well as minimizing selection and ascertainment bias. Among the limitations of our study, it should be noted that the Maternal Health Care Register does not have nationwide coverage and regional variations in demographics may have influenced the available data and thereby results. Nonetheless, the register includes both urban and rural populations and has a geographical spread throughout the country, the population of which is relatively homogeneous. Most of the data regarding pregnancy morbidity was derived from the validated IPR. Although efforts are underway, the Maternal Health Care Register has not yet been formally validated and data quality can therefore not be ascertained.

This study showed that increasing BMI also increased the consumption of health care resources during the antenatal period. Given the major health economic and medical consequences of pregnancy in overweight and obese women, all attempts should be made to prevent obesity in women of childbearing age and to encourage weight loss before pregnancy. In women entering pregnancy with manifest obesity, interventional programs may reduce both health care consumption and morbidity.

## **7. Conclusions**

### **7.1. Study I**

This pilot study showed that an early intervention program, including general dietary advice and increased physical activity, may be successful in helping obese women control gestational weight gain without adverse perinatal outcomes.

### **7.2. Study II**

In this comparative study, fatty acids in breast milk of obese mothers and plasma phospholipids from their neonates differed significantly from the corresponding fatty acids in normal-weight mothers and their neonates. Obese pregnant women and their neonates had lower omega-3 fatty acids and higher omega-6/omega-3 fatty acid ratios than normal-weight mothers and their infants. A general weight control program seemed to improve the fatty acid pattern. The results suggest the importance of health-promoting care for obese pregnant women, which may also influence the early fatty acid pattern in their infants.

### **7.3. Study III**

This large-scale nationwide study provides robust epidemiological evidence that overweight and obesity decrease the risk of obstetric anal sphincter lacerations among primiparas.

### **7.4. Study IV**

This large population-based cohort study showed that obese women generally consume significantly more health care resources during pregnancy, compared to normal-weight women. Obese women were more often admitted for in-patient care, had longer antenatal hospital stays, and were more often sick-listed during pregnancy, compared to normal-weight women. There was a small but significant increase in the number of visits to both obstetrician and midwife with increasing BMI category. Given that obesity during pregnancy is considered a risk, it is somewhat surprising that the difference was not even greater.



## 8. Svensk sammanfattning (Swedish summary)

Fetma ökar i hela Västvärlden. Enligt WHO (World Health Organization) är mer än 300 miljoner människor i världen feta d.v.s. har body mass index över 30 kg/m<sup>2</sup>. 2011 var 50% av alla män och 40% av alla kvinnor överviktiga eller feta i Sverige (feta män 11.8% resp. feta kvinnor 10.5%). Samma år hade 12.6% av alla gravida kvinnor ett BMI som översteg 30. Övervikt och fetma under graviditet ökar risken för ett flertal komplikationer, som ökad risk för missfall, för tidig födsel, havandeskaps-förgiftning, graviditetsdiabetes, blodproppar och kejsarsnitt. Vid förlossningen ökar risken för stora blödningar och risk för allvarliga komplikationer ökar med BMI i samband med kejsarsnitt. Barnen till dessa mödrar har ökad risk för missbildningar, att födas tunga för tiden, att dö innan förlossningen och har högre risk att få syrebrist i samband med förlossningen. Studier visar att stor *viktökning* under graviditeten ökar risken att föda ett barn som är tung för tiden och att kostråd och ökad fysisk aktivitet under graviditet för feta gravida minskar risken för bland annat havandeskapsförgiftning. Förlossningens första del går långsammare hos kvinnor med högt BMI men den senare, aktiva delen av förlossningen påverkas inte av kvinnans BMI.

Fetmaincidensen ökar också bland barn. Orsaker kan vara minskad fysisk aktivitet och ökad intag av snabbmat med högt energiinnehåll. Andra riskfaktorer är att födas av överviktiga föräldrar, föräldrar med låg inkomst, ha en mor som röker, kort amningsperiod och snabb viktökning de första 5 månaderna av livet.

Vad vi äter under graviditet och amningsperioden har stor betydelse för det växande barnet. Under andra världskriget utsattes den av Tyskland ockuperade delen av Holland för svår svält. Studier från detta område har visat att kvinnor som utsattes för svält i tidig graviditet fick barn som hade ökad risk för fetma som vuxna, medan de barn som utsattes för svält under fosterperiodens senare del, hade minskad risk att utveckla fetma som vuxna. Många fler studier har efter detta visat att undermålig näring under fosterlivet kan påverka både det växande barnet men också kan ha effekt på kommande generationer. Detta sammanhang beskrevs först av David Barker 1986 och kallades "*the Developmental Origins of Health and Disease Hypothesis*" eller Barkerhypotesen. Gener har förmåga att uttryckas på olika sätt. Varför förändringen sker, beror bland annat på omgivningens påverkan, t.ex. beroende på hur mycket och vad vi äter. Detta brukar också kallas epigenetik och syftar på vad som sker med uttrycket av DNA utanför själva DNA sekvensen i våra gener.

Omega-3 fettsyran alfa-linoleninsyra (ALA) och Omega-6 linolensyra (LA) är fleromättade fettsyror. De är essentiella fettsyror d.v.s. vi är beroende av dessa i kosten, då vi inte kan producera dem själva i kroppen. Dessa fetter är mycket viktiga för bl.a. hjärnans utveckling och fostret är därför beroende av moderns intag av ALA och LA under fosterlivet och amningsperioden. Vi äter allt mer omega-6 fetter i kosten och mindre omega-3, vilket är ett problem då dessa fettsyror konkurrerar om samma enzym i kroppen. Ett för högt intag av omega-6 fettsyror kan därför ha en negativ påverkan hur vi tillgodogör oss omega-3 fettsyror. Studier har visat risk för både försämrad neurologisk utveckling och ökad risk för fetma hos barn som under fosterlivet och amning fått hög andel omega-6 och låg andel omega-3 fettsyror.

## **I denna avhandling ingår fyra olika studier:**

- I. *Ett pilotprojekt med 25 gravida kvinnor med BMI > 30 som ingått i en interventionsstudie med extra besök hos barnmorskan, läkare, dietist och extra motion, vattengymnastik 1gg/vecka samt egen träning minst 30 minuter/dag under hela graviditeten. Resultaten visade att 56% av kvinnorna gick upp  $\leq 6$  kg vilket var målet för projektet. 3 kvinnor fick en blodtrycksförhöjning under graviditeten, tre kvinnor förlöstes med kejsarsnitt. Alla barn var friska och hade normal födelsevikt.*
- II. *En observationsstudie där fettsyror i bröstmjölk och i blodprov från barnen jämfördes mellan 41 normalviktiga, 41 feta och 29 feta kvinnor från interventionsstudien. Resultaten visade att omega-3 fettsyror var lägst och kvoten omega-6/omega-3 fettsyror högst i bröstmjölk och i blodprov hos de feta kvinnorna och deras barn. Fettsyrorerna i bröstmjölk och blodprov från kvinnor respektive barn med högt BMI som ingått i interventionsstudien var mer lika de normalviktiga kvinnornas fettsyror.*
- III. *En stor nationell studie från Medicinska födelseregistret, med 210,678 förstföderskor, där risk för skador i ändtarmsmuskeln jämfördes mellan kvinnor i olika BMI klasser. Resultatet visade att risken för skador i ändtarmsmuskeln minskade ju högre BMI kvinnan hade.*
- IV. *En stor nationell från Mödrahälsovårdsregistret, Medicinska födelseregistret och Slutenvårdsregistret med 108,103 förstföderskor där sjukvårdskonsumtion och sjukskrivning jämfördes mellan kvinnor i olika BMI klasser. Resultatet visade att kvinnor var mer sjukskrivna ju högre BMI de hade och att de hade mer besök hos barnmorska och läkare på mödravårdscentralen, fler besök för samtal om förlossningsrädsla och var oftare inlagda på sjukhus under graviditeten.*

**Sammanfattning:** Det är känt att med ökande BMI ökar risken för en rad komplikationer under graviditeten. En del av dessa komplikationer går att minska om viktuppgången inte blir för stor. Andra komplikationer kan upptäckas tidigt, eller undvikas, med bättre övervakning under graviditet och förlossning. Förlossningsförloppet är lite olika beroende på kvinnans BMI men risken för allvarliga skador i underlivet är mindre hos kvinnor med högt BMI och information om detta kan hjälpa feta gravida att våga föda vaginalt. Modern och hennes barn påverkas av kost och motion under graviditet och amning och det är därför viktigt att i tidig graviditet hjälpa kvinnor att förbättra sina kost och motionsvanor. Vår interventionsstudie visar hur man skulle kunna hjälpa feta kvinnor under graviditeten, men större randomiserade studier behövs, innan man kan införa detta fullt ut i klinisk praxis.

## 9. Acknowledgements

I would like to express my sincere gratitude and deepest appreciation to all those who supported me and who in different ways have contributed to this thesis.

### In particular I would like to thank:

- All the patients that participated in the studies.
- The Division of Obstetrics and Gynecology, Department of Clinical Science, Karolinska Institutet, for giving me the opportunity to complete my theses.
- Associate Professor Daniel Altman, my principal supervisor, to believing in my capability to research from start. I would not have started or continued this work if it wasn't for you. For inspiration and excellent tutorship, and your ability to always find something positive in every situation.
- Dr. Margareta Norman, my co-supervisor, for being inspiring and guiding me in the obstetrical field and for valuable criticism of the manuscripts
- Dr. Charlotte Palme-Kilander, my co-supervisor, for introducing me to the research field of breast-milk and fatty acids, for inspiring meeting and collaboration.
- Professor Birgitta Strandvik, my co-author, for learning me all I know about fatty acids, for contribution and criticism of manuscript of paper II. For encouragement and for showing me the fun of research.
- Dr. Marie Blomberg, my co-author, for inspiring me to start the research about pregnancy and obesity and for the inspiration and criticism of manuscript of paper IV.
- Professor Arnold Maliniak, my mentor, for support, encouragement and friendship.
- Coordinating midwife Anne-Charlotte Jonsson for enthusiasm, friendship and for all this things you been taking care of while I have been busy writing my theses.
- Camilla Borgström, Elisabeth Rehnfelt Orre, Anette Holst, Catherine Bonnevier, Ann-Catrin Ljusberg and Caroline Ottenborg for excellent work with the "*Våga våga*" project, Your enthusiasm, and for always putting the patients first.
- All friends, colleagues, the midwives and other staff at Department of Obstetrics and Gynaecology, Danderyds hospital, for supportive, warm and professional atmosphere.
- Dr. Birgitta Mörlin, Head of the Division of Obstetrics and Gynecology and Dr. Eva Östlund, Head of the Obstetrics section for providing me possibility to research and allowing me to present my theses at the Department of Obstetrics and Gynecology, Danderyd hospital.
- All my friends for joy, support and encouragement!
- Everyone in my family, and especially my parents Inga, and my late father Gerhard, who always have been wonderful and caring parents, always supportive, always believing in me.
- My nephews' Axel, Ludvig and Peder, always reminding me of my beloved brother Anders, and for being so fine, nice and smart young men.

- My stepdaughter Frida, Per-Olof and their two lovely children Saga and Emil for all taking care of Gustav and Arvid and to our joy of becoming grandparents.
- My cousin Börje and his wife Margareta and their daughters Isabelle and Ellinor and my cousin Gunnar and Maria, for support and friendship through all this years and especially when life have been hard and dark.
- My extra sister Axelina who helped me and my mother when we needed it most.
- My sons, Gustav and Arvid for being the greatest joy of my life, You are the best!
- My wonderful beloved husband Niklas, for standing by my side, always encouraging, supporting and taking care of me and the whole family. The theses hadn't been completed without your skilled help, with reading all manuscripts and for your help with the tables. The life is not complete without you!

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