

**ANXIETY AND DEPRESSION DURING PREGNANCY AND THEIR INFLUENCE ON
BIRTH OUTCOMES: KUOPIO BIRTH COHORT STUDY**

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ANXIETY AND DEPRESSION DURING PREGNANCY AND THEIR INFLUENCE ON BIRTH OUTCOMES: KUOPIO BIRTH COHORT STUDY

Anxiety and depression are common during pregnancy, with the prevalence of 24% anxiety disorders and 18.4% depression during pregnancy. The effect of these disorders on mothers and their unborn child cannot be ignored.

The aim of this study was to investigate associations between anxiety, depression and both during pregnancy as assessed with Edinburgh Postnatal Depression Scale (EPDS), and birth outcomes.

The cohort study included 921 pregnant women who gave birth at the Kuopio University Hospital. Series of self-administered questionnaires were filled up during the first trimester (12+6 weeks), third trimester (28+12 weeks) and at postpartum stage (8 weeks after delivery). The birth outcomes were measured immediately after the delivery in the hospital by the midwives. The EPDS was used to detect the pregnant women who experienced anxiety but not depression (EPDS-3A \geq 4; total EPDS \leq 12), depression but no anxiety (EPDS-3A \leq 4; total EPDS \geq 12) and both anxiety and depression (EPDS-3A \geq 4; total EPDS \geq 12) at third trimester. Descriptive analyses were used to detect the prevalence of adverse birth outcomes in women experiencing anxiety, depression and both during pregnancy and in asymptomatic women. Binary logistic regression analysis was used to measure associations between head circumference at birth and comorbid anxiety and depression vs. the asymptomatic group.

Among all participants, 22 % had anxiety only and 7.2% had both anxiety and depression. None of the participants were observed to have depression only. A multivariate model adjusted for maternal age, relationship status, Body Mass Index (BMI) before pregnancy, smoking before pregnancy and maternal gestational diabetes showed that larger head circumference at birth was associated with an increased likelihood of belonging to combined anxiety and depression group (OR=1.239, 95% CI=,1.034-1.484, P=0.020) during third trimester of pregnancy.

These findings suggest that the head circumference at birth is positively associated with the comorbidity of anxiety and depression during third trimester of pregnancy. This increase in head circumference might be associated with the higher birth weight of the infants.

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ABBREVIATIONS

| | |
|-------------------|---|
| ACTH | Adrenocorticotropin Hormone |
| BDI | Beck Depression Inventory |
| BMI | Body Mass Index |
| CDC | Centers for Disease Control and Prevention |
| CI | Confidence Interval |
| CRH | Corticotropin Releasing Hormone |
| DALY | Disability Adjusted Life Years |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EPDS | Edinburgh Postnatal Depression Scale |
| EPDS 3A | Edinburgh Postnatal Depression Scale-3 Anxiety |
| GDM | Gestational Diabetes Mellitus |
| HAM-D | Hamilton Depression Rating Scale |
| HPA | Hypothalamic–Pituitary–Adrenal |
| HSD2 – 11 β | 11-beta Hydroxysteroid Dehydrogenase |
| IQ | Intelligence Quotient |
| KuBiCo | Kuopio Birth Cohort |
| NICU | Neonatal Intensive Care Unit |
| OR | Odds Ratio |

| | |
|------|--|
| PCL | Post-traumatic Stress Disorder Checklist |
| PTSS | Post-traumatic Stress Symptomatology |
| SD | Standard Deviation |
| WHO | World Health Organization |

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1. INTRODUCTION

Psychiatric morbidity during pregnancy is a major public health concern. World Health Organization (WHO) ranks depression as one of the most burdensome illnesses in the world. Depression is predicted to be the topmost cause of morbidity by 2030 (WHO 2008). It is common during pregnancy with 18.4% of women experiencing depressive symptoms during pregnancy, and 12.7% having an episode of major depression (Gavin et al. 2005). In addition, prevalence of anxiety disorders during pregnancy ranges from 12.2% to 39% with panic disorder and obsessive-compulsive disorder being three times more common among pregnant women than in the general population. Furthermore, generalized anxiety disorder and anxiety disorder due to medical condition were found to be twice as common during pregnancy than in non-pregnant women (Adewuya et al. 2006, Goodman et al. 2014).

The risks related with antenatal anxiety and depression cannot be ignored. Shorter than average gestation period and adverse consequences for fetal neurodevelopment and child developmental outcomes are associated with anxiety disorders during pregnancy (Dunkel & Tanner 2012). The negative events during pregnancy and delivery, including, preeclampsia, preterm delivery and operative deliveries are also associated with antenatal depression (Kurki et al. 2000, Chung et al. 2001, Orr et al. 2002). The effects of anxiety and depression during pregnancy are seen in the long term in cognitive impairment and emotional problems in children, as well as serious illnesses such as asthma and coronary disease during different life phases (Shahhosseini et al. 2015). The offspring of mothers who experienced anxiety during pregnancy were also 1.39 times more likely to be diagnosed with comorbid anxiety and depression at age of 18 years (Capron et al. 2015).

Anxiety and depression during pregnancy remain underdiagnosed and undertreated. Although many studies have shown that antenatal anxiety and depression affect the unborn child and increase the risk of adverse birth outcomes, cognitive impairment and other disorders, obstetric medicine often ignores the emotional aspect of pregnant women, which thus remains neglected (Bowen & Muhajarine 2006). In particular, comorbidity of anxiety and depression is a critical condition as the effects of comorbid anxiety and depression on neonates have been suggested to be higher than those of anxiety alone or depression alone (Field et al. 2010).

In other words, anxiety and depression during pregnancy appear to lead to several pregnancy and delivery complications compared to either conditions alone. However, there are very few studies on the associations between comorbid anxiety and depression and the birth outcomes. The aim of this cohort study was to investigate the influence of comorbid anxiety and depression during pregnancy on birth outcomes.

2. LITERATURE REVIEW

2.1. Anxiety

Anxiety is a universal phenomenon, often challenging and beneficial at the same time. It acts as a biological warning system against danger signs and prepares an individual to take appropriate action. Thus normal anxiety acts as a protective response towards certain risks. A low level of anxiety is beneficial, but high and chronic levels of anxiety result in impairment of physiological and psychological functions. The shift from normal state to anxiety disorders is characterized by distinct nervous system abnormalities (Noyes & Hoehn-Saric 1998). According to the American Psychiatric Association (2013), Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 has classified anxiety into following categories;

- a. Separation anxiety disorder: Characterized by persistent fear and anxiety about separation and the degree is usually inappropriate.
- b. Selective mutism: Characterized by consistent failure to speak only in social circumstances.
- c. Specific phobia: Characterized by consistent fear and anxiety about specific object or situations.
- d. Social anxiety disorder: Characterized by being fearful and anxious and avoiding the social circumstances where there is possibility of being embarrassed.
- e. Panic disorder: Characterized by recurrent panic attacks and persistent concern about having panic attacks or behavioral changes due to panic attacks.
- f. Panic attack specifier: Characterized by intense fear or discomfort which reaches peak within some minutes.
- g. Agoraphobia: Characterized by being fearful and anxious about using public transportation; being in open spaces, being in enclosed places; standing in line or with crowd; or being outside of the home alone in other situations.
- h. Generalized anxiety disorder: Characterized by persistent worry and anxiety about work and performances, which is difficult to control.

- i. Substance/medication-induced anxiety disorder: Characterized by anxiety due to substance use, withdrawal or medical treatment.
- j. Anxiety disorder due to another medical condition: Anxiety due to other medical conditions.
- k. Other specified anxiety disorder
- l. Unspecified anxiety disorder.

The common symptoms include the presence of extreme fear and anxiety, together with behavioral disturbances. Fear is a spontaneous response towards real or perceived threat of immediate danger. Anxiety, however, is directed towards future danger. The only differences among these disorders are the types of situations inducing fear, anxiety and avoidance behavior with linked cognitive dysfunctional ideation. They are highly comorbid with each other but close examination can differentiate the type of anxiety disorder (National Institute of Mental Health 2016).

2.2. Depression

The World Health Organization (WHO) defines depression as “a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration”. It can be long lasting or recurrent and thus hinders normal functioning of life, in the most severe cases potentially leading to suicide (WHO 2016a). According to American Psychiatric Association (2013), DSM-5 has classified depressive disorders into the following categories:

- a. Disruptive mood dysregulation disorder: Characterized by persistent irritability and frequent episodes of extreme lack of behavioral control.
- b. Major depressive disorder: Characterized by discrete episodes that last for at least 2 weeks with changes in affect, cognition and neurovegetative functions and inter-episode remissions.
- c. Persistent depressive disorder: A chronic form of depression in which mood disturbance continues for at least 2 years in adults and 1 year in children.

d. Premenstrual dysphoric disorder: The disorder follows the ovulation and remits within a few days of menses with impact on functioning.

e. Depressive disorder due to another medical condition: Depression-like phenomena due to some medical condition.

f. Substance/medication-induced depressive disorder: Depression due to prescribed medicine and substance abuse.

g. Other specified depressive disorder

h. Unspecified depressive disorder.

The common diagnostic symptoms among all of these disorders includes feeling sad, empty, or irritable mood, which is linked to changes in somatic and cognitive functions. All of these changes hamper individual's ability to function properly. The differences among them focus on illness duration and etiology (American Psychiatric Association 2013).

2.3. Prevalence and impact of anxiety and depression

Anxiety and depression represent a global problem, affecting a large number of people worldwide. According to the joint event co-hosted by the World Bank and WHO in April 2016: "Out of the Shadows: Making Mental Health a Development Priority.", the trend for people suffering from anxiety and depression is increasing nearly by 50%, from 416 million in 1990 to 615 million in 2013 (WHO 2016c). Depression is one of the leading causes of morbidity worldwide, and accounts for 4.3 % of global burden of disease and 11% of disability-adjusted life years (DALY), particularly in women (WHO 2013). It is predicted to be one of the three leading causes for DALY by 2030 (WHO 2008). On the other hand, anxiety is the most prevalent mental disorder with the life time prevalence of 16% in the general population (Kessler et al. 2009). Thus there is globally little focus on the mental health sector and especially for the women's mental health as women are more prone to depression and anxiety than men. For example, the prevalence of lifetime major depression has been reported to be double among women (11.7%) compared with men (5.6%) (Ford & Erlinger 2004). In addition, anxiety disorders are more frequent in women, with one in three women meeting criteria for anxiety disorder during her lifetime (McLean et al. 2011).

The public health importance of these mental disorders is high, and the range of difficulties an individual faces during the onset of these disorders warrants serious action in health reformation. Long-lasting and severe depressive episodes lead to individual suffering and affect an individual's everyday functioning. In the worst case, depression can lead to suicide which is the second leading cause of death among young population (WHO 2016d). Although anxiety and depression are highly treatable, only one third of those suffering from anxiety (Anxiety and Depression Association of America 2014) and less than half of those suffering from depression (WHO 2016d) receive appropriate treatment.

Global economy faces high losses due to morbidity associated with anxiety and depression. The present investment in mental health is much less than needed. The average government budget on mental health is 3% of total budget on health, which ranges from less than 1% in developing countries to 5% in developed countries (WHO 2015b).

2.4. Anxiety and depression during pregnancy

2.4.1. Prevalence

Globally, around 10% of women during pregnancy and 13% of women after a child birth experience mental disorders, particularly depression. The prevalence rates for mental disorders in developing countries are even higher with 15.6% during pregnancy and 19.8% during the postpartum period (WHO 2016b). The severe cases might lead to suicide as the suicidal ideation is detected among 13.1% to 33% of pregnant women (Frautschi et al. 1994, Newport et al. 2007).

Psychiatric morbidity is common during pregnancy with 18.4% of women experiencing depressive symptoms during pregnancy, and 12.7% having an episode of major depression (Gavin et al. 2005). The prevalence of depression is however different among various studies. In high income countries, the prevalence of depression during pregnancy is found to be from 7% to 20% (Evans et al. 2001, Andersson et al. 2003, Marcus et al. 2003, Gavin et al. 2005, Lee et al. 2007, Melville et al. 2010), while it is 20% or more in low and middle income countries (Faisal-Cury et al. 2009, Golbasi et al. 2010, Husain et al. 2011). Additionally, depression may cause an impairment of the mother's general functioning, resulting in a deterioration of the newborn's health (WHO 2016b).

In addition, anxiety disorders have been reported in 24% of pregnant women (Sutter-Dallay et al. 2004). The prevalence of anxiety disorders during pregnancy ranges from 12.2% to 39% with panic disorder and obsessive-compulsive disorder being three times more common among pregnant than in non-pregnant women. Furthermore, the prevalence of generalized anxiety disorder and anxiety disorder due to medical condition were found to be double in pregnant women than in the general population (Adewuya et al. 2006, Goodman et al. 2014).

2.4.2. Socioeconomic and lifestyle factors associated with anxiety or depression during pregnancy

Depressive and anxiety disorders during pregnancy have been associated with smoking, alcohol consumption, substance use, inadequate weight gain and, improper nutrition (Marcus 2009).

A study by Ibanez et al. (2012) found that women with symptoms of depression or anxiety have higher BMI and higher parity. Significant correlation was found among antenatal anxiety or depression, and alcohol consumption before (Lee et al. 2007) and during (Marcus et al. 2003) pregnancy.

A study by Smedberg et al. (2015) found out that women who continue to smoke during pregnancy are at higher risk of antenatal depression than women who quit smoking during pregnancy. In contrast, Jeong et al. (2013) found no associations between smoking during pregnancy and antenatal depression. Another study by Fellenzer & Cibula (2014) found out that the severity of depression during pregnancy increased with the increasing number of cigarettes smoked per day. Also, a study by Lee et al. (2007) found significant associations between history of smoking and antenatal anxiety, but no association between history of smoking and antenatal depression. A study by Ibanez et al. (2012) found that women with both depression and anxiety were frequent smokers. However, Luke et al. (2009) found no associations between smoking during pregnancy and antenatal depression.

Marital status is also associated with anxiety and depression during pregnancy. Some studies have identified that the prevalence of depression during pregnancy was higher among single mothers or those living without partner than married women and those living in a relationship (Marcus et al. 2003, Rubertsson et al. 2003, Jeong et al. 2013, Räisänen et al. 2014). However, a study by Bilszta

et al. (2008) found out that single mothers have more frequent depression when compared to those having supportive partners, but they had less frequent depression when compared to those having unsupportive partners. On the contrary, some other studies did not find any significant association among marital status and antenatal depression (Glazier et al. 2004, Luke et al. 2009, Agostini et al. 2015).

2.4.3. Health related factors associated with anxiety or depression during pregnancy

Depressed and anxious women during pregnancy do not properly access antenatal care and visits (Kim et al. 2006, Redshaw & Henderson 2013). Fear of childbirth during the pregnancy has also been associated with antenatal anxiety and depression (Räisänen et al. 2014, Rubertsson et al. 2014). Women with a history of depression before pregnancy have 22.4 times increased prevalence for major depression during pregnancy compared with those who do not have any prior history of depression (Räisänen et al. 2014).

Depressive symptoms were associated with more sick leave, frequent visits to doctor, obstetric complications and admission to hospital (Larsson et al. 2004). In addition, increased risk of preeclampsia has also been associated with anxiety disorders during pregnancy (Qiu et al. 2009).

Gestational diabetes has been associated with depression during pregnancy, and women with diabetes but no depression were likely to develop postpartum depression (Kozhimannil et al. 2009). A study by Bayrampour et al. (2015) found the history of treating infertility to be associated with antenatal anxiety, but a study by Rubertsson et al. (2003) did not find such association. Also, a planned cesarean section is 1.7 times more frequent among women with anxiety disorder (Rubertsson et al. 2014).

2.5. Comorbid anxiety and depression during pregnancy

In a general population, 60% of the individuals with major depression are at risk of having a comorbid anxiety disorder (Kessler et al. 2003). People suffering from major depression with comorbid anxiety are at greater risk of having severe depressive symptoms with long and chronic episodes of depression. In addition, comorbidity worsens the individual's psychosocial functioning and response to medications. This results in a prolonged recovery period and increased suicidal tendency (Pollack 2005).

Depression and anxiety are highly comorbid during pregnancy (Lancaster et al. 2010, Verreault et al. 2014). Anxious women during their pregnancy are highly at risk for antenatal depression (Edwards et al. 2008). A study by Mohammad Yusuff et al. (2015) revealed that women experiencing anxiety during pregnancy are at a three-fold risk of being depressed compared to women who are not anxious during pregnancy. Anxiety during pregnancy also increases the likelihood of postnatal depression, even after controlling for depression from the antenatal period (Heron et al. 2004).

Comorbidity of depression and anxiety during pregnancy yield even more complications and increased risk to the newborn child (Ibanez et al. 2012). Field et al. (2010) studied the four different groups of pregnant women: with anxiety disorder, depressive disorder, comorbid anxiety-depressive disorder, and with no diagnosis of anxiety or depression, and their newborns. They found that the effects of comorbid anxiety and depression on the offspring were more severe with greater incidence of prematurity than with depression alone or anxiety alone. The neonates from this group also had higher cortisol and norepinephrine and lower dopamine and serotonin levels. The pregnant women belonging to comorbid group had higher scores of anxiety, anger and daily hassles with relationship problems, sleep disturbances and lowered dopamine levels.

2.6. Pregnancy specific measures of anxiety and depression

There are several tools to measure anxiety and depression during pregnancy. Commonly used measures of anxiety include State Trait Anxiety Inventory (Spielberger et al. 1970), General Health Questionnaire (Goldberg 1972), Beck Anxiety Inventory (Beck et al. 1988), Hospital anxiety and depression scale (Zigmond and Snaith 1983) and Kessler 10 (Kessler et al. 2002), which have been validated to use in perinatal populations (Meades & Ayers 2011). Furthermore, the tools such as Edinburgh Postnatal Depression Scale (EPDS) (Cox et al. 1987), Beck Depression Inventory (BDI) (Beck et al. 1961) and Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960) can be used to measure antenatal depression (Castro E Couto et al. 2015).

The Edinburgh Postnatal Depression Scale is a 10 item self-report scale with high reliability of 0.88 and internal consistency of 0.87. The sensitivity and specificity of the tool were found to be 85% and 77% respectively. The cut off score of 12/13 has been suggested to detect individuals suffering from major depressive disorder (Cox et al. 1987). Even though the scale was initially developed

for postpartum depression, it has been validated for use during pregnancy as well. The cut off value of 11 during the first trimester and 10 during the second and third trimester have showed adequate combination of sensitivity, specificity, and positive predictive value (Bergink et al. 2011).

Tuohy & McVey (2008), analyzed the properties of EPDS and suggested that the scale has three identifiable factors that could be used as subscales to measure depressive symptoms, anhedonia and anxiety in postpartum women. EPDS is a widely used measure for depression, and it has also been used to detect anxiety by using anxiety subscale (consisting of EPDS questions 3,4 and 5) with cut off score of ≥ 4 (Swalm et al. 2009). The anxiety subscale score (i.e., EPDS 3A) is a useful tool to detect symptoms of anxiety when scored separately from EPDS total score (Matthey et al. 2013). According to one study by Petrozzi & Gagliardi (2013), EPDS may measure symptoms of anxiety more than the depressive symptoms when measured immediately after the delivery.

Thus, EPDS is a useful tool to measure depression during pregnancy. Similarly, the anxiety subscale score (EPDS 3A) can be considered to be useful tool to measure anxiety during pregnancy.

2.7. Birth outcomes

2.7.1. Gestational age

Gestation refers to the time period between conception and birth, when the fetus grows and matures inside the mother's womb. Similarly, gestational age is a term used to measure the duration of pregnancy, mostly measured in weeks. It starts from the first day of last menstrual cycle to the current date. Pregnancies ranging from 38 to 42 weeks are considered normal. Infants born before 37 weeks are premature or preterm and those born after 42 weeks are post mature infants (U.S. National Library of Medicine 2013). Based on gestational age, preterm birth can be subcategorized as extremely preterm (<28 weeks), very preterm (28 to <32 weeks) and moderate to late preterm (32 to <37 weeks) (WHO 2015a).

Preterm birth highly contributes to infant mortality, with most preterm-related deaths occurring among very preterm (before 32 weeks) babies. The preterm babies who survive, often face long term neurological disabilities in their childhood (CDC 2015). There is no particular cause identified for preterm births. Most of them occur spontaneously, while a proportion of them are due to medical or non-medical induction of labour or caesarean sections. Infections, multiple pregnancies, diabetes

and high blood pressure can also contribute to preterm birth. The genetic influence could also be a reason behind it (WHO 2015a). Maternal depression has also been associated with preterm birth. Fransson et al. (2010) found the depressive symptoms during pregnancy increased the risk of preterm birth by 1.56 times. Thus, further understanding the underlying mechanisms can contribute to prevention of preterm birth.

2.7.2. Head circumference

Head circumference is a measurement around the child's largest head area. It is measured from above the eyebrows to ears and around the back of the head, usually in centimeters or inches. It reflects the size of the brain and its growth. It can also be called as occipital-frontal circumference. If a head is abnormally large and is growing faster than normal, the condition can lead to hydrocephalus, meaning abnormal increase in cerebrospinal fluid on the brain (U.S. National Library of Medicine 2015). The cause of this condition is poorly understood. It may result from genetic abnormalities which cause aqueductal stenosis, or from developmental disorders such as neural tube defects (National Institute of Neurological Disorders and Stroke 2016).

On the contrary, if the head is smaller or the growth rate is lower than normal, the brain is not developing properly and the condition is called microcephaly (U.S. National Library of Medicine 2015). The causes of microcephaly are not known properly. Exposure to infections (e.g., rubella, toxoplasmosis), alcohol, drugs and toxic chemicals during pregnancy, and reduced blood supply to the fetus during brain development might be some of the contributing factors (CDC 2016a).

According to CDC, babies born with head circumference <5th percentile or >95th percentile have developmental problems (CDC 2016b). The head circumference chart in centimeters at birth is attached in appendix 2 (CDC 2001).

2.7.3. Umbilical cord

The umbilical cord is the coiled, twisted or spiraled structure that aids in the growth and development of the fetus, and could also be referred to as the lifeline of fetus. It starts to develop during the first trimester of pregnancy and notably lengthens during the third trimester. The normal length of the umbilical cord is around 55cm. The optimum length is obtained by the 28th week of pregnancy. Cords shorter than 35 cm are considered to be short cords, with estimated occurrence

in 4-6 % of placentas; on the contrary, long cords have a length more than 70-80 cm and occur in approximately 1-2% of placentas. For a vaginal delivery with fundal placental implantation, the minimum length of 35 cm is required. Short cords are associated with various neonatal problems, such as premature separation of the placenta (abruptio), hemorrhage, hematoma or rupture of cords, and prolongation of the second stage of labor. Furthermore, low Apgar scores, fetal distress, developmental anomalies with decreased intelligence quotient (IQ) level are frequently seen in newborns with short cords. Abnormally long cords are usually associated with pathological changes in placenta and other numerous pathological conditions, such as cord edema, villous congestion, and thrombosis of umbilical or chorionic vessels (Baergen 2011).

2.7.4. C section

C section is the delivery of a baby through incision of the abdominal and uterine wall. It is also known as cesarean delivery. There is an increased incidence of cesarean deliveries especially in the industrialized western world, and the rate is increasing each year (Cunningham et al. 2010). Globally, around 18.5 million cesarean deliveries are conducted every year (WHO 2010). The prevalence rate is also increasing in Organisation for Economic Co-operation and Development (OECD) member countries from 20% in 2000 to 28% in 2013 (OECD 2015). No specific reasons could be identified, however there are some explanations behind the rise. The rate of nulliparas is increasing with rise in average maternal age, and nulliparas are at risk of cesarean deliveries. While the prevalence of forceps and vacuum assisted deliveries has decreased, more breech presentations get delivered by C section. The prevalence of obesity, which is a risk factor for cesarean delivery is also dramatically increasing. In addition, vaginal delivery is less likely if prior delivery was cesarean delivery. Even though cesarean delivery is considered a safe technique, there are more complications with cesarean delivery than with vaginal delivery. They include urinary tract injury, bladder or uterus infection and heavy blood loss. Thus, increasing number of repeat cesarean deliveries could increase the risk of wound/uterine infection, transfusion, placenta previa, hysterectomy and placenta accrete (Cunningham et al. 2010).

2.7.5. Apgar score

The Apgar score was invented by Dr. Virginia Apgar in 1952 as a scoring method to assess the clinical status of the newborn at 1 minute of birth, and to manage further complications (Apgar

1953). This is a standardized measure used after the delivery to inform about the overall status of the baby. There are five components in Apgar score,

- a) Color
- b) Heart rate
- c) Reflexes
- d) Muscle tone
- e) Respiration

Each of these signs are scored as 0, 1 or 2 with total of 10 Apgar score. If the score is lower than 7, the newborn needs medical assistance. The lower score indicates that the newborn needs help to adjust outside the mother's womb. If the score is more than 7, the newborn is normal and does not need any medical assistance. The figure 1 shows these components and their scoring during different time periods. The scoring takes place at 1 minute and 5 minutes after the birth and every 5 minutes to 20 minutes if the 5-minute score is less than 7 (American Academy of Pediatrics and American Heart Association 2006).

Figure 1: Form to document elements of Apgar score (from American Academy of Pediatrics and American Heart Association 2006).

| APGAR SCORE | | | | Gestational age _____ weeks | | | | | |
|---------------------|--------------|------------------------------|--------------------------|-----------------------------|-----------|------------|------------|------------|----|
| SIGN | 0 | 1 | 2 | 1 minute | 5 minutes | 10 minutes | 15 minutes | 20 minutes | |
| Color | Blue or pale | Acrocyanotic | Completely pink | | | | | | |
| Heart rate | Absent | <100 minute | >100 minute | | | | | | |
| Reflex irritability | No response | Grimace | Cry or active withdrawal | | | | | | |
| Muscle tone | Limp | Some flexion | Active motion | | | | | | |
| Respiration | Absent | Weak cry: Hypoventilation | Good, crying | | | | | | |
| TOTAL | | | | | | | | | |
| Comments: | | | | Resuscitation | | | | | |
| | | | | Minutes | 1 | 5 | 10 | 15 | 20 |
| | | | | Oxygen | | | | | |
| | | | | PPV/NCPAP | | | | | |
| | | | | EET | | | | | |
| | | | | Chest compressions | | | | | |
| | | | | Epinephrine | | | | | |

PPV/NCAP: Positive-pressure Ventilation/ Nasal Continuous Positive Airway Pressure; EET: Endotracheal Tube

2.7.6. Intensive care

Newborns with neonatal or prenatal difficulties including extreme prematurity, respiratory distress and life threatening birth defects are often taken to Neonatal Intensive Care Unit (NICU), where they are treated and looked after. The newborns in this unit are provided with nasogastric tube for nutrition, oxygen is maintained through nasal or oral tube connected to the ventilator, and an incubator to maintain the temperature. In addition, they are exposed to fluorescent lights or bright sunlight to ensure proper vision and also to sounds of different intensities, including human voice and other noises. In this way, the infant is being prepared to cope in the new environment (Goldson 1999).

According to an epidemiologic time-trend analysis study in United States, NICU admission rate has increased from 2007 to 2012. It showed a relative increase of 23% (64.0 to 77.9 per 1000) in 6 years, even after adjusting for maternal and newborn characteristics likely to influence the chance for NICU admission (Harrison & Goodman 2015).

2.8. Short and long-term effects of anxiety and depression during pregnancy

2.8.1. Immediate effects on birth outcomes

Anxiety disorders during pregnancy have been associated with shorter gestation period and adverse consequences for fetal neurodevelopment and child outcomes (Dunkel & Tanner 2012). The increased level of antenatal anxiety and depression has been found to be associated with obstetric complications and adverse pregnancy outcomes like preterm birth (Alder et al. 2007, Loomans et al. 2013). Depressive and anxiety disorders during pregnancy have also been significantly related with premature contractions, planned cesarean deliveries and longer labor period (Andersson et al. 2004). Some studies have also identified associations between depressive symptoms during pregnancy and various negative events during pregnancy and delivery including, preeclampsia, preterm delivery and operative deliveries (Kurki et al. 2000, Chung et al. 2001, Orr et al. 2002).

Pregnant women suffering from major depression have been found to have adverse outcomes such as low birth weight, Apgar score < 7 at 5 min, admission to NICU, still birth and preterm birth (Räisänen et al. 2014). Specifically, antenatal depression is strongly associated with shorter head circumference (Barros et al. 2013, Brittain et al. 2015). However, when infants having larger head circumference and born to depressed mothers were studied, more signs of stress and abstinence (e.g., neonatal withdrawal syndrome, neonatal abstinence syndrome) on infants were observed (Barros et al. 2013). A study by Engel et al. (2005) found Post-traumatic Stress Symptomatology (PTSS) in the mothers during pregnancy to be inversely associated with head circumference at birth, and with each one unit increase in the scores of Post-traumatic Stress Disorder Checklist (PCL), head circumference was decreased by 0.07 cm. Nevertheless, the same study found no significant association with anxiety or depression and infant head circumference at birth. Similarly, a study by Broekman et al. (2014) did not find any significant association between anxiety, depression and head circumference. In addition, maternal life time depression was also not

associated with infant's head circumference, even though it was found to be associated with shorter duration of pregnancy (Gudmundsson et al. 2011).

2.8.2. Long-term effects on offspring

Maternal stress during pregnancy has been found to influence the child's development and health in a long term. Biological, mental, behavioral and medical complications have been found in children born to anxious mothers. These children may also experience impaired cognitive development, emotional problems and concentration difficulties. Irritability, weak interaction among mother and child and fear in dealing with life events is common. Children of anxious mothers have also been found to be dealing with serious illness, such as shortness of breath, asthma and coronary disease, during different life phases (Shahhosseini et al. 2015).

In addition, mothers who had experienced anxiety during pregnancy had 1.39 times increased risk of their children being diagnosed with comorbid anxiety and depression at the age of 18 (Capron et al. 2015). Similar findings were observed with depression, as the offspring of depressed mothers during pregnancy were 1.28 times more likely to have depression at age of 18 years (Pearson et al. 2013). Also, a slight increase in criminal behavior was significantly observed in the male offspring of mothers who were depressed during the antenatal period in a Finnish cohort study (Mäki et al. 2013). However, these findings need to be interpreted with caution as they are possibly limited by a number of intervening confounding factors such as genetic or environmental influence, life events, etc.

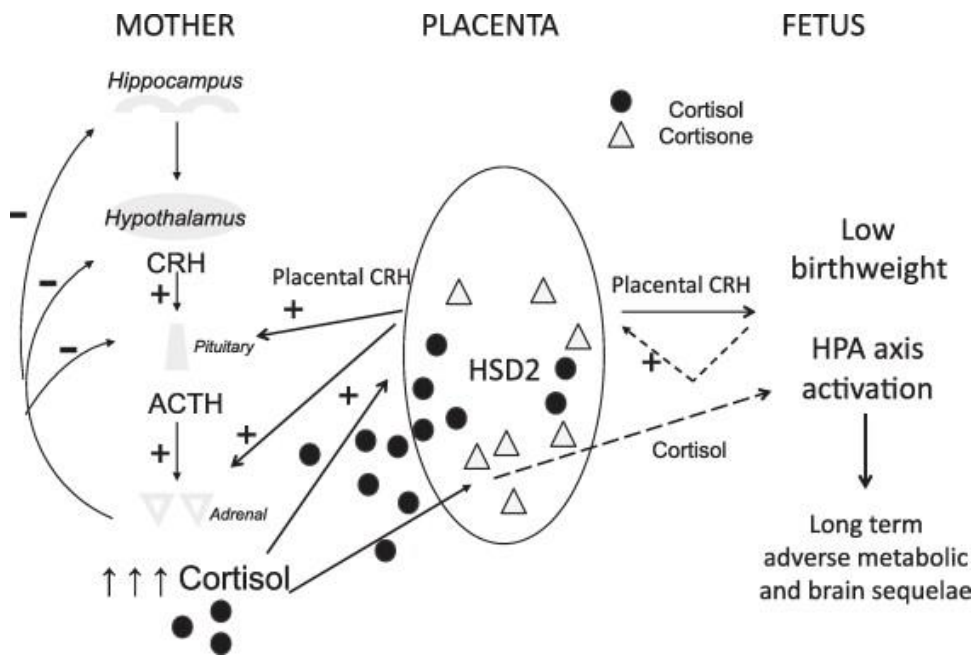
2.9. Possible biological mechanism

Fairly little is known about the mechanism explaining the association between maternal stress and fetal development in humans. One possible explanation could be the decreased blood flow to the fetus. Women with high anxiety were reported to have abnormal blood flow to the uterine arteries (Teixeira et al.1999).

Another explanation could be the high level of cortisol exposure to the fetus. Glucocorticoids, such as cortisol are known to have adverse effect on the fetus, including the fetus' brain (Herbert et al. 2006). Even though they are important for fetal development, in particular tissue formation,

exposure to high levels of glucocorticoids can have adverse effects in later life (Harris & Seckl 2011).

Figure 2: Signaling of glucocorticoid between mother, placenta and fetus (from Reynolds 2013).



CRH – corticotropin releasing hormone; ACTH – adrenocorticotropin hormone; HSD2 – 11 β hydroxysteroid dehydrogenase type 2.

The impact of overexposure to glucocorticoids and the interaction between mother, placenta and fetus during pregnancy are shown in figure 2. Maternal hypothalamic–pituitary–adrenal (HPA) axis is activated, leading to increasing levels of circulating cortisol. In addition, maternal pituitary and adrenal glands are stimulated by placental CRH, which increases cortisol levels. Maternal cortisol again stimulates the production of placental CRH. Cortisol passes through placenta and is then broken by the HSD2 enzyme into inactive cortisone. When fetal metabolic demand increases, the fetus signals to placenta to stimulate placental CRH production. Excessive fetal exposure to cortisol activates fetal HPA axis, which is associated with low birth weight and other adverse outcomes (Reynolds 2013).

3. OBJECTIVES OF THE STUDY

3.1. Main Objective

The main objective of the study was to investigate the associations between anxiety and depression during pregnancy, as assessed with EPDS, and birth outcomes.

3.2. Specific objectives

The specific objectives of the study were to investigate:

1. The prevalence of and differences in adverse birth outcomes between four groups: women experiencing 1) anxiety only 2) depression only 3) both anxiety and depression 4) no anxiety and no depression during third trimester of pregnancy.
2. Whether women in comorbid anxiety and depression group display different birth outcomes from non-anxious, non-depressed pregnant women after taking into account several factors potentially confounding the above associations.

3.3. Research questions and hypotheses

Q1: Is there any difference in the prevalence of adverse birth outcomes among four different groups: women experiencing 1) anxiety only 2) depression only 3) both anxiety and depression 4) no anxiety and no depression during third trimester of pregnancy?

H1: The prevalence of adverse birth outcomes is higher among women experiencing both anxiety and depression during third trimester of pregnancy.

Q2: Are comorbid anxiety and depression during third trimester of pregnancy associated with adverse birth outcomes?

H2: Comorbid anxiety and depression during third trimester of pregnancy are associated with adverse birth outcomes.

4. MATERIALS AND METHODS

4.1. Kuopio Birth Cohort Study

This study was part of the Kuopio Birth Cohort (KuBiCo - Kuopio Birth Cohort 2015), a joint project between University of Eastern Finland, Kuopio University Hospital and National Institute of Health and Welfare. It is a large birth cohort study that aims to include 10,000 mother-child pairs. To date, over 3,500 women have been enrolled. The study includes pregnant women who, based on their place of residence, are estimated to give birth at Kuopio University Hospital, which is the only delivery hospital in North Savo and offers tertiary level perinatal health care. Thus, the study includes the majority of the population of pregnant women in that area. The recruitment for the study started in 2013 and is expected to be completed in 2020.

4.2. Sample

All pregnant women expected to give birth at Kuopio University Hospital were invited to participate in the study. Participants were asked to fill in a series of self-administered electronic questionnaires during their first trimester (12+6 weeks), third trimester (28+12 weeks) and postpartum (8 weeks after delivery).

4.3. Description of data

4.3.1. Background data

The first trimester questionnaire addressed background characteristics such as socio economic status, living environment, ethical issues in participating in the study, physical attributes such as height and weight, nutrition, dietary supplements, social drugs and medications. Questions related to progress of pregnancy and possible illnesses during pregnancy were inquired as part of the third trimester questionnaire.

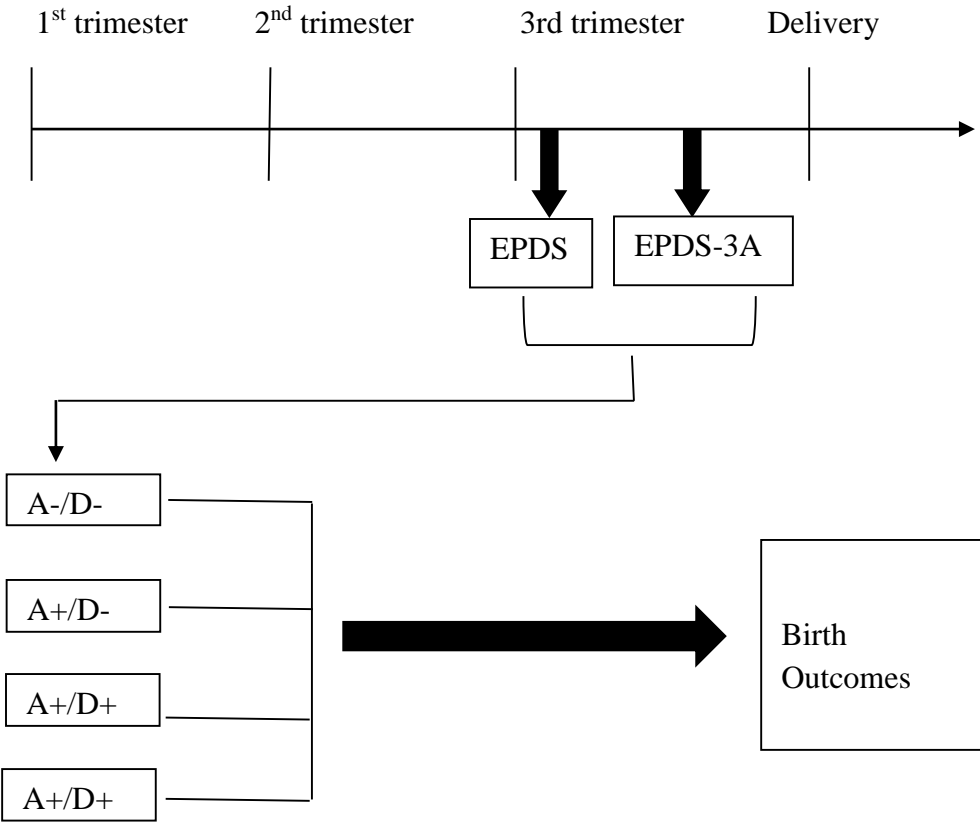
4.3.2. Evaluation of depression and anxiety

Symptoms of depression and anxiety were evaluated using the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al. 1987) and its anxiety subscale (EPDS-3A) (Phillips et al. 2009).

For the purpose of the study, the following four groups of pregnant women were identified on the basis of EPDS and EPDS 3A scores at third trimester (Figure 3):

1. Women with anxiety only (EPDS-3A \geq 4; total EPDS \leq 12)
2. Women with depression only (EPDS-3A \leq 4; total EPDS \geq 12)
3. Women with both anxiety and depression (EPDS-3A \geq 4; total EPDS \geq 12)
4. Women with no anxiety and no depression (EPDS-3A \leq 4; total EPDS \leq 12)

Figure 3: Design of the study

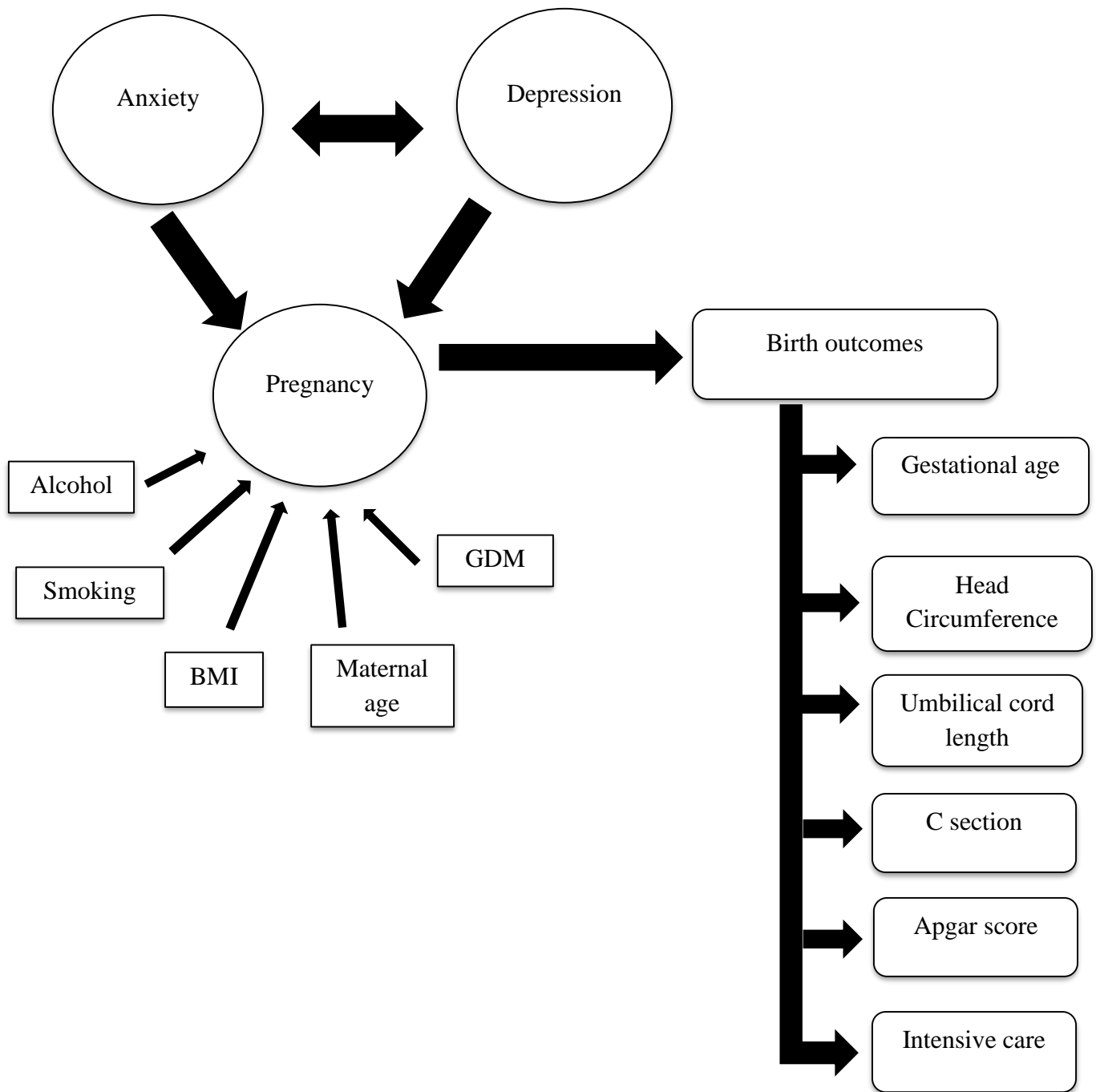


EPDS: Edinburgh Postnatal Depression Scale; A: Anxiety; D: Depression

4.3.3. Birth Outcome measures

The outcome variables for the study were gestational age, birth weight, head circumference, umbilical cord length, Apgar score, C-section (yes/no) and neonatal intensive care (yes/no). These birth outcomes were measured immediately after the delivery at the hospital by the midwives.

Figure 4: Anxiety and depression during pregnancy and birth outcomes



4.4. Statistical analyses

All statistical analyses were performed using SPSS/PASW software (version 18.0) (SPSS Inc., Chicago, IL, USA).

Firstly, descriptive analyses were carried out to detect the prevalence of adverse birth outcomes in four groups: women experiencing 1) anxiety only, 2) depression only, 3) both anxiety and depression, 4) no anxiety and no depression during third trimester of pregnancy. These groups were compared using χ -square test and ANOVA. Secondly, based on the analyses of above four groups, two groups presenting the most prominent differences were chosen for the final analyses. Thirdly, these two chosen groups were compared using χ -square test and Mann-Whitney U-test. Lastly, based on the group comparison, multivariate models were created using binary logistic regression models to study the effect of potential confounding factors on the findings of unadjusted analysis.

4.5. Ethical considerations

The ethical approval for the study has been received from the research ethics committee of the Central Finland health care district (8.12.2011, K-S shp Dnro 18U/2011). All data from this study is coded in order to protect the privacy of the participating individuals.

5. RESULTS

5.1. Characteristics of the study population

The basic characteristics of the study population are reported in table 1. The study included 921 pregnant women in their third trimester of pregnancy. Among total participants, 203 (22%) had anxiety but no depression and 66 (7.2%) had both anxiety and depression (Table 1). None of the participants were observed to have depression only.

The mean age of the participants at the time of the delivery was 29.5 years, and the mean BMI before pregnancy was 24.4. Approximately 58% of the participants were living with their partner. Additionally, 19% had gestational diabetes, 19% smoked before pregnancy and 54.5% consumed alcohol before pregnancy.

Approximately half of the women (50.4%) were having their first pregnancy, and 3.7% of them reported fear of childbirth. History of treating infertility was prevalent among 6% of total pregnant women.

Table 1: General characteristics of the study population (n=921)

| Variables | Mean (SD) |
|---|------------------|
| Mother's age at birth (Years) | 29.5 (5.0) |
| BMI before pregnancy (Kg/m ²) | 24.4 (5.0) |
| | N (%) |
| Partnership status (Without partner) | 389 (42.2) |
| Maternal gestational diabetes (Yes) | 174 (18.9) |
| Smoking before pregnancy (Yes) | 173 (18.8) |
| Alcohol use before pregnancy (Yes) | 502 (54.5) |
| First pregnancy (Yes) | 464 (50.4) |
| Fear of birth (Yes) | 34 (3.7) |

| | |
|-------------------------------------|----------|
| Infertility (Yes) | 56 (6.1) |
| Psychiatric history (Yes) | 68 (7.4) |
| Mental health disorder | |
| With anxiety and without depression | 203 (22) |
| With both anxiety and depression | 66 (7.2) |

5.2. Characteristics of the newborn

The basic characteristics of the newborns are presented in table 2. The mean gestational age was 279.31 days and the mean birth weight was 3508 grams. Additionally, the mean head circumference and umbilical cord length were 35.19 cm and 59.28 cm respectively. An Apgar score lower than 7 at the 1-minute and 5-minutes assessment were reported for 3% and 0.8% of the newborns, respectively. About 10% of the newborns were born by cesarean deliveries and 2.3% needed neonatal intensive care (Table 2).

Table 2: General characteristics of the newborn (n=921)

| Variables | |
|----------------------------------|-------------------|
| | Mean (SD) |
| Gestational age (Days) | 279.31 (10.51) |
| Birth weight (Grams) | 3508.50 (485.471) |
| Head circumference at birth (cm) | 35.19 (1.76) |
| Umbilical cord length (cm) | 59.28 (12.88) |
| | N (%) |
| Apgar score 1 minutes (0-6) | 28 (3) |
| Apgar score 5 minutes (0-6) | 7 (0.8) |
| Neonatal intensive care (Yes) | 21 (2.3) |
| C-Section (Yes) | 96 (10.4) |

5.3. Background characteristics and birth outcomes in mental health categories of interest

The distribution of the study variables in the three groups (women with anxiety and not depression, with both anxiety and depression and with no anxiety and no depression) are shown in table 3. There were significant differences in head circumference at birth, maternal age at birth, BMI at the beginning of pregnancy, C-section, psychiatric history, first pregnancy, smoking before pregnancy and fear of childbirth among the study groups (Table 3).

Table 3: Background characteristics and birth outcomes in mental health categories of interest

| | Anxiety only N=203 | Anxiety and depression N=66 | No anxiety and No depression N=652 | Test value | P- value |
|--|-------------------------------|--|---|-----------------------|---------------------|
| | Mean (SD) | | | | |
| Gestational age (Days) | 280.03 (9.21) | 279.03 (9.86) | 279.11 (10.95) | 0.888 | 0.642 ^c |
| Birth weight (Grams) | 3526.26 (445.30) | 3541.29 (497.72) | 3499.65 (496.50) | 1.631 | 0.443 ^c |
| Head circumference at birth (cm) | 35.18 (2.36) | 35.66 (1.52) | 35.14 (1.55) | 8.600 | 0.014 ^c |
| Umbilical cord length (cm) | 59.29 (13.74) | 60.30 (11.70) | 59.18 (12.72) | 0.833 | 0.659 ^c |
| Maternal age at birth (Years) | 28.90 (5.22) | 28.80 (5.06) | 29.78 (4.90) | 7.970 | 0.019 ^c |
| BMI at beginning of pregnancy (Kg/m ²) | 25.26 (5.67) | 25.85 (6.38) | 24.02 (4.61) | 8.672 | 0.013 ^c |
| | N (%) | | | | |
| Apgar score 1 min (0-6) | 5 (2.5%) | 2 (3%) | 21 (3.2%) | 0.282 | 0.898 ^b |

| | | | | | |
|----------------------------------|-------------|------------|-------------|--------|--------------------|
| Apgar score 5 min (0-6) | 1 (0.5%) | 1 (1.5%) | 5 (0.8%) | 1.201 | 0.624 ^b |
| C section (Yes) | 13 (6.4%) | 11 (16.7%) | 72 (11%) | 6.536 | 0.038 ^a |
| Emergency care (Yes) | 1 (0.5%) | 1 (1.5%) | 19 (2.9%) | 4.186 | 0.116 ^b |
| Marital status (Without partner) | 87 (42.9%) | 26 (39.4%) | 276 (42.3%) | 0.253 | 0.881 ^a |
| Psychiatric history (Yes) | 18 (8.9%) | 15 (22.7%) | 35 (5.4%) | 27.249 | 0.000 ^a |
| First pregnancy (Yes) | 124 (61.1%) | 33 (50%) | 307 (47.1%) | 12.138 | 0.002 ^a |
| Gestational diabetes (Yes) | 41 (20.2%) | 18 (27.3%) | 115 (17.6%) | 3.920 | 0.141 ^a |
| Smoking before pregnancy (Yes) | 57 (28.1%) | 19 (28.8%) | 97 (14.9%) | 22.349 | 0.000 ^a |
| Alcohol before pregnancy (Yes) | 111 (54.7%) | 39 (59.1%) | 352 (54%) | 0.633 | 0.730 ^a |
| Infertility (Yes) | 9 (4.4%) | 2 (3%) | 45 (6.9%) | 2.361 | 0.317 ^b |
| Fear of childbirth (Yes) | 7 (3.4%) | 8 (12.1%) | 19 (2.9%) | 14.333 | 0.001 ^a |

^a Chi-squared test, ^bFisher's exact test, ^c Kruskal-Wallis Test

5.4. Distribution of background characteristics and birth outcomes between comorbid anxiety and depression group vs. the non-anxious, non-depressed group

The distribution and means of the study variables in women with no anxiety and no depression vs. women with comorbid anxiety and depression are shown in table 4. The two groups significantly differed with regard to psychiatric history, smoking before pregnancy, fear of childbirth and the newborn's head circumference at birth (Table 4).

Table 4: Differences in background characteristics and birth outcomes between comorbid anxiety and depression group vs. the non-anxious, non-depressed group

| | No anxiety and no depression N=652 | Comorbid anxiety and depression N=66 | Test value | P-value |
|--|---------------------------------------|---|------------|--------------------|
| | Mean (SD) | | | |
| Gestational age (Days) | 279.11 (10.95) | 279.03 (9.86) | -0.55 | 0.580 ^c |
| Birth weight (Grams) | 3499.65 (496.50) | 3541.29 (497.72) | -1.14 | 0.252 ^c |
| Head circumference at birth (cm) | 35.14 (1.55) | 35.66 (1.52) | -2.81 | 0.005 ^c |
| Umbilical cord length (cm) | 59.18 (12.72) | 60.30 (11.70) | -0.85 | 0.392 ^c |
| Mother's age at birth (Years) | 29.78 (4.90) | 28.80 (5.06) | -1.65 | 0.099 ^c |
| BMI at beginning of pregnancy (Kg/m ²) | 24.02 (4.61) | 25.85 (6.38) | -1.72 | 0.084 ^c |
| | N (%) | | | |
| Apgar score 1 min (0-6) | 21 (3.2%) | 2 (3%) | - | 1.000 ^b |
| Apgar score 5 min (0-6) | 5 (0.8%) | 1 (1.5%) | - | 0.440 ^b |
| C section (Yes) | 72 (11%) | 11 (16.7%) | 1.85 | 0.173 ^a |
| Emergency care (Yes) | 19 (2.9%) | 1 (1.5%) | - | 1.000 ^b |
| Marital status (Without partner) | 276 (42.3%) | 26 (39.4%) | 0.21 | 0.645 ^a |

| | | | | |
|--------------------------------|-------------|------------|-------|--------------------|
| Psychiatric history (Yes) | 35 (5.4%) | 15 (22.7%) | 27.87 | 0.000 ^a |
| First pregnancy (Yes) | 307 (47.1%) | 33 (50%) | 0.20 | 0.651 ^a |
| Gestational diabetes (Yes) | 115 (17.6%) | 18 (27.3%) | 3.68 | 0.055 ^a |
| Smoking before pregnancy (Yes) | 97 (14.9%) | 19 (28.8%) | 8.56 | 0.003 ^a |
| Alcohol before pregnancy (Yes) | 352 (54%) | 39 (59.1%) | 0.62 | 0.428 ^a |
| Infertility (Yes) | 45 (6.9%) | 2 (3%) | - | 0.301 ^b |
| Fear of childbirth (Yes) | 19 (2.9%) | 8 (12.1%) | 14.03 | 0.000 ^a |

^a Chi-squared test, ^b Fisher's exact test, ^c Mann-Whitney U-test

5.5. Multivariate modeling

In a binary logistic regression model, head circumference at birth was significantly associated with comorbid anxiety and depression during pregnancy after controlling for possible confounding factors (Table 5). With each 1-unit increase in head circumference, the likelihood of comorbidity was 1.2 fold (OR=1.239, 95% CI=,1.034-1.484, P=0.020). Similarly, smoking before pregnancy (OR=1.872, 95% CI=1.018-3.443, P=0.043), and BMI before pregnancy (OR=1.055, 95% CI=1.002-1.110, P=0.041) were significantly associated with increased likelihood of belonging to the comorbid anxiety and depression group.

Table 5: Multivariate model for birth outcomes and comorbidity

| | OR | 95% CI (for OR) | P-value |
|-----------------------------|-----------|------------------------|----------------|
| Head circumference at birth | 1.239 | 1.034 - 1.484 | 0.020 |
| Maternal age at birth | 0.959 | 0.908 - 1.012 | 0.127 |
| Relationship status | | | |
| With partner | 1.194 | 0.702 - 2.033 | 0.513 |
| Smoking before pregnancy | | | |
| Yes | 1.872 | 1.018 - 3.443 | 0.043 |

| | | | |
|-------------------------------|-------|---------------|-------|
| BMI before pregnancy | 1.055 | 1.002 - 1.110 | 0.041 |
| Maternal gestational diabetes | | | |
| Yes | 1.351 | 0.714 - 2.556 | 0.355 |

6. DISCUSSION

6.1. Summary of main findings

Comorbid anxiety and depression during third trimester of pregnancy were found to be significantly associated with larger head circumference at birth, higher BMI before pregnancy and smoking before pregnancy. In specific, with every 1-unit increase in head circumference, the likelihood of belonging to the comorbid anxiety and depression group increased by 20% even after controlling for maternal age, relationship status, BMI before pregnancy, smoking before pregnancy and maternal gestational diabetes.

6.2. Comparison with previous studies

Many studies have analysed the potential associations between anxiety only or depression only and several birth outcomes. However, only a limited number of studies have specifically examined head circumference as birth outcome. Among those studies, maternal depression was shown to be associated with decreased head circumference (Brittain et al. 2015), and no significant association was established with head circumference and anxiety (Engel et al. 2005, Broaekman et al. 2014). Previous studies have identified relationships between smaller head circumference and maternal stress (Lou et al. 1994, Singer et al. 2002).

In the present study, I studied the combined effect of anxiety and depression on head circumference, while Broaekman et al. (2014) assessed anxiety and depression scores separately. In addition, the Broaekman study was conducted in an Asian cohort, while the present study comprised Finnish participants. The difference in lifestyle among Asian and European mothers might also play an important role in having discrepant findings.

The present study found a positive association among head circumference at birth and comorbid anxiety and depression during third trimester of pregnancy. This is a novel finding. The larger head circumference might be due to greater birth weight of the newborns. We observed that the mean birth weight was greater, though not significantly, among those who were born by the mothers with comorbid anxiety and depression than without anxiety and without depression. In addition, BMI before pregnancy was significantly associated with combined anxiety and depression. Moreover,

maternal BMI before pregnancy has been associated with greater birth weight in newborns (Frederick et al. 2008).

A study by Barros et al. (2013) revealed that the infants born to depressed mothers and with larger head circumference, showed more signs of stress and abstinence (e.g., neonatal withdrawal syndrome, neonatal abstinence syndrome) when diagnosed by Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNS) at 24 to 72 hours of life. Larger head circumference has also been associated with major adverse labor outcomes (e.g., maternal distress, fetal distress) and increased risk for prolonged labor (Kennelly et al 2003, Elvander et al. 2012). Moreover, it is associated with higher prevalence of vacuum assisted vaginal delivery and cesarean section (Elvander et al. 2012, Mujugira et al. 2013, Lipschuetz et al. 2015).

The association between smoking and comorbid anxiety and depression has been well established in other studies (Ibanez et al. 2012). Most of the studies are focused on anxiety only or depression only. The history of smoking was associated with anxiety only (Lee et al. 2007) and depression only (Jeong et al. 2013) separately. However, other studies (Lee et al. 2007, Luke et al. 2009) found no significant associations between smoking and antenatal depression.

High maternal BMI before pregnancy was significantly associated with comorbid anxiety and depression which is in line with previous studies (Ibanez et al. 2012). Thus this can be considered to represent an established association. Anxiety and depression individually are also associated with BMI before pregnancy (Carter et al. 2000).

6.3. Strengths and limitations of the study

All the pregnant women who were expected to give birth at Kuopio University Hospital were offered a possibility to participate in the study, thus limiting the selection bias. Since the whole study sample was collected within the same hospital, an exactly similar protocol was used to gather all data. Moreover, the birth outcome data was recorded immediately after the delivery at the hospital. In addition, EPDS is also a very established measure of depression, which can be considered to be a strength. Using EPDS as a tool to measure anxiety is a newer approach, but EPDS-3A has been shown to evaluate anxiety in an appropriate manner in previous works (Swalm et al. 2009, Matthey et al. 2013).

Some limitations need to be taken into consideration while interpreting the findings from this study. First, there were several cases with missing data, which reduced the sample size, thus also affecting the statistical power. Second, we did not have information on family support or antidepressants use during pregnancy. Being able to take these variables into account in statistical analyses might have reduced the possible confounding effects. Also, present status of smoking and drinking alcohol during pregnancy were not used in the study as the participants are less likely to disclose these negatively viewed behaviors during pregnancy. Furthermore, in a small pilot study conducted as part of the KuBiCo study, we observed large discrepancy between self-reported smoking and biomarkers detecting active smoking. Thus, we used smoking and drinking alcohol before pregnancy as more general descriptors of maternal health behaviors. Third, a self-administered questionnaire was used to measure anxiety and depression, which could be less accurate than the psychiatric examination. However, subjective measures were calculated by EPDS questionnaire, which is a well-validated tool with high reliability and internal consistency. Fourth, there was no separate measure for anxiety as an EPDS subscale was also used to measure anxiety. However, previous evidence supports the use of EPDS in measuring anxiety (Swalm et al. 2009, Matthey et al. 2013).

7. CONCLUSION

The evidence from this study suggest that the head circumference at birth may be associated with comorbid anxiety and depression during third trimester of pregnancy. Given the potential influence of anxiety and depression on birth outcomes, further research on the possible underlying biological mechanisms is required, along with longitudinal studies on maternal health and later effect on newborns.

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9. APPENDICES

Appendix 1: EPDS Questionnaire

Edinburgh Postnatal Depression Scale¹ (EPDS)

Name: _____ Address: _____

Your Date of Birth: _____

Baby's Date of Birth: _____ Phone: _____

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:

- Yes, all the time
 Yes, most of the time This would mean: "I have felt happy most of the time" during the past week.
 No, not very often Please complete the other questions in the same way.
 No, not at all

In the past 7 days:

- | | |
|---|--|
| 1. I have been able to laugh and see the funny side of things <input type="checkbox"/> As much as I always could <input type="checkbox"/> Not quite so much now <input type="checkbox"/> Definitely not so much now <input type="checkbox"/> Not at all | *6. Things have been getting on top of me <input type="checkbox"/> Yes, most of the time I haven't been able to cope at all <input type="checkbox"/> Yes, sometimes I haven't been coping as well as usual <input type="checkbox"/> No, most of the time I have coped quite well <input type="checkbox"/> No, I have been coping as well as ever |
| 2. I have looked forward with enjoyment to things <input type="checkbox"/> As much as I ever did <input type="checkbox"/> Rather less than I used to <input type="checkbox"/> Definitely less than I used to <input type="checkbox"/> Hardly at all | *7. I have been so unhappy that I have had difficulty sleeping <input type="checkbox"/> Yes, most of the time <input type="checkbox"/> Yes, sometimes <input type="checkbox"/> Not very often <input type="checkbox"/> No, not at all |
| *3. I have blamed myself unnecessarily when things went wrong <input type="checkbox"/> Yes, most of the time <input type="checkbox"/> Yes, some of the time <input type="checkbox"/> Not very often <input type="checkbox"/> No, never | *8. I have felt sad or miserable <input type="checkbox"/> Yes, most of the time <input type="checkbox"/> Yes, quite often <input type="checkbox"/> Not very often <input type="checkbox"/> No, not at all |
| 4. I have been anxious or worried for no good reason <input type="checkbox"/> No, not at all <input type="checkbox"/> Hardly ever <input type="checkbox"/> Yes, sometimes <input type="checkbox"/> Yes, very often | *9. I have been so unhappy that I have been crying <input type="checkbox"/> Yes, most of the time <input type="checkbox"/> Yes, quite often <input type="checkbox"/> Only occasionally <input type="checkbox"/> No, never |
| *5. I have felt scared or panicky for no very good reason <input type="checkbox"/> Yes, quite a lot <input type="checkbox"/> Yes, sometimes <input type="checkbox"/> No, not much <input type="checkbox"/> No, not at all | *10. The thought of harming myself has occurred to me <input type="checkbox"/> Yes, quite often <input type="checkbox"/> Sometimes <input type="checkbox"/> Hardly ever <input type="checkbox"/> Never |

Administered/Reviewed by _____ Date _____

¹Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786 .

²Source: K. L. Wisner, B. L. Parry, C. M. Piontek, Postpartum Depression N Engl J Med vol. 347, No 3, July 18, 2002, 194-199

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Edinburgh Postnatal Depression Scale¹ (EPDS)

Postpartum depression is the most common complication of childbearing.² The 10-question Edinburgh Postnatal Depression Scale (EPDS) is a valuable and efficient way of identifying patients at risk for "perinatal" depression. The EPDS is easy to administer and has proven to be an effective screening tool.

Mothers who score above 13 are likely to be suffering from a depressive illness of varying severity. The EPDS score should not override clinical judgment. A careful clinical assessment should be carried out to confirm the diagnosis. The scale indicates how the mother has felt **during the previous week**. In doubtful cases it may be useful to repeat the tool after 2 weeks. The scale will not detect mothers with anxiety neuroses, phobias or personality disorders.

Women with postpartum depression need not feel alone. They may find useful information on the web sites of the National Women's Health Information Center <www.4women.gov> and from groups such as Postpartum Support International <www.chss.iup.edu/postpartum> and Depression after Delivery <www.depressionafterdelivery.com>.

SCORING

QUESTIONS 1, 2, & 4 (without an *)

Are scored 0, 1, 2 or 3 with top box scored as 0 and the bottom box scored as 3.

QUESTIONS 3, 5-10 (marked with an *)

Are reverse scored, with the top box scored as a 3 and the bottom box scored as 0.

Maximum score: 30
Possible Depression: 10 or greater
Always look at item 10 (suicidal thoughts)

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Instructions for using the Edinburgh Postnatal Depression Scale:

1. The mother is asked to check the response that comes closest to how she has been feeling in the previous 7 days.
2. All the items must be completed.
3. Care should be taken to avoid the possibility of the mother discussing her answers with others. (Answers come from the mother or pregnant woman.)
4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.

¹Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786.

²Source: K. L. Wisner, B. L. Parry, C. M. Piontek, Postpartum Depression N Engl J Med vol. 347, No 3, July 18, 2002, 194-199

Appendix 2: Growth chart for Infant Head Circumference-for-age

Table 6: Growth chart for Infant Head Circumference-for-age (CDC 2001).

| | 3rd Percentile | 5th Percentile | 10th Percentile | 25th Percentile | 50th Percentile | 75th Percentile | 90th Percentile | 95th Percentile | 97th Percentile |
|---------------|---------------------------|---------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| Male | 31.48762 | 32.14881 | 33.08389 | 34.46952 | 35.81367 | 37.00426 | 37.97379 | 38.51574 | 38.85417 |
| Female | 31.9302 | 32.2509 | 32.75949 | 33.65187 | 34.71156 | 35.85124 | 36.9535 | 37.65138 | 38.1211 |