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The Role of Eating Disorders for Pregnancy, Neonatal Outcome and the Child's Early Development

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To my beloved husband, and my beloved sons Jamel & Adel

ABSTRACT

Little is known about the impact of eating disorders (ED) on pregnancy, infant growth and cognitive development. Preliminary reports indicate increased complications during pregnancy and lower birth weight in children of mothers with ED. There is need of prospective long-term follow-up of growth and cognitive development of the children of these mothers.

Aims: To study the impact of ED on pregnancy and neonatal outcomes, maternal adjustment, and infant growth and cognitive development compared with controls.

Method: Forty-nine nulliparous, nonsmoking women with a history of ED, 24 with anorexia nervosa (AN), 20 with bulimia nervosa (BN), 5 with non-specific ED (EDNOS), and 68 healthy controls were followed during pregnancy and up to three months postpartum. The women were recruited in early pregnancy from 13 antenatal clinics in northwestern Stockholm. Three months after delivery, the women completed the maternal adjustment and maternal attitude questionnaire (MAMA) and were asked about mental health problems postpartum. Furthermore, the children's growth (weight, height and head circumference) and neurocognitive development (questionnaire: Five to Fifteen) were followed up to five years of age. Blood samples during early pregnancy were analyzed for nutrition-related markers and stress factors (ferritin, cortisol, thyroid-stimulating hormone (TSH), free thyroxine (T4), insulin, insulin-like growth factor-I and binding protein 1). Serum levels of these biomarkers were related to head circumference and neurocognitive development of the offspring.

Result: Eleven of the patients (22%) had verified relapse of ED during pregnancy. Pregnant women with past or active ED were at greater risk of delivering infants being small for gestational age, having lower birth weight and smaller head circumference than controls (Paper I). Three months after delivery, 92% of mothers with ED before pregnancy reported problems regarding their maternal adjustment compared to 13% in the control group, whereas there were no differences between the subgroups of ED. Fifty percent of mothers with previous ED reported that they had been in contact with health services after delivery because of depression or other mental problems (Paper II). Children of mothers with previous ED demonstrated an early catch-up in body mass index, while the average head circumference continued to be delayed up to at least 18 months of age. The reduced head growth was related to delayed neurocognitive development in the ED group (Paper III). Serum levels of ferritin were significantly lower in the AN group, but not in the BN group, and correlated to impaired memory in the children at five years of age (Paper IV). Furthermore, maternal serum levels of free T4 were positively associated with head circumference of the children in both the AN group and the BN group, but not in the controls.

Conclusion: Pregnant women with a history of AN or BN should be considered a risk group for prenatal and delivery complications. More research is needed, especially directed to the long-term growth and neurocognitive development of these children. Health care needs to improve its methods to identify a possible history of AN and BN in pregnant women and optimize care in order to prevent adverse health effects for mother and baby.

LIST OF PUBLICATIONS

This thesis is based on on the following papers, which will be discussed in the text by their Roman numerals I-IV:

I.   Koubaa S, Hällström T, Lindholm C, Hirschberg AL. Pregnancy and neonatal outcomes in women with eating disorders. Obstet Gynecol 2005;105:255-260.

II.   Koubaa S, Hällström T, Hirschberg AL. Early maternal adjustment in women with eating disorders. Int J Eat Disord 2008; 41:405-410.

III.   Koubaa S, Hällström T, Hagenäs L, Hirschberg AL. Retarded head growth and neurocognitive development in infants of mothers with a history of eating disorders: longitudinal cohort study. BJOG 2013, [Epub ahead of print]

IV.   Koubaa S, Hällström T, Brismar K, Hellström PM, Hirschberg AL. Biomarkers of nutrition and stress in pregnant women with a history of eating disorders in relation to head circumference and neurocognitive function of the offspring. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

AN	Anorexia nervosa
ANOVA	Analysis of variance
APA	American psychiatric association
BbK	Karolinska biobank
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
CBT	Cognitive-behavioral therapy
CI	Confidence interval
CV	Coefficient of variation
DSM-IV	Diagnostic and statistical manual of mental disorders, ed 4
DSM-V	Diagnostic and statistical manual of mental disorders, ed 5
ED	Eating disorders
EDNOS	Eating disorders not otherwise specified
FSH	Follicle-stimulating hormone
FTF	Five to Fifteen
GnRH	Gonadotropin releasing-hormone
IGFBP1	IGF bindningsprotein 1
IGF-I	Insulin like growth factor-I
LH	Luteinizing hormone
LSD	Least significant difference test
MAMA	Maternal adjustment and maternal attitude questionnaire
OR	Odds ratio
PCOS	Polycystic ovary syndrom
PPD	Postpartum depression
RIA	Radioimmunoassay
SD	Standard deviation
SDS	Standard deviation score
SGA	Small for gestational age
SSRI	Selective serotonin reuptake inhibitor
T4	Thyroxine
TSH	Thyroid-stimulating hormone

FOREWORD

About 13 years ago, I took on the task of examining pregnant women with eating disorders (ED) compared to healthy controls. My long experience from working as a midwife had given me some insight to women with ED and the challenges they face in their pregnancy. I started to plan a research project focusing on ED during pregnancy at Karolinska Institutet. Even though I was not sure about the scope of the project at the time, I was convinced that there was a need to shed light on this complex subject. From my experiences at the outpatient clinic for youths, I realized that this field was characterized by preconceptions, probably due to the limited amount of research that had been done within the field. Most studies at the time on pregnant women with ED were small and inconclusive, e.g. parity and maternal smoking were not reported and there was a lack of control groups. To our knowledge, no research addressing the head circumference development had been conducted and, with one exception, children had not been followed up for longer than one year in earlier studies. I decided to dig deeper into the subject by taking a closer look at pregnancy, fetal development and growth of children to women with ongoing, or a history of ED. I contacted the Knowledge Centre for Eating Disorder in Stockholm, sought funding and got guidance on how to start the project. This has been a very long journey for me, but really an extremely exciting one!

1 INTRODUCTION

1.1 EATING DISORDERS

ED are divided into the main diagnoses of anorexia nervosa (AN), bulimia nervosa (BN) and eating disorder not otherwise specified (EDNOS) according to the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV (APA 2000). Together, these disorders constitute one of the leading causes of disease burden in terms of years of life lost through disability or death for young women (Sattar et al., 1999). The peak age at onset occurs at a developmentally sensitive time in adolescence. Lifetime prevalence rates for full and partial AN in women range from 0.9% to 4.3% and from 1.5% to 7% for full and partial BN (Favaro et al., 2003; Currin et al., 2005; Anderluh et al., 2009). Studies of time trends in ED show that the incidence and prevalence of AN and BN are stabilizing in Western countries (Favaro et al., 2003), whereas the prevalence of EDNOS continues to increase (Mond et al., 2008; Mond et al., 2009). ED are usually explained by multifactorial models including psychological, social, and biological risk factors. However, little research has attempted to bring together information about various types of risk factors and explore interactions among parental health and social characteristics, early-life environment, and individual aspirations in influencing the risk and long-term outcome of ED (Ahren-Moonga et al., 2009).

1.2 ANOREXIA NERVOSA

1.2.1 Clinical Characteristics

AN is a serious psychiatric illness characterized by pronounced underweight; often well below 85 % of ideal body weight. Young individuals who are still growing fail to make expected increases in weight (and often height) and bone density. Despite severe underweight, individuals with AN remain dissatisfied with the perceived size of their bodies, and continue with unhealthy behaviors to perpetuate weight loss (e.g., dieting, purging, excessive exercise). In psychological terms, the weight and shape of the body may reflect the individual's self-esteem. Although amenorrhea is a diagnostic criterion, it is of questionable relevance for the disease (Watson & Andersen, 2003). Typical personality features of individuals with AN include perfectionism, compulsivity, anxiety, harm avoidance, and low self-esteem (Wonderlich et al., 2005).

The most common comorbid psychiatric conditions include major depression and anxiety disorders (Halmi et al., 1991; Kendler & Walters, 1995). Anxiety disorders often predate the onset of AN (Gendall et al., 1997; Frank et al., 2004) and depression often persists post-recovery (Sullivan et al., 1998).

1.2.2 Diagnostic criteria

Diagnostic criteria for AN according to DSM-IV (APA 2000) are shown below.

Anorexia nervosa

- Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g. body weight less than 85% of that expected or body mass index < 17.5)
- Intense fear of gaining weight or becoming fat, even though underweight
- Disturbance in the way in which one´s body weight or shape is experienced
- Amenorrhea, i.e. the absence of at least three consecutive menstrual cycles

Subtypes

<u>Restricting type</u>: The person has not regularly engaged in binge-eating or purging behaviour

<u>Binge eating/purging type</u>: The person has regularly engaged in binge-eating or purging behaviour   (APA 2000)

1.2.3 Epidemiology

The lifetime prevalence of AN has been assessed in three large population-based cohort studies of twins reporting similar results. In a Swedish study, the overall prevalence of AN was 1.2% for females and 0.3% for male participants in the largest twin study from the 1935–1958 birth cohorts (Bulik et al., 2006). In an Australian study of female twins aged 28–39 years, the lifetime prevalence of AN was 1.9 % (Wade et al., 2006). In a Finnish study, the lifetime prevalence of AN was 2.2 % in a large sample of women from the 1975–1979 birth cohorts of Finnish twins (Keski-Rahkonen et al., 2007). From the same birth cohorts, the lifetime prevalence of AN in men was 0.24 % (Raevuori et al., 2009). The overall incidence rate of AN has been stable over the past decades, but there has been an increase in the high risk-group of 15-19 year old girls (Smink et al., 2012).

1.2.4 Etiology

The etiology of AN remains incompletely understood. Although numerous psychological, social, psychosocial stress, biological and genetic factors have been implicated as potentially causal, few specific risk factors have been consistently replicated in studies of the etiology of the disorder. Common risk factors across ED include female sex, childhood eating and gastrointestinal problems, elevated shape and weight concerns, negative self-confidence, sexual abuse, and general psychiatric comorbidity (Brambilla, 2001; Jacobi et al., 2004; Bentley et al., 2005). In addition, prematurity and small for gestational age (SGA) have been identified as risk factors for AN in adulthood (Cnattingius et al., 1999).

Several pharmacologic, genetic, and neuroimaging studies have identified fundamental disturbances in serotonergic function in individuals with AN even after recovery (Kaye et al., 2005). Although serotonin has received considerable research attention, other neurotransmitter systems, most notably dopamine, are also implicated in the disorder (Barbarich et al., 2003; Aaltonen et al., 2008). The ultimate understanding of AN etiology will likely include main effects of both biological and environmental factors, as well as their interactions and correlations.

1.2.5 Medical complications

Medical complications of AN are common and can affect multiple organ systems. Severe AN is associated with serious and potentially fatal cardiovascular complications including bradycardia, arrhythmias and hypovolemia, as well as electrolyte disturbances leading to sodium depletion, hypophosphatemia, and hypomagnesemia.

AN is also associated with extensive endocrine abnormalities, which may affect puberty development in the young individuals and result in amenorrhea. Furthermore, low levels of estrogen together with nutritional deficiency will result in bone loss, particularly of trabecular bone, such as in the spine. Up to 50% of patients with AN have been found to have osteoporosis in the lumbar spine (Legroux-Gérot et al., 2005). Other common medical complications are gastrointestinal disturbances including gastric dilatation, dental problems and dermatological changes. Medical consequences of AN can persist even after major recovery and may include continued low body mass index (BMI), osteoporosis (Rigotti et al., 1991) reproductive problems

(Bulik et al., 1999), and depression (Barraclough & Harris, 1998; Sullivan et al., 1998).

1.2.6 Treatment and prognosis

The treatment of AN aims at restoring weight, normalizing eating behavior, treating psychological disturbances such as distortion of body image, low self-esteem, interpersonal conflicts, and achieving long-term remission and rehabilitation, and eventually full recovery (NICE 2004; APA 2006). In the acute phase of malnutrition and severe weight loss, hospitalization is needed for re-feeding and medical stabilization. In the outpatient treatment of AN, there is evidence for family-based therapy in young individuals (Bulik & Watson, 2012). In adults, different types of psychotherapy such as specialist supportive clinical management, cognitive behavioral therapy and interpersonal psychotherapy have demonstrated similar results (Bulik & Watson, 2012). Pharmacotherapy with antidepressants may be a compliment but is not recommended as single treatment.

About half of the patients fully recover, 30% partially improve and the remainder are chronically ill (Berkman et al., 2007). AN is a potentially life-threatening disorder with increased risk for premature death caused by starvation or suicide. A recent meta-analysis of 35 studies with a mean follow-up of 14 years found a standardized mortality ratio of 5.9 (95% CI: 4.2-8.3) (Arcelus et al., 2011).

1.3 BULIMIA NERVOSA

1.3.1 Clinical Characteristics

BN is characterized by recurrent episodes of binge eating in combination with some form of inappropriate compensatory behavior. Binge eating is the consumption of an abnormally large amount of food coupled with a feeling of being out of control. Compensatory behaviors (aimed at preventing weight gain) include self-induced vomiting; the misuse of laxatives, diuretics, or other agents; fasting; and excessive exercise.

The onset of BN usually occurs in adolescence or early adulthood and is most frequently seen in women who are of normal body weight (APA 2000). Although the gender ratio is approximately 9:1, women to men (Bulik et al., 1997; Hoek & van Hoeken, 2003), the diagnostic criteria themselves are gender-biased. In contrast to

women, men tend to present with a greater reliance of no purging forms of compensatory behavior such as excessive exercise. Considerations of differences in the clinical presentation of BN in men may lead to revised estimates (Fichter & Quadflieg, 1997; Levitan et al., 2001; Lewinsohn et al., 2002). Approximately 80% of patients with BN are diagnosed with another psychiatric disorder at some time in their life (Braun et al., 1994). Commonly comorbid psychiatric conditions include anxiety disorders, major depression, dysthymia, substance use, and personality disorders (Brewerton et al., 1995; Weltzin et al., 1995; Lilenfeld et al., 1997). Personality features of individuals with BN include some features shared with AN as high harm avoidance, perfectionism, and low self-esteem. Features more specific to BN include higher novelty seeking, higher impulsivity, lower self-directedness, and lower cooperativeness (Barraclough & Harris, 1998; Bulik, & Kendler, 1998; Fassino et al., 2004; Steiger et al., 2004).

1.3.2 Diagnostic criteria

A diagnosis of BN requires a minimum of three months of binge eating and compensatory behavior occurring twice a week or more (APA 2000), see below. Similar to AN, individuals have to report the undue influence of weight and shape on their self-esteem. In addition, BN is diagnosed secondary to AN, i.e., the illness is diagnosed as BN only if the criteria for AN are not met. Thus, to be diagnosed with BN, individuals should have a BMI greater than 17.5 or the equivalent in children and adolescents. The DSM-IV distinguishes two subtypes of BN based on the individual's compensatory behavior: purging (including vomiting and misuse of laxatives, diuretics, or enemas) and no purging (restricted eating and exercise).

1.3.3 Epidemiology

The estimated prevalence of BN is 1-3% among young females and 0.1-0.3% among men (Smink et al., 2012). For instance, Keski-Rahkonen and colleagues found a lifetime prevalence of 1.7% for BN in women from the 1975–1979 birth cohorts of Finnish twins (Keski-Rahkonen et al., 2009). There is support for a decrease in the incidence of BN since the early nineties of the last century (Currin et al 2005). The peak age of incidence of BN is 16-20 years of age. However, several studies suggest that age at onset of BN is decreasing (Keel et al., 2006; Smink et al., 2012).

Bulimia nervosa

- Recurrent episodes of binge eating characterized by eating in a discrete period of time an amount of food that is definitely larger than most people would eat and a sense of lack of control over eating
- Recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics or other medications, fasting, or excessive exercise
- The binge eating and inappropriate compensatory behaviours both occur, on average, at least twice a week for three months
- Self-evaluation is unduly influenced by body shape and weight
- The disturbance does not occur exclusively during episodes of AN

Subtypes

Purging type: The person regularly engages in self-induced vomiting or the misuse of laxatives, diuretics or enemas

Non-purging type: The person uses other inappropriate compensatory behaviours, such as fasting or excessive exercise   (APA 2000)

1.3.4 Etiology

Historically, like AN, BN has been conceptualized as having sociocultural origins. Furthermore, substantial familial aggregation of BN has been reported (Kaye et al., 1998). Twin studies reveal a moderate to substantial contribution of additive genetic factors (between 54% and 83%) and unique environmental factors to BN (Wade et al., 1999; Carter et al., 2003). Linkage analyses have identified areas on chromosome 10p that may be associated with BN (Bailer et al., 2004). Numerous candidate genes have been studied for their role in the risk of the disorder (Van Furth, 2005). Ongoing biological studies suggest fundamental disorders in serotonergic function in individuals with BN (Bulik & Kendler, 1998; Wade et al., 1999). The ultimate understanding of the etiology of BN and of other disturbances that contribute to the development of inappropriate responses to satiety clues (Mitchell et al., 1991) will most likely include main effects of both biological and environmental factors as well as their interactions and correlations.

1.3.5 Medical complications

Although BN is not typically associated with the serious physical complications normally associated with AN, patients commonly report physical symptoms such as fatigue, lethargy, bloating and gastrointestinal problems. Individuals with BN who engage in frequent vomiting may experience electrolyte abnormalities, metabolic alkalosis, erosion of dental enamel, swelling of the parotid glands, and scars and calluses on the backs of their hands. Those who frequently misuse laxatives can have edema, fluid loss and subsequent dehydration, electrolyte abnormalities, metabolic acidosis, and potentially permanent loss of normal bowel function (Lasater & Mehler, 2001).

BN is also associated with endocrine disorders including amenorrhea/oligomenorrhea although most women with bulimia are of normal body weight. Some bulimic women may have low bone mass and particularly those with previous AN (Naessén et al., 2006).

1.3.6 Treatment and prognosis

The primary goal of treatment for bulimia is to reduce or eliminate binge eating and purging behaviour. Nutritional rehabilitation, psychosocial intervention, cognitive behavioural psychotherapy (CBT) and family treatment are often employed. Establishment of a pattern of regular, non-binge meals, improvement of attitudes related to eating, encouragement of healthy but not excessive exercise, and resolution of co-occurring conditions such as mood or anxiety disorders are among the specific aims of these strategies (NICE 2004; APA 2006).

In addition to psychotherapy, medical treatment can be necessary in many cases. The selective serotonin reuptake inhibitor (SSRI) fluoxetine, has been shown to reduce the frequency of binge eating and purging and is effective also in patients who are not depressed (Leombruni et al., 2006).

Little is known about the long-term cause and outcome of BN. However, available data indicate remission rates up to 70% or more by 10-year follow-up of BN (Keel & Brown 2010). This ED is associated with lower mortality rates than AN. In a recent meta-analysis of 12 studies of patients with BN the overall standardized mortality ratio was 1.9 (95% CI: 1-4-2.6) (Arcelus et al., 2011).

1.4 EATING DISORDERS NOT OTHERWISE SPECIFIED

1.4.1 Clinical Characteristics

EDNOS is a diagnostic category that captures those individuals with ED who do not meet all criteria for AN or BN, see below. The patient's weight might be just above the diagnostic threshold for AN or she might still be menstruating. Binge eating and purging may occur less frequently than specified for a diagnosis of BN. Concern with weight and shape is generally present in these disorders, although in some the primary focus is on maintaining strict control over eating. Although the diagnostic criteria may not be met, many atypical ED are as severe and long lasting as AN and BN. Patients' treatment needs and prognosis may be virtually identical.

A sub-type of EDNOS is the binge-eating disorder (BED). The defining characteristics of BED are consumptions of an objectively large amount of food in discrete time periods, a lack of control during eating episodes and a lack of compensatory behavior. BED affects approximately 30% of obese individuals seeking treatment. The binge eaters represent a distinct subgroup among the obese with higher prevalence of comorbid psychiatric disturbances, as well as higher rates of eating pathology, as compared to normal obese women (Latzer & Tzchisinki, 2003).

1.4.2 Epidemiology

EDNOS is the most common ED diagnosis made in most outpatient settings other than those that attract highly specialist referrals (Shafran & Fairburn, 2002). However, there are very few epidemiological studies on EDNOS, probably because of its heterogeneity. In a nation-wide community sample of young females, the point prevalence of EDNOS was 2.4 % (Machado et al., 2007). The lifetime prevalence of BED in European women has been estimated to 1.9% (Preti et al., 2009).

1.4.3 Diagnostic Criteria

Diagnostic criteria for EDNOS according to DSM-IV (APA 2000) are shown below.

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Eating disorder not otherwise specified

- All of the criteria for AN are met except that the individual has regular menses
- All of the criteria for AN are met except that, despite significant weight loss, the individual's current weight is in the normal range
- All of the criteria for BN are met except that the binge-eating and inappropriate compensatory mechanisms occur at a frequency of less than twice a week or for a duration of less than three months
- The regular use of inappropriate compensatory behaviour by an individual of normal body weight after eating small amounts of food
- Repeatedly chewing and spitting out, but not swallowing, large amounts of food
- Binge-eating disorder (BED): recurrent episodes of binge-eating in the absence of the regular use of inappropriate compensatory behaviours characteristic of BN

(APA 2000)

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1.4.4 Etiology

It has been a matter of debate whether EDNOS is a specific entity or not. Cross-sectional studies generally demonstrate few clinical differences between individuals with full-syndrome AN or BN and their EDNOS (Thomas et al., 2009). The latter diagnosis is therefore commonly considered to be a residual category of AN or BN. However, there is support that patients with EDNOS have more comorbidity, such as depression and obsessive compulsive disorder, compared to BN (Schmidt et al., 2008). As with AN and BN, the cause of EDNOS is not determined but it is most likely a combination of environmental and biological factors that contribute to the development and expression of the disorder.

1.4.5 Medical complications

The medical problems associated with EDNOS are dependent on the type and severity of ED symptoms but similar to the full criteria syndromes of AN or BN. In adolescents with EDNOS it was demonstrated that partial AN was a more medically severe condition than partial BN, and that these categories differed more from each other than

from AN and BN, respectively (Peebles et al., 2010). Furthermore, many of those with BED will suffer similar physical complications of binge eating to those with BN, though purging carries greater physical risk than binge eating (Bulik & Reichborn-Kjennerud 2003). Those who are obese are at risk of the psychological and physical disabilities associated with this condition, namely low self-esteem, diabetes, heart disease, hypertension and stroke.

1.4.6 Treatment and prognosis

Although there have been many studies of the course and outcome of AN and BN, few have considered EDNOS as a specific outcome. Treatment studies specifically for EDNOS are rare. However, in a recent small comparative study it was demonstrated that the treatment response to CBT, nutritional support and psychotropic drugs was 43% for patients with EDNOS and similar to BN and AN (Larrañaga et al., 2013).

Remission rates at 20-year follow-up have been reported to be 75% for EDNOS compared to 72% for BN, with no significant difference between these rates (Keel & Brown 2010). Furthermore, remission rates do not appear to differ between different forms of EDNOS, i.e. partial AN, partial BN and BED (Keel & Brown 2010). A recent meta-analysis of six studies of patients with EDNOS reported an overall standardized mortality ratio of 1.9 (95% CI: 1.5-2.5) (Arcelus et al., 2011).

1.5 DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS (DSM-V)

Recently, the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) was released. Among the most substantial changes are recognition of BED, and revisions to the diagnostic criteria for AN and BN as summarized below:

1.5.1 Binge Eating Disorder

BED was approved for inclusion in DSM-V as its own category of ED. In DSM-IV, BED was not recognized as a disorder but rather described as a category of EDNOS. BED is defined as recurring episodes of eating significantly more food in a short period of time than most people would eat under similar circumstances, with episodes marked by feelings of lack of control. Someone with BED may eat too quickly, even when he

or she is not hungry. The person may have feelings of guilt, embarrassment, or disgust and may binge eat alone to hide the behavior. This disorder is associated with marked distress and occurs, on average, at least once a week over three months.

1.5.2 Anorexia Nervosa

AN, which primarily affects adolescent girls and young women, is characterized by distorted body image and excessive dieting that leads to severe weight loss with a pathological fear of becoming fat. The new criteria focus on behaviors, like restricting calorie intake, and no longer include the word "refusal" in terms of weight maintenance. The DSM-IV criterion amenorrhea will be deleted. This criterion cannot be applied to males, pre-menarchal females, females taking oral contraceptives and postmenopausal females. In some cases, individuals exhibit all other symptoms and signs of AN but still report some menstrual activity.

1.5.3 Bulimia Nervosa

BN is characterized by frequent episodes of binge eating followed by inappropriate behaviors such as self-induced vomiting to avoid weight gain. DSM-V criteria reduce the frequency of binge eating and compensatory behaviors that people with BN must exhibit from twice weekly to once a week.

The above changes of the diagnostic criteria of ED do not influence the results and conclusions of the present thesis.

1.6 EATING DISORDERS AND FERTILITY

The reproductive capacity of women with ED is reduced depending on several factors. One of the diagnostic criteria for AN is amenorrhea. In AN, the usual mechanism of menstrual disturbance is hypothalamic amenorrhea due to starvation and low body weight (Chan & Mantzorors, 2005). Hypothalamic inhibition of the reproductive system will lead to a disruption of gonadotropin releasing hormone (GnRH) secretion from the hypothalamus. This will result in reduced pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to low production of estradiol from the ovaries, which will cause anovulation and amenorrhea. Because of anovulation, it is rare for AN women to become pregnant spontaneously although such

cases are reported. Furthermore, AN is associated with reduced libido and reduced sexual activity (Pinheiro et al., 2010).

Women with BN also have menstrual disturbance in increased frequency even though they usually are of normal weight (Gendall et al., 2000; Naessén et al., 2006). Various mechanisms may explain oligomenorrhea and amenorrhea in bulimics. The temporary starvation periods associated with bulimia may be responsible for the hypothalamic inhibition of the reproductive axis, as well as low levels of thyroid hormones as in AN (Gendall et al 2000). Furthermore, several studies indicate a link between bulimic behavior and increased occurrence of polycystic ovary syndrome (PCOS) (Naessén et al., 2006). This suggestion is based on an increased frequency of polycystic ovaries, anovulation, elevated serum levels of testosterone and hirsutism in bulimic women (Naessén et al. 2006).

Weight restoration seems to be the most important factor in recovering normal menstrual function among women with ED. However, impaired fertility may remain despite normal weight after recovery of an ED. Life-time history of both AN and BN has been associated with fertility problems, unplanned pregnancies and negative attitudes to pregnancy (Easter et al., 2011). In a recent register-based study, it was demonstrated that women treated for ED were more likely to be childless, and had lower pregnancy and childbirth rates than controls (Linna et al., 2013).

1.7 PREGNANCY AND NEONATAL OUTCOME

Even if fertility is reduced in women with ED, these disorders do not exclude spontaneous pregnancy. Women with ED may also become pregnant with assisted reproductive technologies. Furthermore, there is an increased risk of relapse of ED during pregnancy (Micali et al 2007). It has been reported that the prevalence of ED among pregnant women is more than 1 percent but it is probably higher than what is diagnosed because many patients hide their symptoms (Bulik et al., 2007).

Data about the influence of ED on the course of pregnancy and delivery are scarce. Studies suggest that both AN and BN may have negative impact on pregnancy and perinatal outcomes. Higher rates of maternal complications, such as miscarriages, hyperemesis, preterm delivery, intrauterine growth restriction and cesarean deliveries

have been reported (Bulik et al., 1999; Lacey & Smith, 1987; Brinch et al 1988; Mitchell et al., 1991; Franko et al., 2001).

Little is also known about birth outcomes and the health of infants born to women with ED. The findings in the studies published before this thesis, suggest that both anorectic and bulimic behavior may affect fetal outcome negatively. However, most of these studies are retrospective reports or small prospective follow-up studies without control groups.

Past or active ED have been associated with stillbirth, low birth weight, increased incidence of SGA and low Apgar scores in the offspring (Lacey & Smith, 1987; Stewart et al., 1987; Brinch et al 1988; Treasure & Russel, 1988; Conti et al., 1998; Franko et al., 2001). In a register-based study, the risk of SGA was reported to be nearly twice the size of the children of women with ED compared to children of healthy women (Petersen Sollid et al., 2004). Furthermore, individual studies have reported a high incidence of birth defects in infants of bulimics and increased perinatal mortality in children of women with previous AN (Lacey & Smith, 1987; Brinch et al 1988; Franko et al., 2001).

It has been reported that ED symptoms may improve during pregnancy (Lacey & Smith, 1987; Blais et al., 2000; Crow et al., 2004). Binge-eating and self-induced vomiting decreased gradually during pregnancy in 20 women with BN (Lacey & Smith, 1987). However, after delivery the symptoms tended to return and in half of the women eating was more disturbed postpartum than before pregnancy (Lacey & Smith, 1987; Blais et al., 2000). Women with AN have also demonstrated improvements in ED symptoms during pregnancy, however, these symptoms returned to prepregnancy levels postpartum (Blais et al., 2000).

1.8   EARLY ADJUSTMENT TO MOTHERHOOD

1.8.1 Adjustment postpartum of healthy mothers

After the birth of a child, the mother finds herself in an adjustment of life and attitude that not only brings physical changes but also much of her psychological life as well. Delivery does not immediately bring back the woman's previous body, perhaps intensifying psychological dynamics. Potential areas of concern for new mothers include infant feeding, maternal-child bonding, and postpartum adjustment. A

qualitative study of women who become mothers for the first time revealed the experience of unexpected hard work and exhaustion of caring for the baby, which can leave women confused and ambivalent about their early mothering experiences (Miller, 2011). In a Swedish prospective study it was demonstrated that maternal prenatal attachment during the third trimester of pregnancy is a good predictor of the postnatal mother-infant interaction (Hägglöf & Siddiqui, 2000). This knowledge can be used to identify women at risk for sub-optimal early mother-child interaction.

1.8.2 Postpartum depression

To have a baby, and particularly to become a mother for the first time, entails very great changes in maternal intrapsychic and interpersonal adjustment. It is well-known that childbearing and the postpartum period are associated with an increased risk of psychiatric disorders such as depression (Leight et al., 2010). Postpartum depression is a common and serious mental health problem. The prevalence is around 10% and the illness is associated with increased risk of suicide. Furthermore, postpartum depression is associated with disturbances in the mother-infant relationship. Risk factors for the disease are depression and or anxiety during pregnancy, premenstrual dysphoric disorder, stressful life events, poor social or partner support and low socioeconomic status (Leight et al., 2010). There is an on-going discussion and suggestion to introduce screening of postpartum depression in primary care.

1.8.3 Early adjustment in mothers with eating disorders

The postpartum period may be particularly stressful for women with ED. Over 40% of new mothers, regardless of having a diagnosis of an ED or not, report being dissatisfied with their weight during the postpartum period (Walker et al., 1988). Once the child is born, women often feel a need to lose the excess weight quickly and may use unhealthy measures to do so (Edelstein et al., 1992). Women with a history of ED who minimize their ED behaviours during pregnancy remain at high risk for relapse of ED behaviours during the postpartum period (Lacey & Smith, 1987; Blais et al., 2000). In fact, 80% of women with ED relapse in the postpartum period and attribute this to feeling fat and wanting to lose the weight gained during pregnancy (Lemberg et al., 1989).

There are very few studies about ED mothers' early adaptation to motherhood apart from related to infant feeding. Brinch and co-workers (1988) reported in a retrospective study, that among 50 mothers with AN, 68% felt they had managed well in the maternal role, 25% that they had managed tolerably, and 7% that they had managed poorly. However, Woodside and Shekter-Wolfson (1990), found a high prevalence of parenting dysfunction and marital dysfunction in a small clinical sample of patients with AN and BN.

1.8.4 Postpartum depression in women with eating disorders

The psychosocial stressors of motherhood combined with body image concerns intensified by the bodily changes of the pregnancy, may predispose women with ED to the development of postpartum mood disorders. In a longitudinal study of 49 women with AN and BN, Franko and co-workers (2001) found that 37% of the ED women experienced postpartum depression and mainly those with active ED symptoms during pregnancy. In agreement, a retrospective case-control study showed an increased risk for postpartum depression in women with active bulimia during pregnancy (Morgan et al., 2006). Furthermore, a population-based study concluded that women with lifetime BN and BED seem to be at particular risk of developing postpartum depression (Mazzeo et al., 2006).

1.8.5 Feeding the infant

Feeding is thought to be important in parent-infant bonding. Mothers with ED can exhibit problems in feeding their offspring starting during the postpartum period with breastfeeding (Lacey & Smith, 1987; Evans & Grange, 1995; Waugh & Bulik, 1999; Agras et al., 1999). Women with ED report a lack of desire to breastfeed and may experience difficulty in doing so (Stewart et al., 2001). One study found that 14 of 20 mothers with BN reported having breastfeeding difficulties (Lacey & Smith, 1987). In addition, breastfeeding while restricting caloric intake may put the baby at risk for malnutrition. Women who worry that their child will become obese may be more likely to restrict that child's calories, which could lead to nutritional deprivation (Russel et al., 1998). Controlling parenting style in mothers with ED is associated with feeding problems in the offspring (Stein et al., 2001). Furthermore, children of mothers with ED may have an increased risk to develop disturbed eating behavior themselves (Stein et al., 2006).

1.9 GROWTH DEVELOPMENT IN THE OFFSPRING

There is little information about the long-term consequences of maternal ED on growth development in the offspring. In an early report, seven infants born to mothers with AN were underweight at birth but caught up to normal weight at 30 weeks of age (Treasure & Russell 1988). In another study by Stein and co-workers (1996), 33 infants of mothers with ED (BN and EDNOS) were found to have the same length, but to weigh less than control children at one year of age. However, follow-up at 10 years of age showed no difference in BMI between the groups (Stein et al., 2006). Furthermore, Waugh and Bulik (1999) demonstrated in a small clinical material that children of women with ED (AN and BN) had significantly lower birth weights and lengths than controls, but these differences were no longer significant at three months of age. In a more recent large study by Micali and co-workers (2009), infants at nine months of age of mothers with self-reported BN (n = 194) were significantly more likely to be over-weight compared to the general population.

To our knowledge, no previous study has investigated head circumference and neurocognitive development in children of mothers with ED.

2 OBJECTIVE

2.1 OVERALL OBJECTIVE

The overall objective of this thesis was to increase the knowledge about the influence of a history of ED on pregnancy complications and neonatal outcome, as well as the mother's adaptation to motherhood and the early growth and neurocognitive development of the child.
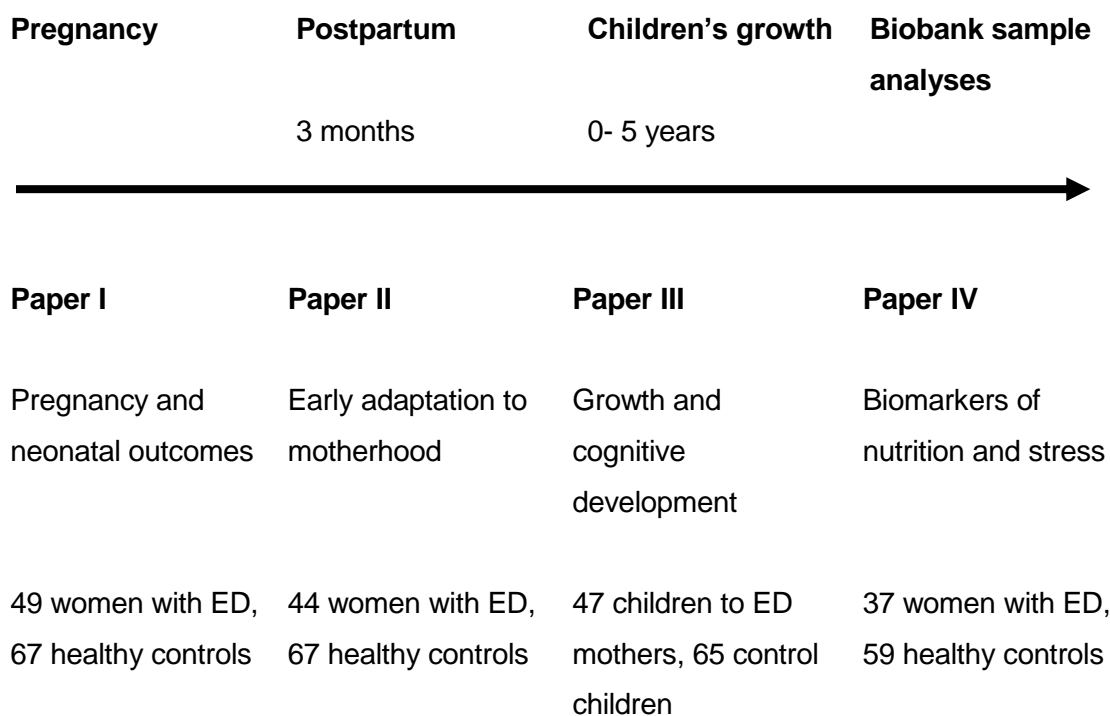
2.2 SPECIFIC AIMS

- To identify pregnancy complications in women with previous ED, and to describe neonatal outcomes (prematurity, SGA, and weight, height and head circumference at birth) as compared to healthy controls.

- To compare early adaptation to motherhood in mothers with a history of ED and control mothers.

- To describe growth pattern (weight, height from birth to five years of age and head circumference up to 18 months) and neurocognitive development up to five years of age in children of mothers with AN or BN before pregnancy compared to control children.

- To describe levels of biomarkers of nutrition and stress in early pregnancy of women with a previous history of AN or BN and controls and to relate these results to head circumference at birth and neurocognitive development at five years of age of the offspring.

3 MATERIALS AND METHODS

3.1 PROJECT DESIGN

This is a longitudinal cohort study, in which women with a history of ED and healthy controls were followed from about pregnancy week 10 to three months after delivery. Pregnancy course and neonatal outcome were evaluated, as well as early maternal adjustment. Furthermore, growth development in children to the same mothers with previous ED and control children was followed from birth up to five years of age and cognitive development was evaluated at five years of age. The outline of the project is illustrated below:

Pregnancy	Postpartum	Children's growth	Biobank sample analyses
	3 months	0- 5 years	

Paper I	Paper II	Paper III	Paper IV
Pregnancy and neonatal outcomes	Early adaptation to motherhood	Growth and cognitive development	Biomarkers of nutrition and stress
49 women with ED, 67 healthy controls	44 women with ED, 67 healthy controls	47 children to ED mothers, 65 control children	37 women with ED, 59 healthy controls

3.2 STUDY POPULATION OF WOMEN

The initial study population consisted of forty-nine women with a history of ED (24 AN, 20 BN, 5 EDNOS) and 67 controls. They were recruited in early pregnancy from 13 prenatal clinics in the northwest area of Stockholm in early pregnancy. They were all nonsmoking, nulliparous and had conceived spontaneously. As part of the first prenatal visit, pregnant women with a history of ED received oral and written information about the study and were invited to participate. Women who were willing to participate were interviewed by a trained midwife about previous and present ED

symptoms. These screening interviews were conducted between August 1997 and June 2001. The screening proceeded until 50 consecutive cases of pregnant women with a history of ED had been recruited. Another six screening-positive patients were not willing to participate further.

The screening-positive participants were interviewed again to confirm previous and present diagnoses of AN, BN and EDNOS according to the diagnostic criteria of DSM-IV. The preliminary diagnoses were confirmed in each case. Information about the course and duration of the disease and about past or current therapy for ED was also obtained and confirmed from medical records when available. Table I demonstrates types of lifetime ED among the women. The mean duration of ED was nine years (range 3-15 years) and the duration of recovery before study recruitment was 2 (0.5-14) (median and total range) years.

Table I. DSM-IV categories of life-time eating disorders before pregnancy

Main Diagnosis	N
Anorexia nervosa	24
Bulimia nervosa	20
Eating disorders not otherwise specified	5
Total	49

During the same time period, 68 controls were recruited from the same prenatal clinics by interview, using the same inclusion criteria as for the patients but without a history of ED. In each group of patients and controls there was one twin pregnancy diagnosed at the first ultrasound. These two pregnancies were excluded from the study. Thus, the final study population consisted of 49 women with a history of ED and 67 controls.

3.3 ETHICAL APPROVAL (I, II)

The research protocol was approved by the local Committee of Medical Ethics (97-058) including supplement 2000-09-04, and informed consent was obtained from all women.

3.4 PROCEDURE STUDY I

Pregnant women were assessed at weeks 10, 20, 25, 28, 31, 34, 36, and 40 of gestation according to routine prenatal care. Maternal measurements during pregnancy included weight, height, blood pressure, hemoglobin, and screening for gestational diabetes and preeclampsia. Apart from a screening ultrasound during weeks 16-18 of gestation, an extra ultrasound was performed during weeks 33-36 of gestation for measurement of fetal growth. Data on antenatal complications including hyperemesis, anemia (hemoglobin < 110 g/L), gestational hypertension, preeclampsia and gestational diabetes were collected from medical records. Gestational hypertension was defined as two or more antenatal systolic blood pressure readings of 140 mm Hg or more, or two or more antenatal diastolic readings of 90 mm Hg or more. Preeclampsia was diagnosed as blood pressure $\geq$ 140/90 in combination with proteinuria $\geq$ 0.3 g/24 hours. Gestational diabetes was diagnosed as plasma glucose > 12.2 mmol/l after oral glucose tolerance test. Obstetric complications including intrauterine growth retardation and preterm delivery (before 37 completed weeks of gestation) were also evaluated. Intrauterine growth retardation was based on the second ultrasound examination and defined as fetal growth less than 22% of fetal growth distribution of a Swedish reference population (Marsal et al., 1996). Data of mode of delivery and obstetric complications such as induction of labor, vacuum extraction, and use of forceps, caesarian delivery and postpartum bleeding were evaluated from the medical records.

Neonatal outcome parameters were also evaluated. The primary outcome variable was birth weight. Furthermore, data on length, head circumference, small for gestational age (SGA) and neonatal care were collected from medical records. SGA was defined as a birth weight less than two standard deviations of birth weight distribution of a Swedish reference population stratified by gender and gestational age at delivery (Persson & Weldner, 1986). Microcephaly was defined as less than two standard deviations of head circumference distribution of the same Swedish reference population.

3.5 PROCEDURE STUDY II

Three months after delivery, the same women as in study I were asked to participate in a questionnaire study about early maternal adjustment and mental health problems postpartum. The women with a history of EDNOS were not included in this study because of the small size of the subgroup. Thus, the study population consisted of 44

women with a history of ED and 67 controls. The questionnaire was sent by mail to the women to be completed at home and was then sent back to the responsible midwife.

3.5.1 Maternal adjustment and maternal attitude

The maternal adjustment and maternal attitude questionnaire (MAMA) is a 60-item self-report survey developed by Kumar et al. (1984). The complete questionnaire consists of five subscales: body image, somatic symptoms, marital relationships, attitudes to sex, and attitudes to pregnancy and the baby. In this study, we used a postnatal version of the latter subscale regarding maternal adjustment and attitudes to the baby. It consists of 12 items and uses a four-point scale from 1 = never/not at all to 4 = very often/very much during the last month (Table II). We have used the same Swedish version as used by Börjesson et al. (2005). The sum of scores was calculated for the whole subscale, range 12–48. Higher scores reflect lower levels of adjustment or more negative attitudes. There is no established cut-off point to distinguish between positive and negative maternal adjustment according to the MAMA questionnaire. We defined a less favorable adjustment to motherhood as a score of 3 or 4 in at least one of the 12 items.

Table II. The 12 items of the MAMA questionnaire

Item
1. Have you been worrying that you might not be a good mother?
2. Have you worried about hurting your baby?
3. Have you had enough time for yourself since you had the baby?
4. Have you regretted having the baby?
5. Have you felt proud of being a mother?
6. Have you been feeling happy that you have a baby?
7. Has the thought of having more children appealed to you?
8. Have you felt disappointed by motherhood?
9. Have you enjoyed caring for your baby's needs?
10. Have you been wondering whether your baby will be healthy and normal?
11. Has life been more difficult since the baby was born?
12. Have you enjoyed feeding your baby?

The test-retest reliability for the 12 items of the MAMA questionnaire was previously found to be satisfactory (0.84), as well as split-half reliability (0.73) (Kumar et al., 1984). We calculated Cronbach's alpha for the MAMA and found internal consistency to be satisfactory high (alpha = 0.86). Furthermore, comparisons with other interview findings and questionnaire data have provided good evidence for criterion validity (Kumar et al., 1984).

The patients were also asked if they had been in contact with the health services owing to depression or any other mental health problem during the first three months after delivery.

3.6 STUDY POPULATION OF CHILDREN

Growth and neurocognitive development of the children to the same mothers with previous ED and controls were followed up to five years of age. Two children born to mothers with a history of EDNOS were not included because one child died shortly after birth due to heart malformation and another child was lost to follow-up. One of the mothers in the control group was missed at follow-up and another mother in the same group declined to participate. Thus, the final study population comprised 47 children born to mothers with previous ED (24 AN, 20 BN, 3 EDNOS) and 65 control children.

3.7 ETHICAL APPROVAL (III)

The research protocol was approved by the local Committee of Medical Ethics (04-199/1), and informed consent was obtained from all mothers.

3.8   PROCEDURE STUDY III

3.8.1 Weight, height, head circumference

Data on weight and height at 3, 6, 12 and 18 months, and 3, 4 and 5 years of age were obtained from medical records at child health clinics, whereas data on head circumference was obtained from birth up to 18 months of age. The weight was recorded within 10 g, the height and head circumference (maximal fronto-occipital circumference) to the nearest mm. The weights, heights, BMIs and head circumferences were expressed as standard deviations below or above the mean of a large reference population of Swedish children used in the national pediatric health care for body growth monitoring (standard deviation score, SDS) (Albertsson Wikland et al., 2002). Measures of growth development were related to items in the subscale of the MAMA questionnaire.

3.8.2 Neurocognitive function

Neurocognitive function of the children was investigated at the age of five years by the use of a validated parent questionnaire, The Fife to Fifteen (FTF) (Kadesjö et al., 2004). This questionnaire was mailed and completed by the mothers. The complete questionnaire consists of 181 items on neurocognitive development divided into eight domains (motor skills, executive functions, perception, memory, language, learning, social skills, and emotional/behavioral problems) and their subdomains, but for children who are five years old the domain learning is not used. Table III shows the domains and subdomains used in the present study. The response alternatives to each statement were: 0 = "Does not apply", 1 = "Applies sometimes/to some extent" or 2 = "Definitely applies". Higher scores reflect difficulties in neurocognitive function, and scoring above the 90th percentile of a reference population was considered significant and clinically relevant.

The FTF has relatively high internal consistency (Cronbach´s alpha 0.69-0.94) and an acceptable to excellent inter-rater and test-retest reliability (Kadesjö et al., 2004). The clinical validity and utility of the FTF have been demonstrated (Korkman et al., 2004, Trillingsgard et al., 2004).

Table III. Domains and subdomains of neurocognititive function of the Five to Fifteen questionnaire

Domains	Items	Subdomains	Items
Motor skills	1-17	Gross motor skills	1-7
		Fine motor skills	8-17
Executive functions	18-42	Attention	18-26
		Hyperactive/impulsive	27-35
		Hypoactive	36-39
		Planning/organizing	40-42
Perception	43-60	Relation in space	43-47
Memory	61-71	Memory	61-71
Language	72-92	Comprehension	72-76
		Language skills	77-89
		Communication	90-92
Social skills	122-148	Social skills	122-148
Emotional/behavioral	149-181	Internalizing	149-154

3.9   PROCEDURE STUDY IV

A routine blood sample was collected during early pregnancy in connection with the first visit in about week ten of pregnancy at the prenatal clinic for screening of infections (hepatitis B, human immunodeficiency virus infection, syphilis, rubella) and blood typing. Remaining serum was stored at the biobank of Karolinska University Hospital. All women gave consent for the sample to be used for research purposes. Biobank samples from 37 women with a history of ED (20 AN, 17 BN) and 59 controls were available for analysis of biomarkers of nutrition (ferritin, thyroid-stimulating hormone (TSH), free thyroxine (T4), insulin, insulin-like growth factor I (IGF-I) and IGF binding protein 1 (IGFBP1) and stress (cortisol). Maternal serum levels of biomarkers were related to head circumference at birth and neurocognitive function at five years of age of the offspring.

3.10 ETHICAL APPROVAL (IV)

The research protocol was approved by the local Committee of Medical Ethics (2011/815-32) and the Karolinska biobank (BbK-00682).

3.11 ANALYTICAL METHODS OF SERUM BIOMARKERS

Serum levels of ferritin were analyzed by a routine chemiluminiscent assay at the Department of Clinical Chemistry, Karolinska University Hospital. The detection limit was 0.2 µg/L and the total coefficient of variation (CV) was 8.6%. Cortisol was analyzed using the instrument Modular E170/Cobas E (Roche Diagnostics, Mannheim, Germany). CVs for total cortisol were 3.1% at 284 nmol/L and 3.8% at 750 nmol/L. The assay measures both the free fraction and protein-bound cortisol. Serum levels of thyroid-stimulating hormone (TSH) and free thyroxine (fT4) were measured with enzyme immunoassays involving direct chemiluminescence, as described previously (Naessén et al., 2006). Insulin was analyzed using a magnetic bead-based metabolic hormone panel from Millipore, Billerica, MA, USA (Cat# HMHMAG-34K-06). The plate reader was a Luminex MagPix (Millipore) and the plate washer was a Tecan Hydroflex (Tecan, Männedorf, Switzerland) fitted with a magnetic holder. The inter- and intra-assay CVs were 12.5% and 8.3%. Following separation from IGFBPs by extraction with acidic ethanol and cryoprecipitation, IGF-I was determined by radioimmunoassay (RIA) utilizing des [1-3] IGF-I as the radio ligand to minimize interference from any IGFBPs that might have still been present (Bang et al., 1991). The concentrations of IGFBP1 in serum samples were determined by RIA according to Póvoa and co-workers (1984).

3.12 STATISTICS

Power calculation for the initial study population was based on birth weight as the primary outcome variable. We included 50 patients and 68 controls to detect a difference between groups of approximately 10% with 80% power. Characteristics of the participants were presented as mean and standard deviation (SD) or median and inter-quartile range. In comparisons between women with different types of ED and controls, one-way analysis of variance (ANOVA) followed by Fisher´s least significant difference test (LSD post-hoc test) (I, IV) was performed for continuous data and

Kruskal-Wallis test (II, III) followed by multiple comparisons between groups based on ranks for ordinal- or skewed distributed data. The p-values were then corrected according to the Bonferroni procedure. The Chi-square test and Fisher's exact test (I, II) were used for data measured on a nominal scale. In paper III, Mixed procedure with a random coefficient model was used to compare the subgroups of ED and controls regarding variables of growth development (measured as SD-scores) with adjustments for mother's BMI and the child's sex. Also in paper III, a general linear model was employed to compare the ED and controls regarding the growth at birth, 3, 6, 12, 18 months and 3, 4, and 5 years of age with adjustment for mother's BMI, the child's sex and the true age. Correlations were evaluated with Spearman rank correlation or Pearson's product moment correlation coefficient (III, IV). Forward stepwise multiple linear regression analysis (III) was performed to evaluate the association between growth development and different background variables. To assess the significance of the difference between two correlation coefficient (III) Fisher's Z-transformation was carried out. $P<0.05$ was considered to be statistically significant.

4 RESULTS

4.1 PREGNANCY CHARACTERISTICS OF PARTICIPANTS (I, II, III & IV)

Physical and pregnancy characteristics of the initial study population of 49 nulliparous non-smoking women with a history of ED (AN (n = 24), BN (n = 20) and EDNOS (n = 5)) and 67 healthy controls are shown in Table IV.

Body weight and BMI in week 10 of gestation were significantly lower in the ED mothers than the controls but maternal weight gain did not differ between groups. However, weight gain in the subgroup of AN was significantly lower than the control group (p <0.05). Women with a history of ED were at increased risk of hyperemesis and anemia (hemoglobin < 110 g/L) evaluated at gestational week 25. Furthermore, gestational hypertension/preeclampsia, intrauterine growth restriction and cesarean section tended to be more common among the ED women. Weeks of gestation and events of preterm delivery were not significantly different between groups.

Table IV. Physical and pregnancy characteristics in women with a history of ED and Controls

	ED mothers (n= 49)	Controls (n= 67)	Significance
Age (y)	29.3 ± 4.6	30.0 ± 3.7	
BMI (kg/m^2)	20.5 ± 3.0	22.3 ± 2.8	< 0.001
Maternal weight gain (kg)	11.3 ± 3.9	12.1 ± 2.6	
Hyperemesis (%)	33	9	< 0.01
Anemia (%)	49	12	< 0.001
Gestational hypertension/preeclampsia (%)	12	3	0.07
Intrauterine growth restriction (%)	8	0	0.07
Weeks of gestation	38.9 ± 1.8	39.2 ± 1.8	
Preterm delivery (%)	18	12	
Cesarean section (%)	26	13	0.07

Values are mean ± standard deviation or percentage

Eleven of the 49 patients (22%) had a verified relapse of ED during pregnancy. Of those, eight women were previously diagnosed with AN and three women had a history of BN and they relapsed to similar symptoms during pregnancy.

4.2 NEONATAL OUTCOMES (I)

Pregnant women with a history of ED delivered infants with significantly lower birth weight, whereas birth length was comparable to controls (Table V). The frequency of SGA was also significantly increased in infants of mothers with previous ED. When comparing subgroups of ED, birth weight was significantly lower only in the AN group but not in the BN group and there was no difference in length between groups (Figure 1). Furthermore, there were no differences between those with and without verified relapse of ED during pregnancy.

The main finding in this study was significantly smaller head circumference in children of mothers with a history of ED (Table V). Furthermore, the prevalence of microcephaly was 8% (2 AN, 1 BN, 1 EDNOS) in the same group of children but 0% in the control group. It is noteworthy that infants of both the anorectic and the bulimic subgroup had significantly smaller head circumference than controls although birth weight was lower only in the AN group (Figure 1).

Table V. Neonatal characteristics in offspring of mothers with a history of ED and Controls

	Offspring of ED mothers (n= 49)	Offspring of control mothers (n= 67)	Significance
Weight (g)	3233 ± 606	3516 ± 515	< 0.01
Length (cm)	49.6 ± 2.7	50.2 ± 2.4	
Head circumference (cm)	33.7 ± 1.4	35.2 ± 1.6	< 0.001
Small for gestational age (%)	12	1	< 0.05
Microcephaly (%)	8	0	< 0.05
Malformations (%)	2	0	

Values are mean ± standard deviation or percentage

Figure 1. Birth weight, length and head circumference in offspring of mothers with a history of AN or BN and Controls. Values are medians and inter-quartile ranges (P25 – P75). *p < 0.05, **p < 0.01 and ***p < 0.001 in comparison to controls.
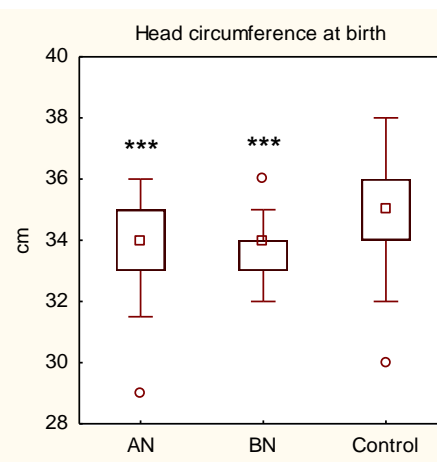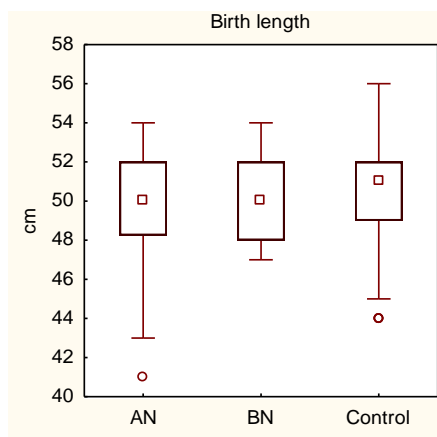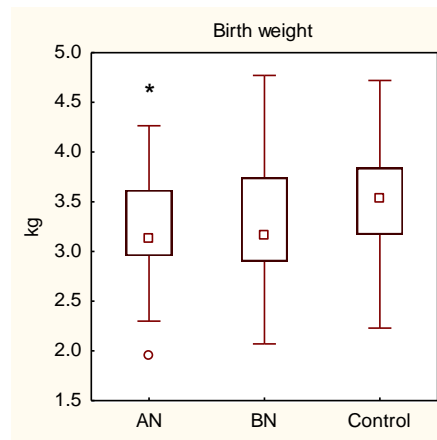
4.3   EARLY ADAPTATION TO MOTHERHOOD (II)

The response rate to the MAMA questionnaire of early maternal adjustment was 100%.
In this study, we found that 92% of the women with a history of AN or BN had a less
favorable early maternal adjustment, as estimated with the MAMA questionnaire, in
comparison to 13% in the control group (p < 0.001) (Figure 2). However, there were no
differences between the subgroups of ED and no differences between patients having
verified relapse during pregnancy compared to those not having this. Figure 2 shows
the prevalence of women with a less favorable maternal adjustment for each item of the
MAMA questionnaire.

Figure 2. The percentage of women in subgroups of ED and in the control group with
less favorable maternal adjustment (MAMA score ≥ 3) for each item of the
questionnaire. *p < 0.05, **p < 0.01 and ***p < 0.001 in comparison to controls.
Bonferroni adjustments for multiple comparisons were performed.
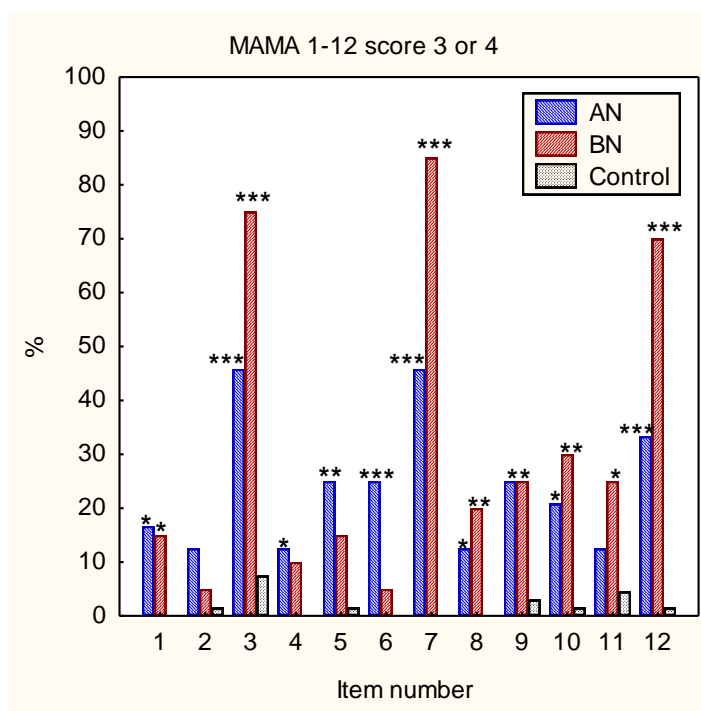
Item
1. Have you been worrying that you might not be a good mother?
2. Have you worried about hurting your baby?
3. Have you had enough time for yourself since you had the baby?
4. Have you regretted having the baby?
5. Have you felt proud of being a mother?
6. Have you been feeling happy that you have a baby?
7. Has the thought of having more children appealed to you?
8. Have you felt disappointed by motherhood?
9. Have you enjoyed caring for your baby's needs?
10. Have you been wondering whether your baby will be healthy and normal?
11. Has life been more difficult since the baby was born?
12. Have you enjoyed feeding your baby?

In 11 of the 12 MAMA items, at least one subgroup of ED had significantly higher mean score than the control group. The ED groups had the highest score for item 3 (Have you had enough time for yourself since you had the baby?), item 7 (Has the thought of having more children appealed to you?) and item12 (Have you enjoyed feeding your baby?). For item 7, the BN group responded with significantly higher score than the AN group ($p<0.05$).

Twenty-two mothers with ED (50%), of which five had a verified relapse of ED during pregnancy, had been in contact with health services because of depression or other mental health problems within three months after delivery, as compared to 10% in the control group ($p < 0.001$). There were no significant differences between subgroups of AN and BN (Figure 3).

Figure 3. The frequency of mental health problems postpartum in women with a history of AN or BN and controls. ***p < 0.001 in comparison to controls.

Mental problems postpartum
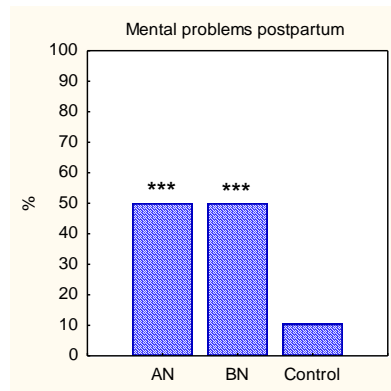
The ED women who had been in contact with health services postpartum due to mental problems had significantly higher MAMA score than patients not reporting such contact with the health services (p < 0.001). Figure 4 shows the percentage of women in subgroups of AN and BN and controls with a less favorable MAMA adjustment in three or more of the 12 items and who reported or did not report mental health problems postpartum. In the AN group, the percentage of women with a less favorable MAMA adjustment was significantly higher among those who reported mental problems postpartum (p<0.01).

Figure 4. The percentage of women in subgroups of ED and in the control group having a less favorable MAMA adjustment and who reported or did not report mental problems postpartum.

MAMA score 3 or 4 in three or more of the 12 items of the questionaire
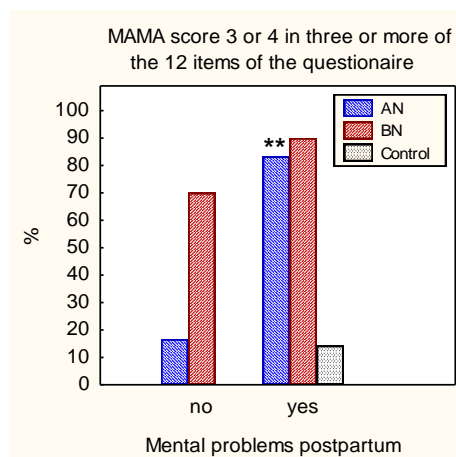
4.4 GROWTH DEVELOPMENT (III)

Children of mothers with a history of ED demonstrated an early catch-up in weight and BMI but head circumference continued to be delayed until at least 18 months of age. The mean weight and BMI at birth of the children of mothers with previous ED were significantly lower than in the control children (p < 0.05, respectively) although gestational age was similar between groups. However, from the age of three months there were no longer any differences in weight and BMI between groups. Figure 5 shows BMI in the infants of mothers with previous AN or BN and control children from birth to five years of age (p-values adjusted for the mother's BMI, the child's sex and the true age). BMI was lower at birth in both subgroups of infants born to mothers with AN or BN than controls but not at older ages. Similarly, the SDS of BMI in the AN group was significantly lower at birth (p < 0.05) but thereafter comparable to the controls, whereas the SDS of BMI in the BN group was comparable to controls at all time points.

Figure 5. BMI at birth to five years of age in subgroups of children born to mothers with AN or BN and control children. The values are means and 95% CI and the figures are adjusted for the mother's BMI, the child's sex and the true age.
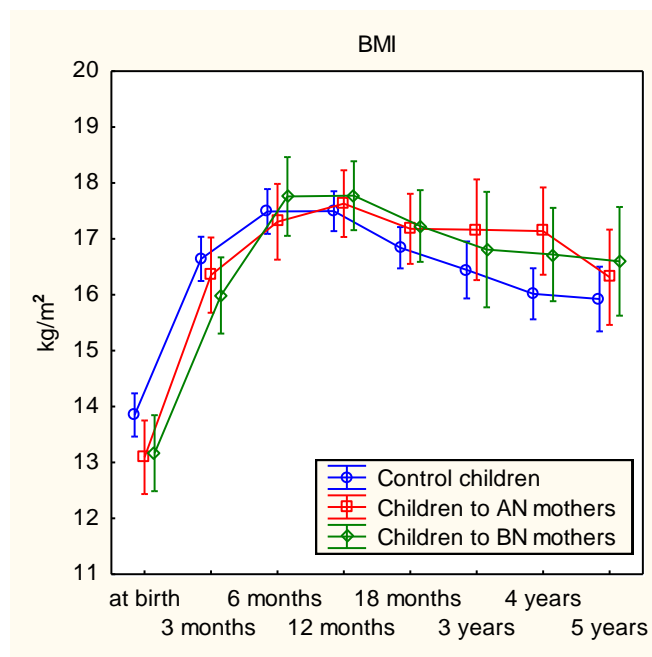
In contrast to BMI, head circumferences of the children born to mothers with ED were smaller throughout the observation period ($p < 0.01$- $p < 0.001$). Figure 6 shows head circumference in the infants of mothers with previous AN or BN and control children from birth to 18 months of age (p-values adjusted for the mother's BMI, the child's sex and the true age). Head circumference was significantly lower for both subgroups of ED compared to controls ($p < 0.05$-0.001, respectively). Furthermore, the SDS for head circumference was significantly lower over time in both the AN group and the BN group ($p < 0.001$, respectively).

Dysfunctional answers to MAMA question 1 (Have you been worrying that you might not be a good mother?) correlated with an impaired increase in head circumference development ($p < 0.01$). This factor together with head circumference at birth and sex of the child explained 53% of the variance (R^2) in head circumference development ($p < 0.001$).

Figure 6. Head circumference at birth to 18 months of age in subgroups of children born to mothers with AN or BN and control children. The values are means and 95% CI and the figures are adjusted for the mother's BMI, the child's sex and the true age.

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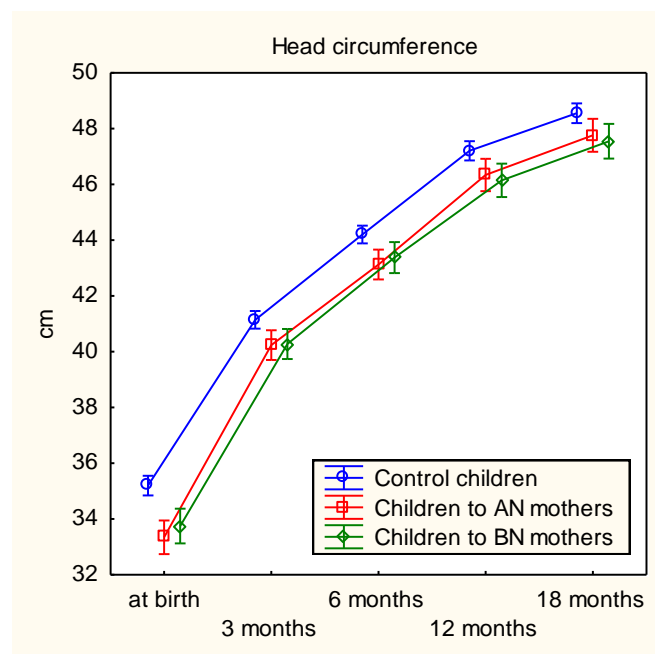
4.5   NEUROCOGNITIVE FUNCTION (III)

The response rate to the FTF questionnaire of neurocognitive function was 96%. Children of mothers with ED had significantly higher mean raw scores of cognitive abilities (impaired function) for all domains ($p < 0.05 - p < 0.001$) except for perception ($p = 0.10$) and emotional problems ($p = 0.07$) than controls. There were no significant differences in mean domain raw scores for children of mothers with a history of AN and BN. Forty-one percent of children of mothers with ED and 11% control children had a domain mean score above the 90th percentile in one or more domains ($p < 0.0001$). Figure 7 shows the percentage of children of mothers with AN or BN and controls with impaired neurocognitive development at five years of age in different domains of the FTF questionnaire. The percentage of children of mothers with AN and BN with impaired function was significantly increased for motor skills and language skills, and the BN group also for memory function compared to controls (Figure 7).

Figure 7. Percentage of children of mothers with AN, BN and controls with impaired neurocognitive development (score above the 90th centile) in different domains of the FTF questionnaire. Bonferroni adjustments for multiple comparisons were performed.
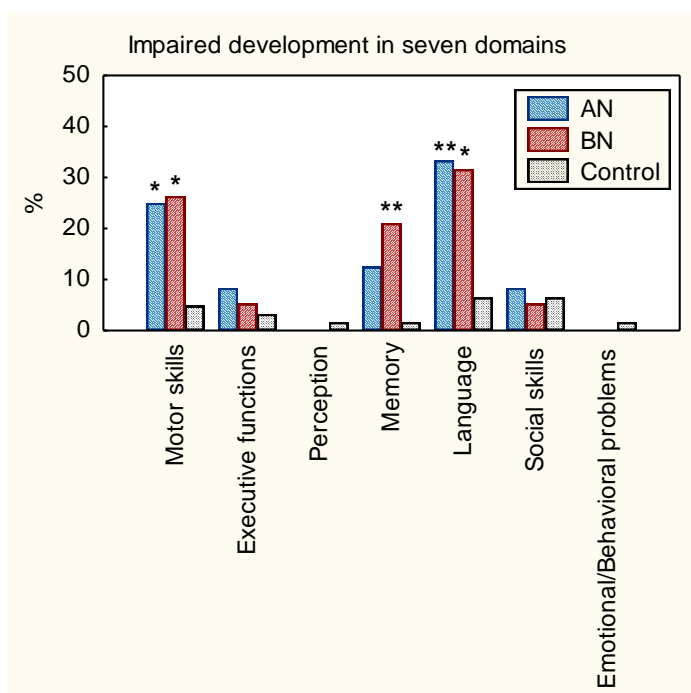
In the children of mothers with ED, head circumference at birth correlated significantly with language skills ($r_s = 0.32$, $p < 0.05$). In children to mothers with a history of BN, head circumference at birth also correlated with planning/organising ($r_s = 0.64$, $p < 0.01$) and social skills ($r_s = 0.51$, $p < 0.05$). Similar correlations were not found in the AN group or the control group.

4.6   BIOMARKERS OF NUTRITION AND STRESS (IV)

Maternal serum biomarkers of nutrition (ferritin, TSH, T4, insulin, IGF-I and IGFBP1) and stress (cortisol) were determined in early pregnancy of the women with a previous history of AN or BN and controls. We found significantly lower serum levels of ferritin in women with previous AN ($p < 0.05$), but not in those with previous BN, compared to the controls (Figure 8). Only in the combined material of patients and controls, there was a positive correlation between serum ferritin and head circumference at birth of the offspring ($r_s = 0.21$, $p < 0.05$). Furthermore, serum ferritin in the mothers with a history of AN was significantly associated with memory impairment of the offspring at five years of age ($r_s = -0.70$, $p < 0.001$) (Figure 9). Similar association was not found in those with a history of BN ($r_s = 0.17$, $p = 0.52$) and controls ($r_s = -0.23$, $p = 0.11$).

There were no significant differences between the groups in the other biomarkers investigated, including cortisol. However, maternal serum levels of free T4 were positively associated with head circumference of the children in the BN group ($r_p = 0.48$, $p < 0.05$) with the same tendency in the AN group ($r_p = 0.42$, $p = 0.07$) but not in the controls ($r_p = 0.006$).

Figure 8. Serum levels of ferritin in pregnant women with a history of AN or BN and controls. The dashed line indicates the normal lower range for pregnant women. Values are medians and inter-quartile ranges (P25 – P75). **p < 0.01 in comparison to controls.
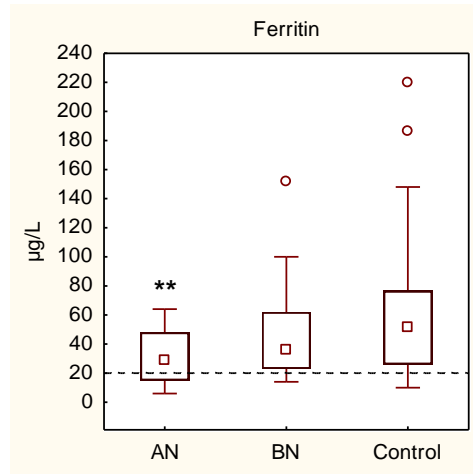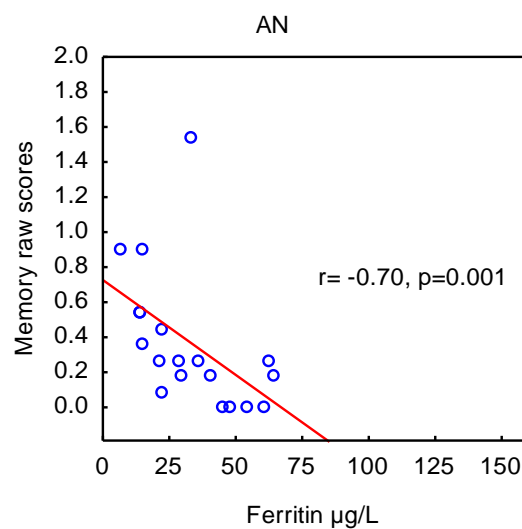

Figure 9. Correlation between maternal serum levels of ferritin and raw scores of memory function (higher scores reflect impaired function) in the group of mothers with a history of AN.

5   DISCUSSION

5.1   PREGNANCY AND NEONATAL OUTCOMES

In this longitudinal cohort study (I) we demonstrated an increased rate of SGA and significantly lower birth weight in infants of nulliparous, nonsmoking women with a history of ED compared to healthy controls from the same living area, whereas birth length of the offspring was comparable between groups. When comparing the subgroups of EDs, we found that only the women with a history of AN had lower maternal weight gain and delivered infants with significantly lower birth weight than the controls.

These results are in agreement with the majority of published studies at the time (Lacey & Smith, 1987; Stewart et al., 1987; Treasure & Russel, 1988; Conti et al., 1998; Bulik et al., 1999; Franko et al., 2001; Petersen Sollid et al., 2004), although a few reports suggested that pregnancy outcome was not affected by ED (Willis & Rand, 1988; Lemberg & Phillips, 1989). However, most of the studies were retrospective (Stewart et al., 1987; Conti et al., 1998 Bulik et al., 1999), or small follow-up studies without a control group (Lacey & Smith, 1987; Treasure & Russel, 1988; Franko et al., 2001). One exception was a large Danish register-based study, demonstrating a doubled risk of both SGA and low birth weight in children of mothers with a history of EDs compared to control women (Petersen Sollid et al., 2004). Later on, a Swedish register study also reported lower birth weight in newborns of women with a history of AN (Ekéus et al 2006). However, in the Norwegian Mother and Child Cohort Study it was demonstrated that women with a previous diagnosis of BED delivered babies with higher birth weight, lower risk of SGA and higher risk of large for gestational age (Bulik et al 2009). In our study, we had no woman with a history of BED.

5.1.1 Head circumference

A new finding in our study was smaller head circumference at birth and increased frequency of microcephaly in children of mothers with a history of ED. Similar data have never been reported before. The frequency of microcephaly of 8% in the ED group is considered high in comparison with 2.5% in the general population, using the same definition of microcephaly as in our study (Vargus et al 2001). Importantly, head circumference was significantly smaller in infants of both the AN and the BN

subgroups, although only the infants of the anorectic subgroup had lower birth weight than the offspring of controls.

The mechanisms for lower birth weight and smaller head circumference in infants of mothers with a history of ED are not known. Gestational hypertension/preeclampsia and intrauterine growth restriction tended to be more common in the ED mothers than the controls. Whether these results also imply placental insufficiency in the ED group remain to be elucidated. Unfortunately, we have no information on placental tissues in our material. However, maternal smoking, as a well-known contributor to growth restriction, was excluded in this study.

We hypothesized that nutritional deficiency and/or stress in the pregnant women with previous ED might be underlying causes for impaired neonatal outcomes. Low maternal BMI, reduced weight gain and high frequency of anemia among the pregnant women with previous AN clearly indicate nutritional deficiency in this subgroup. In contrast, the women in the BN group had BMI and pregnancy characteristics similar to the control group. This discrepancy between the subgroups might reflect different underlying mechanisms behind decreased head circumference in the infants.

There is evidence that maternal stressors could influence fetal growth and brain development (Singh et al., 2012). Thus, fetal exposure to increased endogenous cortisol levels as a consequence of maternal stress has been associated with low birth weight and impaired mental and motor development in the infant (Buitelaar et al 2003, Singh et al., 2012). Animal studies have furthermore shown that prenatal exposure to synthetic glucocorticoids can have deleterious effects on brain development, including the hippocampus, as well as adverse behavioral and learning effects (Uno et al., 1994; Rodriguez et al., 2011). It has previously been demonstrated that ED is associated with elevated stress hormones including cortisol (Monteleone et al., 2001; Naessén et al 2006). Moreover, poor maternal nutrition decreases placental activity of 11ß-hydroxysteroid dehydrogenase type 2, thereby enhancing maternal cortisol production (Seckl et al., 2007). Hypothetically, maternal hypercortisolism in ED women could have an adverse on fetal brain development.

5.2 MATERNAL BIOMARKERS OF NUTRITION AND STRESS

In order to explore possible mechanisms of impaired growth and head development in infants of mothers with a previous history of AN or BN, we investigated maternal serum biomarkers of nutrition and stress in these women and compared to controls (IV). In blood samples collected in early pregnancy and stored at the Karolinska biobank, we analyzed serum levels of ferritin, cortisol, TSH, free T4, insulin, IGF-I and IGFBP1and related to head circumference at birth and neurocognitive function at five years of age of the offspring.

5.2.1 Ferritin

In comparison to controls, we found significantly lower serum levels of maternal ferritin in women with a history of AN, but not in the BN group. This is in agreement with the highest frequency of anemia in the AN group (70%). In the combined group of patients and controls, there was a week positive association between maternal serum ferritin and head circumference at birth of the offspring. Furthermore, maternal serum ferritin correlated strongly with impaired memory of the offspring at five years of age in the AN group but not in the BN group or the controls.

Iron is essential for normal fetal development including the brain and cognitive abilities of the infant, whereas iron deficiency during pregnancy is associated with increased risk of preterm birth and low birth weight (Milman, 2012). Other studies have also found associations between both low and high maternal levels of ferritin and preterm birth, preeclampsia and intrauterine growth restriction (Tamura et al., 1996; Hou et al., 2000; Scholl, 2005; Soubasi et al., 2010). Serum ferritin is considered an indicator of iron stores and low levels diagnostic of iron deficiency. However, high levels of ferritin, particularly during the third trimester, may be secondary to acute-phase reaction in response to an acute or chronic infection (Tamura et al., 1996; Hou et al., 2000). This could explain the diverse associations between maternal ferritin and pregnancy complications.

Our results suggest that maternal iron deficiency in the mothers with a history of AN may negatively affect neurocognitive development of the infant. The same association was not found in the BN group and there seem to be different mechanisms for impaired head growth and neurocognitive development in children of mothers with a history of AN and BN.

5.2.2 Cortisol and thyroid hormones

The other analyzed biomarkers, including cortisol, were comparable between the groups. Although both AN and BN are known to be associated with increased circulating levels of stress hormones like cortisol (Monteleone et al., 2001; Naessén et al 2006), there are no previous reports on serum cortisol in pregnant women with a history of ED. Thus, our data do not support the hypothesis of a link between maternal hypercortisolism in the ED women and reduced head circumference of the offspring.

There is evidence that maternal thyroid hormone function is of great importance for neurocognitive development of the offspring (Haddow et al., 1999; Henrichs et al., 2010; Li et al., 2010). There were no differences in serum levels of thyroid hormones between groups but we found clear positive correlations between maternal serum levels of free T4 and head circumference at birth in both subgroups of AN and BN but not in the controls. These results support a role of maternal thyroid hormones in neurocognitive development of the fetus.

There are several limitations with the present study and the results should therefore be interpreted with caution. Serum biomarkers were determined only at one occasion in early pregnancy and there was no repeated blood sampling throughout pregnancy. Our results may therefore not be representative for the course of pregnancy. Furthermore, the blood sampling was not standardized according to time of the day and food intake. The sample size was also limited since not all blood samples of the cohort were available.

5.3   EARLY ADAPTATION TO MOTHERHOOD

Three months postpartum we investigated early adaptation to motherhood in our mothers with a history of ED and control mothers using the validated MAMA questionnaire (II). The main finding was that 92% of the women with a history of AN or BN had impaired adjustment to motherhood compared to 13% of the controls.

Hardly anything is known from previous studies about the early relationship between mother and baby and bonding in women with a history of ED, a part from studies related to problems with infant feeding. Our results, based on self-reported data, indicate a high risk for a general impairment of early maternal adjustment in mothers

with previous ED. In average, they reported a score of less favourable adjustment in more than three of the 12 MAMA items. For instance, they perceive they have no longer enough time for themselves and the thought of having more children is not an appealing one. In 11 of the 12 items, at least one subgroup of ED had significantly higher mean score than the controls. There were no differences between subgroups of ED or between those having verified relapse of ED during pregnancy or not.

Several studies have described feeding related problems in women with ED, starting with breast-feeding and continued during infancy (Lacey & Smith, 1987; Evans & Grange, 1995; Russel et al., 1998; Waugh & Bulik, 1999; Agras et al., 1999; Stein et al., 2001). However, these older studies have been limited by small sample sizes. Recently, a large longitudinal population-based study demonstrated that past and active ED during pregnancy increases the risk for infant feeding difficulties via maternal distress (Micali et al., 2011). Furthermore, the prospective Norwegian Mother and Child Cohort Study showed that mothers with BN and BED were more likely to report restrictive feeding styles and infant problems when their child was 36 months old than mothers without ED (Reba-Harrelson et al., 2010). In agreement, we found that 70% in the BN group and 33% in the AN group compared to 1% in the control group reported dysfunctional answer to MAMA item 12: Have you enjoyed feeding your baby?

5.3.1 Mental health problems

We also demonstrated that 50% of the mothers with previous ED, as compared to 10% in the control group, had been in contact with health services because of depression or other mental health problems postpartum. These results are in line with several previous reports showing increased risk of postpartum depression in women with lifetime ED (Franko et al., 2001; Morgan et al., 2006; Mazzeo et al., 2006). In the study by Mazzeo and co-workers (2006), women with a history of BN and BED had the highest prevalence and three times the risk of postpartum depression than women without ED. In our study, there was no difference in frequency between the subgroups of AN and BN.

It is obvious that women with a history of ED constitute a risk group for postpartum mental health problems including depression. It is therefore of great importance to identify these women as early as possible during pregnancy in order to give them

extra support and hopefully preventing the risk for mental illness and obstetric complications.

5.4 GROWTH AND NEUROCOGNITIVE DEVELOPMENT IN THE OFFSPRING

5.4.1 Growth development

In a follow-up study of the children born to mothers with a history of ED (III), we characterized data on weight, height and BMI until five years of age and of head circumference up to 18 months of age and compared to control children. Furthermore, neurocognitive function was assessed at the age of five years and related to head growth. We were first to report retarded head growth throughout the observation period despite an early catch-up in BMI in children of mothers with previous ED. Moreover, reduced head circumference was related to delayed neurocognitive development in the same children.

Significantly lower birth weight and BMI in the children of mothers with a previous history of ED were normalized already after three months. These results confirm previous reports (Treasure & Russell, 1988; Waugh & Bulik, 1999). In contrast, mean levels and SDS of head circumference (adjusted for the mother's BMI, the child's sex and the true age) were reduced up to at least 18 months of age in infants of both subgroups of mothers with AN or BN. Children who displayed the most pronounced delays in head growth were offspring of mothers who worried much about not being a good mother (MAMA item 1).

Retarded head growth may be associated with impaired brain development. Our hypothesis is that nutritional deficiency and/or stress during pregnancy could be the underlying mechanisms. Poor fetal nutrition may impact on brain development and the risk of neuropsychiatric disease. The Chinese and Dutch famines have provided evidence in support of this theory (Altschuler, 2005; Kyle & Pitcherd, 2006; Penner & Brown, 2007). Furthermore, fetal growth may reflect maternal food intake, which is probably true for the AN subgroup. In this group, women were characterized by a low weight gain during pregnancy, high frequency of anemia and low levels of ferritin indicating nutritional deficiency. They delivered infants with both a low weight and a small head circumference.

In contrast, the infants born to mothers with BN had a normal birth weight, but a decreased head circumference. As pointed out earlier, this discrepancy between the subgroups might reflect different underlying causes behind delayed head growth. We suggested previously that fetal exposure to elevated levels of neuroactive steroids including cortisol, as a consequence of higher maternal stress, could affect brain development. However, our recent results of maternal serum biomarkers of nutrition and stress could not support this hypothesis since maternal levels of cortisol were comparable between the ED groups and the controls.

An alternative factor of importance may be anxiety in the mothers since their answers to MAMA item 1 (Have you been worrying that you might not be a good mother?) correlated with delayed head growth in the offspring. It has furthermore been demonstrated that high levels of anxiety in pregnancy and postpartum are associated with active ED symptoms in pregnancy (Micali et al., 2009). However, the potential mechanism for how maternal anxiety might influence fetal growth remains to be elucidated.

5.4.2 Neurocognitive function

Neurocognitive development in the children was studied at the age of five years by the validated parent questionnaire FTF (III). The children of mothers with ED had higher mean raw scores (lower neurocognitive function) for motor skills, executive functions, memory, language skills and social skills than the control children. Forty-one percent of the children of mothers with ED and 11% of the control children had a score above the 90th percentile of a large national reference population in at least one domain, which is considered clinically significant. There were no significant differences in FTF scores between the ED subgroups, and both the AN and BN subgroups had scores reflecting difficulties in motor skills and language skills.

Reduced head circumference at birth correlated significantly with impaired language skills in the children of mothers with ED. These results indicate that reduced head growth may be of importance for neurocognitive development in children born to mothers with ED. Furthermore, low maternal serum ferritin in mothers with a history of AN, but not in those with BN, correlated with impaired memory function in the offspring, suggesting that deficient iron stores in the AN mothers may negatively affect neurocognitive development of the infant.

5.5   CLINICAL CONSIDERATIONS

Our results indicate that pregnant women with ED should be considered a risk group for serious health consequences, obstetric complications and impaired neonatal outcome. Health care needs to improve its methods to identify these women and optimize care in order to prevent adverse health effects for the mother and her baby. The father should also be involved in the support. In maternal care, there is a great need for increased knowledge about the role of ED for pregnancy, neonatal outcome and the child's development, and the way women at risk should be treated.

A systematic use of screening for ED history early in pregnancy followed by an offer for a support program for identified pregnant women with ED history should probably reduce some of their stress and decrease the incidence rates of obstetric and neonatal complications. Motherhood could be a moment of opportunity since many women are motivated to make changes for the sake of their children.

After parturition, attention should be paid to symptoms of depression in the mother and breastfeeding problems. Assessment of parenting skills early after delivery followed by appropriate interventions should improve coping strategies and the parent-child relationship, increase self-esteem and reduce feeling of inadequacy. On the long term, these interventions might reduce the risk for psychological disturbances in the children of mothers with a history of ED.

5.6   A CRITICAL EVALUATION

The present longitudinal cohort study has a number of significant strengths, such as an area-based sampling of the ED and control mothers to enhance generalizability; only nulliparous women and non-smokers were included; the diagnosis of ED was based on interviews; a longitudinal design; the period of the observation was prolonged and included repeated monitoring; there was no attrition up to 18 months of age of the children and little even up to 5 years of age. However, the sample size was limited; there was sparse information on breast-feeding and eventual feeding problems; and also a lack of information about a possible paternal influence. Furthermore, we have no data on head circumference of the parents. The MAMA questionnaire is based on self-reported data and the FTF profiles were based on parent information of the mothers. Although the FTF test has demonstrated high inter-rater and test-retest reliability and

validity, we cannot exclude reporter bias due to the possibility of worries and feelings of guilt in the mothers with a history of ED.

6 GENERAL CONCLUSIONS

- This longitudinal cohort study demonstrates that nulliparous nonsmoking pregnant women with past or active ED are at increased risk of hyperemesis and delivering infants with SGA and lower birth weight compared to healthy controls from the same living area. A new finding was also a significantly smaller head circumference and increased occurrence of microcephaly in children of mothers with a history of AN or BN. The proposed mechanisms behind these findings are deficient nutrient supply to the fetus and/or stress in the pregnant women.

- Early adaptation to motherhood was clearly impaired and related to mental health problems postpartum in mothers with ED before pregnancy. Over 90% of nulliparous mothers with a history of AN or BN, compared to 13% of the controls, reported problems regarding their maternal adjustment and parenting during the first three months after delivery. Furthermore, 50% of the mothers with previous ED, as compared to 10% in the control group, had been in contact with health services because of depression or other mental problems. It should be notified that women with a history of ED are at increased risk for postpartum mental health problems indicating a strong need for support.

- Children of mothers with a previous history of ED demonstrate an early catch-up in BMI from a decreased value at birth, but the head growth of children born to mothers with either AN or BN was retarded up to at least 18 months of age. Maternal stress and prenatal nutritional deficiency are possible causes of this delayed head growth. Our results also indicate that reduced head growth may be of importance for neurocognitive development in children born to mothers with ED who perceived difficulties in expressive language skills and social skills. Clinicians should be aware of the potential influence of maternal ED on head growth of the offspring to prevent later negative outcomes.

- Low maternal serum ferritin in the AN group, but not in the BN group, seems to be of importance for the development of impaired memory capacity in the offspring at five years of age. Furthermore, the positive association between serum free T4 in pregnant mothers with previous ED and head circumference of the offspring

suggests that maternal thyroid hormone function also is important for fetal brain development. However, our study did not demonstrate maternal hypercortisolism in the mothers with previous ED. Therefore, these results give no support for our hypothesis of a link between high maternal serum cortisol, as a consequence of stress in the mothers with ED, and a reduced head circumference in the offspring.

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8 REFERENCES

Aaltonen, T., Adelman, J., Akimoto, T., Albrow, M. G., Alvarez Gonzalez, B., Amerio, S., Collaboration, C. D. F., 2008. Measurement of the single-top-quark production cross section at CDF. *Phys Rev Lett, 101,* 252-300.

Abrams BF, Laros RK Jr., 1986. Prepregnancy weight, weight gain, and birth weight. *Am J Obstet Gynecol,* 154, 503-509.

Agras S, Hammer L, McNicholas F., 1999. A prospective study of the influence of eating-disordered mothers on their children. *Int J Eat Disord*, 25, 253–262.

Ahren-Moonga, J., Silverwood, R., Klinteberg, B. A., & Koupil, I., 2009. Association of higher parental and grandparental education and higher school grades with risk of hospitalization for eating disorders in females: the Uppsala birth cohort multigenerational study. *Am J Epidemiol, 170*, 566-575.

Albertsson Wikland K, Luo ZC, Niklasson A, Karlberg J., 2002. Swedish population-based longitudinal reference values from birth to 18 years of age for height, weight and head circumference. *Acta Paediatr*, 91, 739–754.

American Psychiatric Association (APA), 1994., Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM-IV). Washington DC: *American Psychiatric Association.*

Anderluh, M., Tchanturia, K., Rabe-Hesketh, S., Collier, D., & Treasure, J., 2009. Lifetime course of eating disorders: design and validity testing of a new strategy to define the eating disorders phenotype. *Psychol Med, 39*, 105-114.

Arcelus, J., Mitchell, A. J., Wales, J., & Nielsen, S., 2011. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. *Arch Gen Psychiatry, 68*, 724-731.

Bailer, U. F., Price, J. C., Meltzer, C. C., Mathis, C. A., Frank, G. K., Weissfeld, L., Kaye, W. H., 2004. Altered 5-HT(2A) receptor binding after recovery from bulimia-type anorexia nervosa: relationships to harm avoidance and drive for thinness. *Neuropsychopharmacology, 29*, 1143-1155.

Bang, P., Eriksson, U., Sara, V., Wivall, I,L,, Hall, K., 1991. Comparison of acid ethanol extraction and acid gel filtration prior to IGF-I and IGF-II radioimmunoassays: improvement of determinations in acid ethanol extracts by the use of truncated IGF-I as radioligand. *Acta Endocrinol*, 124, 620-629.

Barbarich, N. C., Kaye, W. H., & Jimerson, D., 2003. Neurotransmitter and imaging studies in anorexia nervosa: new targets for treatment. *Curr Drug Targets CNS Neurol Disord, 2*, 61-72.

Bentley, K. J., Walsh, J., & Farmer, R. L., 2005. Social work roles and activities regarding psychiatric medication: results of a national survey. *Soc Work, 50*, 295-303.

Blais, M. A., Becker, A. E., Burwell, R. A., Flores, A. T., Nussbaum, K. M., Greenwood, D. N., Herzog, D. B., 2000. Pregnancy: outcome and impact on symptomatology in a cohort of eating-disordered women. *Int J Eat Disord, 27*, 140-149.

Brambilla, F., 2001. Social stress in anorexia nervosa: a review of immuno-endocrine relationships. *Physiol Behav, 73*, 365-369.

Braun, D. L., Sunday, S. R., & Halmi, K. A., 1994. Psychiatric comorbidity in patients with eating disorders. *Psychol Med, 24*, 859-867.

Brewerton, T. D., Lydiard, R. B., Herzog, D. B., Brotman, A. W., O'Neil, P. M., & Ballenger, J. C., 1995. Comorbidity of axis I psychiatric disorders in bulimia nervosa. *J Clin Psychiatry, 56*, 77-80.

Brinch, M., Isager, T., & Tolstrup, K., 1988. Anorexia nervosa and motherhood: reproduction pattern and mothering behavior of 50 women. *Acta Psychiatr Scand, 77*, 611-617.

Bulik, C. M., Sullivan, P. F., & Kendler, K. S., 1998. Heritability of binge-eating and broadly defined bulimia nervosa. *Biol Psychiatry, 44*, 1210-1218.

Bulik, C. M., Sullivan, P. F., Fear, J. L., Pickering, A., Dawn, A., & McCullin, M., 1999. Fertility and reproduction in women with anorexia nervosa: a controlled study. *J Clin Psychiatry, 60*, 130-135.

Bulik CM, Reichborn-Kjennerud T., 2003. Medical morbidity in binge eating disorders. *Int J Eat Disord*, 37, S39-46.

Bulik, C. M., Sullivan, P. F., Tozzi, F., Furberg, H., Lichtenstein, P., & Pedersen, N. L., 2006. Prevalence, heritability, and prospective risk factors for anorexia nervosa. *Arch Gen Psychiatry, 63*, 305-312.

Bulik, C. M., Berkman, N. D., Brownley, K. A., Sedway, J. A., & Lohr, K. N., 2007. Anorexia nervosa treatment: a systematic review of randomized controlled trials. *Int J Eat Disord, 40*, 310-320.

Bulik, C. M., Von Holle, A., Hamer, R., Knoph Berg, C., Torgersen, L., Magnus, P., Reichborn-Kjennerud, T., 2007. Patterns of remission, continuation and

incidence of broadly defined eating disorders during early pregnancy in the Norwegian Mother and Child Cohort Study (MoBa). *Psychol Med, 37*, 1109-1118.

Bulik, C. M., Baucom, D. H., & Kirby, J. S., 2012. Treating Anorexia Nervosa in the Couple Context. *J Cogn Psychother, 26*, 19-33.

Börjesson K, Ruppert S, Wager J, Bågedahl-Strindlund M. 2007. Personality disorder, psychiatric symptoms and experience of childbirth among childbearing women in Sweden. *Midwifery*, 23, 260-268.

Carter, F. A., McIntosh, V. V., Joyce, P. R., Frampton, C. M., & Bulik, C. M., 2003. Bulimia nervosa, childbirth, and psychopathology. *J Psychosom Res, 55*, 357-361.

Chan, J. L., & Mantzoros, C. S., 2005. Role of leptin in energy-deprivation states: normal human physiology and clinical implications for hypothalamic amenorrhoea and anorexia nervosa. *Lancet, 366*, 74-85.

Cnattingius, S., Hultman, C. M., Dahl, M., & Sparen, P., 1999. Very preterm birth, birth trauma, and the risk of anorexia nervosa among girls. *Arch Gen Psychiatry, 56*, 634-638.

Conti J, Abraham S, Taylor A., 1998. Eating behavior and pregnancy outcome. *J Psychosom*, 44, 465-477.

Currin, L., Schmidt, U., Treasure, J., & Jick, H., 2005. Time trends in eating disorder incidence. *Br J Psychiatry, 186*, 132-135.

Dadds, M. R., Stein, R. E., & Silver, E. J., 1995. The role of maternal psychological adjustment in the measurement of children's functional status. *J Pediatr Psychol, 20*, 527-544.

De Weerth, C., van Hees, Y., & Buitelaar, J. K., 2003. Prenatal maternal cortisol levels and infant behavior during the first 5 months. *Early Hum Dev, 74,* 139-151.

Drewnowski, A., Halmi, K. A., Pierce, B., Gibbs, J., & Smith, G. P., 1987. Taste and eating disorders. *Am J Clin Nutr*, 46, 442-450.

Easter, A., Treasure, J., & Micali, N., 2011. Fertility and prenatal attitudes towards pregnancy in women with eating disorders: results from the Avon Longitudinal Study of Parents and Children. *BJOG, 118*, 1491-1498.

Edelstein CK, King BH. Pregnancy and eating disorders. In: Yager J, Gwirtsman HE, eds., 1992. Special problems in managing eating disorders. Clinical practice No. 20. Washington, DC: *American Psychiatric Association*, 163, pg. 181.

Ekeus, C., Lindberg, L., Lindblad, F., & Hjern, A., 2006. Birth outcomes and pregnancy complications in women with a history of anorexia nervosa. *BJOG*, 113, 925-929.

Evans, J., & le Grange, D., 1995. Body size and parenting in eating disorders: a comparative study of the attitudes of mothers towards their children. *Int J Eat Disord, 18*, 39-48.

Fassino, S., Piero, A., Gramaglia, C., & Abbate-Daga, G., 2004. Clinical, psychopathological and personality correlates of interoceptive awareness in anorexia nervosa, bulimia nervosa and obesity. *Psychopathology, 37*, 168-174.

Favaro, A., Ferrara, S., & Santonastaso, P., 2003. The spectrum of eating disorders in young women: a prevalence study in a general population sample. *Psychosom Med, 65*, 701-708.

Fichter, M. M., & Quadflieg, N., 1997. Six-year course of bulimia nervosa. *Int J Eat Disord, 22*, 361-384.

Fitelson, E., Kim, S., Baker, A. S., & Leight, K., 2010. Treatment of postpartum depression: clinical, psychological and pharmacological options. *Int J Womens Health, 3*, 1-14.

Frank, G. K., Bailer, U. F., Henry, S., Wagner, A., & Kaye, W. H., 2004. Neuroimaging studies in eating disorders. *CNS Spectr, 9*, 539-548.

Franko, D. L., Blais, M. A., Becker, A. E., Delinsky, S. S., Greenwood, D. N., Flores, A. T., Herzog, D. B., 2001. Pregnancy complications and neonatal outcomes in women with eating disorders. *Am J Psychiatry*, 158, 1461-1466.

Gao, Y., Mengana, Y., Cruz, Y. R., Munoz, A., Teste, I. S., Garcia, J. D., Zhang, C., 2011. Different expression patterns of Ngb and EPOR in the cerebral cortex and hippocampus revealed distinctive therapeutic effects of intranasal delivery of Neuro-EPO for ischemic insults to the gerbil brain. *J Histochem Cytochem*, 59, 214-227.

Gendall, K. A., Sullivan, P. F., Joyce, P. R., & Bulik, C. M., 1997. Food cravings in women with a history of anorexia nervosa. *Int J Eat Disord, 22*, 403-409.

Gendall KA, Bulik CM, Joyce PR, McIntosh VV, Carter FA., 2000. Menstrual cycle irregularity in bulimia nervosa. Associated factors and changes with treatment. *J Psychosom*, 49, 409-415.

Goldenberg, R. L., Tamura, T., DuBard, M., Johnston, K. E., Copper, R. L., & Neggers, Y., 1996. Plasma ferritin and pregnancy outcome. *J Obstet Gynecol*, 175, 1356-1359.

Grimm, E. R., & Venet, W. R., 1966. The relationship of emotional adjustment and attitudes to the course and outcome of pregnancy. *Psychosom Med, 28*, 34-49.

Haddow, J. E., Palomaki, G. E., Allan, W. C., Williams, J. R., Knight, G. J., Gagnon, J., Klein, R. Z., 1999. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med,* 341, 549-555.

Halmi, K. A., Eckert, E., Marchi, P., Sampugnaro, V., Apple, R., & Cohen, J. 1991. Comorbidity of psychiatric diagnoses in anorexia nervosa. Arch Gen Psychiatry, 48, 712-718.

Hammer, L. D., Bryson, S., & Agras, W. S., 1999. Development of feeding practices during the first 5 years of life. *Arch Pediatr Adolesc Med, 153*, 189-194.

Harris, E. C., & Barraclough, B., 1998. Excess mortality of mental disorder. *Br J Psychiatry, 173*, 11-53.

Henrichs, J., Bongers-Schokking, J. J., Schenk, J. J., Ghassabian, A., Schmidt, H. G., Visser, T. J., Tiemeier, H., 2010. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *J Clin Endocrinol Metab*, 95, 4227-4234.

Herzog, D. B., Greenwood, D. N., Dorer, D. J., Flores, A. T., Ekeblad, E. R., Richards, A., Keller, M. B., 2000. Mortality in eating disorders: a descriptive study. *Int J Eat Disord, 28*, 20-26.

Hoek, H. W., & van Hoeken, D., 2003. Review of the prevalence and incidence of eating disorders. *Int J Eat Disord, 34*, 383-396.

Hou, J., Cliver, S. P., Tamura, T., Johnston, K. E., & Goldenberg, R., 2000. Maternal serum ferritin and fetal growth. *Obstet Gynecol*, 95, 447-452.

Jacobi, C., Hayward, C., de Zwaan, M., Kraemer, H. C., & Agras, W. S., 2004. Coming to terms with risk factors for eating disorders: application of risk terminology and suggestions for a general taxonomy. *Psychol Bull, 130*, 19-65.

Johnson, C. D., Cunningham, J., Sullivan, C. C., & Bebermeyer, R., 1999. A case report: recognizing factitious injuries secondary to multiple eating disorders. *J Gt Houst Dent Soc, 70*, 14-16.

Kadesjö B, Janols L-O, Korkamn M, Michelson K, Strand G, Trillingsgaard A, et al. 5–15-formuläret (Five to Fifteen), 2004: the development of a parent questionnaire for the assessment of AD/HD and comorbid conditions. *Eur Child Adolesc Psychiatry*, 13, 3–13.

Kaye, W. H., Greeno, C. G., Moss, H., Fernstrom, J., Fernstrom, M., Lilenfeld, L. R., 1998. Mann, J. J., 1998. Alterations in serotonin activity and psychiatric symptoms after recovery from bulimia nervosa. *Arch Gen Psychiatry, 55*, 927-935.

Kaye, W. H., Bailer, U. F., Frank, G. K., Wagner, A., & Henry, S. E., 2005. Brain imaging of serotonin after recovery from anorexia and bulimia nervosa. *Physiol Behav, 86*, 15-17.

Keel, P. K., Heatherton, T. F., Dorer, D. J., Joiner, T. E., & Zalta, A. K., 2006. Point prevalence of bulimia nervosa in 1982, 1992, and 2002. *Psychol Med, 36*, 119-127.

Keel PK, Brown TA., 2010. Update on course and outcome in eating disorders. *Int J Eat, 43*, 195-204.

Kendler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J., 1995. The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Arch Gen Psychiatry*, 52, 374-383.

Kerr, D. C., Lopez, N. L., Olson, S. L., & Sameroff, A. J., 2004. Parental discipline and externalizing behavior problems in early childhood: the roles of moral regulation and child gender. *J Abnorm Child Psychol, 32*, 369-383.

Keski-Rahkonen, A., Hoek, H. W., Susser, E. S., Linna, M. S., Sihvola, E., Raevuori, A., Rissanen, A., 2007. Epidemiology and course of anorexia nervosa in the community. *Am J Psychiatry, 164*, 1259-1265.

Keski-Rahkonen, A., Hoek, H. W., Linna, M. S., Raevuori, A., Sihvola, E., Bulik, C. M., Kaprio, J., 2009. Incidence and outcomes of bulimia nervosa: a nationwide population-based study. *Psychol Med, 39*, 823-831.

Korkman M, Jaakola M, Ahlroth A, Personen A-E, Turunen M-M., 2004. Screening of developmental disorders in five-year-olds using the FTF (Five to Fifteen) questionnaire. A validation study. *Eur Child Adolesc Psychiatry*, 4, 31–38.

Krafft, A., Murray-Kolb, L., & Milman, N., 2012. Anemia and iron deficiency in pregnancy. *J Pregnancy,* Epub Aug 28.

Kumar, R., Robson, K. M., & Smith, A. M.,1984. Development of a self-administered questionnaire to measure maternal adjustment and maternal attitudes during pregnancy and after delivery. *J Psychosom Res, 28*, 43-51.

Lacey JH, Smith G. Bulimia nervosa., 1987. The impact of pregnancy on mother and baby. *Br J Psychiatry*, 150, 777–781.

Larrañaga A, Fluiters E, Docet MF, Fernández Sastre JL, García-Mayor RV., 2013. Comparative study of cognitive-behavioral psychotherapy and nutritional support in patients with different types of eating disorders. *Med Clin*, Epub ahead of print.

Lasater, L. M., & Mehler, P. S.,2001. Medical complications of bulimia nervosa. *Eat Behav,* 2, 279-292.

Latzer, Y., & Tzchisinki, O., 2003. [Binge eating disorder (BED)--new diagnostic category]. *Harefuah, 142*, 544-549, 564.

Legroux-Gerot, I., Vignau, J., Collier, F., & Cortet, B., 2005. Bone loss associated with anorexia nervosa. *Joint Bone Spine, 72*, 489-495.

Leombruni, P., Amianto, F., Delsedime, N., Gramaglia, C., Abbate-Daga, G., & Fassino, S.,2006. Citalopram versus fluoxetine for the treatment of patients with bulimia nervosa: a single-blind randomized controlled trial. *Adv Ther, 23*, 481-494.

Levitan, R. D., Kaplan, A. S., Masellis, M., Basile, V. S., Walker, M. L., Lipson, N., Kennedy, J. L., 2001. Polymorphism of the serotonin 5-HT1B receptor gene (HTR1B) associated with minimum lifetime body mass index in women with bulimia nervosa. *Biol Psychiatry, 50*, 640-643.

Lewinsohn, P. M., Seeley, J. R., Moerk, K. C., & Striegel-Moore, R. H., 2002. Gender differences in eating disorder symptoms in young adults. *Int J Eat Disord, 32*, 426-440.

Li, Y., Shan, Z., Teng, W., Yu, X., Li, Y., Fan, C., Hua, T., 2010. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. *Clin Endocrinol,* 72, 825-829.

Lilenfeld, L. R., Kaye, W. H., Greeno, C. G., Merikangas, K. R., Plotnicov, K., Pollice, C., Nagy, L., 1997. Psychiatric disorders in women with bulimia nervosa and their first-degree relatives: effects of comorbid substance dependence. *Int J Eat Disord, 22*, 253-264.

Linna, M. S., Raevuori, A., Haukka, J., Suvisaari, J. M., Suokas, J. T., & Gissler, M., 2013. Reproductive health outcomes in eating disorders. *Int J Eat Disord, 46*, 826-833.

Machado PP, Machado BC, Gonçalves S, Hoek HW., 2007. The prevalence of eating

markers of medical severity? *Pediatrics,*125, 1193-1201.

Marsal K, Persson PH, Larsen T, Lilja H, Selbing A,Sultan B., 1996. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*, 85, 843–848.

Mazzeo, S. E., Slof-Op't Landt, M. C., Jones, I., Mitchell, K., Kendler, K. S., Neale, M. C., Bulik, C. M., 2006. Associations among postpartum depression, eating disorders, and perfectionism in a population-based sample of adult women. *Int J Eat Disord, 39*, 202-211.

Micali, N., Treasure, J., & Simonoff, E.,2007. Eating disorders symptoms in pregnancy: a longitudinal study of women with recent and past eating disorders and obesity. *J Psychosom Res, 63*, 297-303.

Micali, N., Simonoff, E., & Treasure, J., 2009. Infant feeding and weight in the first year of life in babies of women with eating disorders. *J Pediatr, 154*, 55-60.

Micali, N., Simonoff, E., Stahl, D., & Treasure, J., 2011. Maternal eating disorders and infant feeding difficulties: maternal and child mediators in a longitudinal general population study. *J Child Psychol Psychiatry*, 52, 800-807.

Milasinovic, L., Lemberger, J., & Zrnic, S., 1989. Prolactin in the serum of mothers and neonates and in the amniotic fluid of pregnant women with hypertensive disease. *Jugosl Ginekol Perinatol, 29*, 97-101.

Miller, T., 2011. Transition to first-time motherhood. *Pract Midwife, 14*, 12-15.

Miotto, P., Pollini, B., Restaneo, A., Favaretto, G., Sisti, D., Rocchi, M. B., & Preti, A., 2010. Symptoms of psychosis in anorexia and bulimia nervosa. *Psychiatry Res, 175*, 237-243.

Mitchell, J. E., Specker, S. M., & de Zwaan, M., 1991. Comorbidity and medical complications of bulimia nervosa. *J Clin Psychiatry, 52 *, 13-20.

Mond, J. M., Myers, T. C., Crosby, R. D., Hay, P. J., Rodgers, B., Morgan, J. F., Mitchell, J. E., 2008. Screening for eating disorders in primary care: EDE-Q versus SCOFF. *Behav Res Ther, 46*, 612-622.

Mond, J. M., Hay, P. J., Darby, A., Paxton, S. J., Quirk, F., Buttner, P., Rodgers, B., 2009. Women with bulimic eating disorders: When do they receive treatment for an eating problem? *J Consult Clin Psychol, 77*, 835-844.

Monteleone P, Luisi M, Colurcio B, Casaroa E, Monteleone P, Ioime R, et al., 2001. Plasma levels of neuroactive steroids are increased in untreated women with anorexia nervosa or bulimia nervosa. *Psychosom Med *, 63, 62–68.

Morgan, J. F., Lacey, J. H., & Chung, E., 2006. Risk of postnatal depression, miscarriage, and preterm birth in bulimia nervosa: retrospective controlled study. *Psychosom Med, 68*, 487-492.

Naessen, S., Carlstrom, K., Garoff, L., Glant, R., & Hirschberg, A. L., 2006. Polycystic ovary syndrome in bulimic women-an evaluation based on the new diagnostic criteria. *Gynecol Endocrinol, 22*, 388-394.

Peebles, R., Hardy, K. K., Wilson, J. L., & Lock, J. D.,2010. Are diagnostic criteria for eating disorders markers of medical severity? *Pediatrics, 125*, 193-194.

Persson PH, Weldner BM., 1986. Normal range growth curves for fetal biparietal diameter, occipito frontal diameter, mean abdominal diameters and femur length. *Acta Obstet Gynecol Scand*, 65, 759–761.

Pinheiro AP, Raney TJ, Thornton LM, Fichter MM, Berrettini WH, Goldman D, Halmi KA, Kaplan AS, Strober M, Treasure J, Woodside DB, Kaye WH, Bulik CM., 2010. Sexual functioning in women with eating disorders. *Int J Eat Disord,* 43, 123-129.

Raevuori, A., Hoek, H. W., Susser, E., Kaprio, J., Rissanen, A., & Keski-Rahkonen, A., 2009. Epidemiology of anorexia nervosa in men: a nationwide study of Finnish twins. *PLoS One, 4*, e4402.

Reba-Harreleson L, Von Holle A, Hamer RM, Torgersen L, Reichborn- Kjennerud T, Bulik CM., 2010. Patterns of maternal feeding and child eating associated with eating disorders in the Norwegian Mother and Child Cohort Study (MoBa). *Eat Behav*, 11, 54–61.

Rigotti, N. A., Neer, R. M., Skates, S. J., Herzog, D. B., & Nussbaum, S. R., 1991. The clinical course of osteoporosis in anorexia nervosa. A longitudinal study of cortical bone mass. *JAMA, 265*, 1133-1138.

Rocco, P. L., Orbitello, B., Perini, L., Pera, V., Ciano, R. P., & Balestrieri, M., 2005. Effects of pregnancy on eating attitudes and disorders: a prospective study. *J Psychosom Res, 59*, 175-179.

Russell GFM, Treasure J, Eisler I., 1998. Mothers with anorexia nervosa who underfeed their children: Their recognition and management. *Psychol Med*, 28, 93–108.

Sattar, N., Greer, I. A., Galloway, P. J., Packard, C. J., Shepherd, J., Kelly, T., & Mathers, A., 1999. Lipid and lipoprotein concentrations in pregnancies complicated by intrauterine growth restriction. *J Clin Endocrinol Metab, 84*, 128-130.

Savitz, D. A., Stein, C. R., Ye, F., Kellerman, L., & Silverman, M., 2011. The epidemiology of hospitalized postpartum depression in New York State, 1995-2004. *Ann Epidemiol, 21*, 399-406.

Seckl JR, Holmes MC., 2007. Mechanisms of disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. *Nat Clin Pract Endocrinol Metab*, 3, 479–488.

Shafran, R., & Fairburn, C. G., 2002. A new ecologically valid method to assess body size estimation and body size dissatisfaction. *Int J Eat Disord, 32*, 458-465.

Siddiqui, A., & Hagglof, B., 2000. Does maternal prenatal attachment predict postnatal mother-infant interaction? *Early Hum Dev, 59*, 13-25.

Singh, R., Goyal, M., Tiwari, S., Ghildiyal, A., Nattu, S. M., & Das, S., 2012. Effect of examination stress on mood, performance and cortisol levels in medical students. Indian J Physiol Pharmacol, 56, 48-55.

Slof-Op 't Landt MC, van Furth EF, Meulenbelt I, Slagboom PE, Bartels M, Boomsma DI, Bulik CM., 2005, Eating disorders: from twin studies to candidate genes and beyond. *Twin Res Hum Genet,* 8, 467-482.

Smink, F. R., van Hoeken, D., & Hoek, H. W., 2012. Epidemiology of eating disorders: incidence, prevalence and mortality rates. *Curr Psychiatry Rep, 14*, 406-414.

Sollid, C. P., Wisborg, K., Hjort, J., & Secher, N. J. 2004. Eating disorder that was diagnosed before pregnancy and pregnancy outcome. *Am J Obstet Gynecol, 190*, 206-210.

Soubasi, V., Petridou, S., Sarafidis, K., Tsantali, C., Diamanti, E., Buonocore, G., & Drossou-Agakidou, V., 2010. Association of increased maternal ferritin levels with gestational diabetes and intra-uterine growth retardation. *Diabetes Metab*, 36, 58-63.

Stagnaro-Green, A., Chen, X., Bogden, J. D., Davies, T. F., & Scholl, T. O., 2005. The thyroid and pregnancy: a novel risk factor for very preterm delivery. *Thyroid*, 15, 351-357.

Steiger, H., Gauvin, L., Israel, M., Kin, N. M., Young, S. N., & Roussin, J., 2004. Serotonin function, personality-trait variations, and childhood abuse in women with bulimia-spectrum eating disorders. *J Clin Psychiatry, 65*, 830-837.

Stein A, Woolley H, Murray L, Cooper P, Cooper S, Noble F, et al., 2001. Influence of psychiatric disorder on the controlling behaviour of mothers with 1-year- old infants. *Br J Psychiatr*,179, 157–162.

Stein, A., Woolley, H., Cooper, S., Winterbottom, J., Fairburn, C. G., & Cortina-Borja, M., 2006. Eating habits and attitudes among 10-year-old children of mothers with eating disorders: longitudinal study. *Br J Psychiatry, 189*, 324-329.

Stewart DE, Erlick Robinson G., 2001. Eating disorders and reproduction. In: Stotland NL, Stewart DE, eds. Psychological aspects of women's health care: The interface between psychiatry and obstetrics and gynecology, 2nd ed. *American Psychiatric Publishing*, 441.

Sullivan, P. F., Bulik, C. M., & Kendler, K. S., 1998. The epidemiology and classification of bulimia nervosa. *Psychol Med, 28*, 599-610.

Thomas, M. A., & Rebar, R. W., 1990. The endocrinology of anorexia nervosa and bulimia nervosa. *Curr Opin Obstet Gynecol*, 2, 831-836.

Treasure, J. L., & Russell, G. F., 1988. Intrauterine growth and neonatal weight gain in babies of women with anorexia nervosa. *Br Med J (Clin Res Ed), 296*, 1038.

Trillingsgard A, Damm D, Sommer S, Jepsen JRM, Ostergaard O, Frydenberg M, et al., 2004. Developmental profiles on the basis of the FTF (Five to Fifteen) questionnaire. *Eur Child Adolesc Psychiatry*, 13, 39–49.

Uno, S., Guo, D. F., Nakajima, M., Ohi, H., Imada, T., Hiramatsu, R., Inagami, T., 1994. Glucocorticoid induction of rat angiotensin II type 1A receptor gene promoter. *Biochem Biophys Res Commun*, 204, 210-215.

van der Spuy ZM, Steer PJ, McCusker M, Steele SJ, Jacobs HS., 1988. Outcome of pregnancy in underweight women after spontaneous and induced ovulation. *Br Med J, 296*, 962-965.

Vargas JE, Allred EN, Leviton A, Holmes LB., 2001. Congenital microcephaly: phenotypic features in a consecutive sample of newborn infants. J Pediatr, 139, 210–214.

Wade, T., Neale, M. C., Lake, R. I., & Martin, N. G., 1999. A genetic analysis of the eating and attitudes associated with bulimia nervosa: dealing with the problem of ascertainment in twin studies. *Behav Genet, 29*, 1-10.

Wade, T. D., Bergin, J. L., Tiggemann, M., Bulik, C. M., & Fairburn, C. G., 2006. Prevalence and long-term course of lifetime eating disorders in an adult Australian twin cohort. *Aust N Z J Psychiatry, 40*, 121-128.

Wagner, A., Wockel, L., Bolte, S., Radeloff, D., Lehmkuhl, G., Schmidt, M. H., & Poustka, F., 2008. Mental disorders among relatives of patients with anorexia nervosa and bulimia nervosa. *Z Kinder Jugendpsychiatr Psychother, 36*, 177-184.

Walker, L., 1988. Weight-related distress in the early months after childbirth. *West J Nurs Res*, 20, 30.

Watson, T. L., & Andersen, A. E., 2003. A critical examination of the amenorrhea and weight criteria for diagnosing anorexia nervosa. *Acta Psychiatr Scand, 108*, 175-182.

Waugh E, Bulik CM., 1999. Offspring of women with eating disorders. *Int J Eat Disord,* 25, 123–133.

Weltzin, T. E., Bulik, C. M., McConaha, C. W., & Kaye, W. H., 1995. Laxative withdrawal and anxiety in bulimia nervosa. *Int J Eat Disord, 17*, 141-146.

Willi J, Limacher B, Helbling P, Nussbaum P., 1988. A 10-year follow-up of cases with anorexia first hospitalized in the Canton of Zürich. *Schweiz Med Wochenschr*, 4, 147-155.

Wonderlich, S. A., Lilenfeld, L. R., Riso, L. P., Engel, S., & Mitchell, J. E., 2005. Personality and anorexia nervosa. *Int J Eat Disord, 37,*68-71.

Woodside DB, Shekter-Wolfson LF., 1990 Parenting by patients with anorexia nervosa and bulimia nervosa. *Int J Eat Disord ,* 9, 303–309.