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Eclampsia, maternal deaths, and hypertensive diseases of pregnancy and long term maternal health risk

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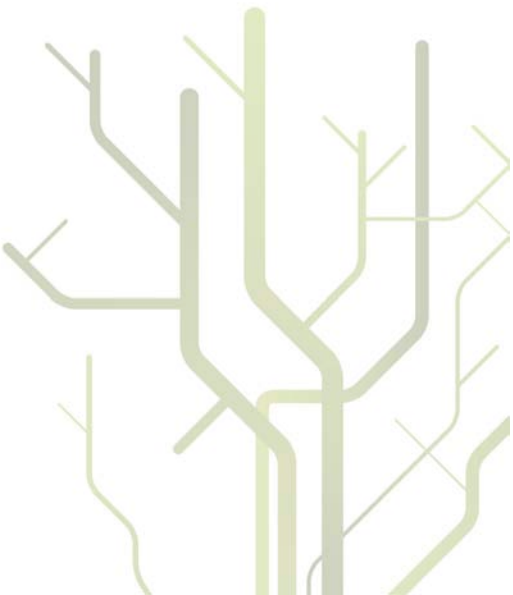

EXAMINATION COMMITTEE

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3RD OPPONENT

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CONTENTS

1. ACKNOWLEDGEMENTS

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2. LIST OF PAPERS

This thesis is based on the following papers

Study I

Andersgaard AB, Herbst A, Johansen M, Ivarsson A, Ingemarsson I, Langhoff-Roos J, Henriksen T, Straume B, Øian P. Eclampsia in Scandinavia: incidence, substandard care, and potentially preventable cases. Acta Obstet Gynecol Scand 2006;85:929-36.

Study II

Andersgaard AB, Herbst A, Johansen M, Borgström A, Bille AG, Øian P. Follow-Up Interviews after Eclampsia. Gynecol Obstet Invest 2009;67:49-52.

Study III

Andersgaard AB, Acharya G, Ellisiv Mathiesen, Stein Harald Johnsen, Straume B, Øian P. Recurrence and long-term maternal health risks of hypertensive disorders of pregnancy: a population based study. Submitted.

Study IV

Andersgaard AB, Langhoff-Roos J and Øian P. Direct maternal deaths in Norway 1976-1995. Acta Obstet Gynecol Scand 2008;87:856-61.

3. ABBREVIATIONS

ALAT	Alanin-aminotransferase
ASAT	Aspartat-aminotransferase
BMI	Body mass index
BP	Blood pressure
CVD	Cardio vascular disease
CI	Confidence interval
GP	general practitioner
HDL	High density lipoprotein
HELLP	Haemolysis, elevated liver enzymes and low platelet count
ICD 10	International Statistical Classification of Diseases and Related Health Problems. Tenth Revision.
IMT	Intima-media thickness
LDL	Low density lipoprotein
MBRN	Medical Birth Registry of Norway
$MgSO_4$	Magnesium sulphate
MMR	Maternal Mortality Ratio defined as number of maternal deaths per 100,000 live births (WHO)
MRI	Magnetic resonance imaging
NNT	Numbers needed to treat
RCOG	Royal College of Obstetricians and Gynaecologists
SGA	Small for gestational age
UK	United Kingdom

4. BACKGROUND

4.1 General introduction

Hypertensive diseases of pregnancy are the leading causes of fetal and maternal morbidity and mortality. Pre-eclampsia is a multiorgan disease process of unknown aetiology characterized by the development of hypertension and proteinuria after 20 weeks of gestation. Delivery is the only cure for pre-eclampsia. Decisions regarding the timing and mode of delivery are based on a combination of maternal and fetal factors.

Ten percent of women have high blood pressure during pregnancy and pre-eclampsia complicates 3-5% of all pregnancies (1). Eclampsia is the occurrence of convulsions in association with the signs and symptoms of pre-eclampsia. It is traditionally considered a more severe form of pre-eclampsia and complicates nearly one in 2000 pregnancies (2;3).

Pre-eclampsia and cardiovascular diseases share many risk factors and increased risk of cardiovascular disease among women with a previous history of pre-eclampsia is well described. It is suggested that pregnancy is a screening test for later hypertension and diabetes (4). This might reflect a common cause for pre-eclampsia and cardiovascular disease or an effect of pre-eclampsia on development of cardiovascular diseases.

Pre-eclampsia is together with thromboembolism, the leading underlying causes of maternal death. Maternal death in Europe is a rare event and the maternal mortality ratios (MMR) in European countries are low compared to that in developing countries (5-12). Hogan et al estimated that there were 342,900 (uncertainty interval 302,100-394,300) maternal deaths worldwide in 2008 (6), thus 940 women die from complication in pregnancy or childbirth every day. Each death of a mother represents a tragedy and most deaths are avoidable.

4.2 Definitions

Hypertensive diseases of pregnancy

The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000, defined four categories of hypertension in pregnancy: pre-eclampsia/eclampsia, gestational hypertension, chronic hypertension and pre-eclampsia superimposed on chronic hypertension (1).

Pre-eclampsia is defined as a pregnancy-specific syndrome observed after the 20th week of pregnancy with systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mmHg, accompanied by significant proteinuria. Proteinuria is defined as the urinary excretion of 0.3g protein or greater in a 24-hour specimen. This will usually correlate with 30mg/dL ("1+ dipstick") or greater in a random urine determination with no evidence of urinary tract infection.

Eclampsia is the occurrence of seizure(s) superimposed on pre-eclampsia, during pregnancy or in the first 10 days postpartum, that cannot be attributed to other causes.

Gestational hypertension is determined by increased blood pressure of ≥140 / 90 mm Hg in a woman normotensive before 20 weeks without proteinuria.

Chronic hypertension is defined as hypertension that is present and observable before pregnancy or that is diagnosed before the 20th week of gestation. Hypertension is defined as a blood pressure ≥140 mm Hg systolic or ≥ 90 mm Hg diastolic.

Pre-eclampsia superimposed on chronic hypertension is pre-eclampsia that occurs in women with chronic hypertension. Distinguishing superimposed pre-eclampsia and worsening chronic hypertension is difficult.

In the definition of pre-eclampsia from The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 1990, pre-eclampsia included BP elevation ≥ 30 mmHg systolic or 15 mmHg diastolic from measured levels prior to the 20^{th} gestational week (13).

Maternal death

The World Health Organization and the tenth revision of the International Classification of Diseases (ICD-10), define a maternal death as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes (14). Maternal deaths are subdivided into further groups according to ICD-9/ICD-10.

*Direct maternal death***.** Deaths resulting from obstetric complications of the pregnant state (pregnancy, labour and puerperium), from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above.

*Indirect maternal death***.** Deaths resulting from previous existing disease, or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by the physiologic effects of pregnancy.

*Late maternal deaths***.** Deaths occurring between 42 days and one year after legal termination, miscarriage or delivery that are due to direct or indirect maternal causes.

*Coincidental deaths***.** Deaths from unrelated causes which happen to occur in pregnancy or the puerperium.

4.3 Pre-eclampsia and eclampsia

Pre-eclampsia is a pregnancy-specific form of hypertension that represents a major health problem and affects both fetal and maternal health. Approximately 10% of pre-eclampsia occurs before 34 weeks of gestational age and delivery for pre-eclampsia is responsible for 15% of preterm births in USA (15). The incidence of eclampsia is 5.0/10,000 maternities in United Kingdom (UK) and Scandinavia (2;3). In the study from UK nearly one in 50 women affected by eclampsia died of the condition as did one in 14 of their offspring.

Pre-eclampsia is an important indicator of an underlying multisystem syndrome and few of the adverse effects of pre-eclampsia are directly due to increased blood pressure (16).

Pathogenesis of pre-eclampsia – the underlying multisystem syndrome

The pathophysiology of pre-eclampsia involves maternal and fetal/placental factors. Redman et al argued in 1999 that pre-eclampsia is the extreme end of the range of maternal adaptation to pregnancy (17). Pre-eclampsia has been considered a two-stage disease, where the first stage involves abnormal placentation and the second the transition to the maternal systemic disorder (15;18).

First stage

Placental tissue is necessary for development of the disease. In pre-eclampsia the cytotrophoblast cells infiltrate the decidual portion of the spiral arteries, but fail to penetrate the myometrial segment (19). The spiral arteries fail to develop into large vascular channels but remain narrow and a shallow placentation leads to a dysfunctional placenta and this combined with atherosis may cause reduced placental perfusion. It is proposed that the poor placental perfusion is the cause of pre-eclampsia.

Second stage

The second stage of pre-eclampsia is described as the transition into a maternal systemic disorder. Roberts et al proposed in 1991 that reduced placental perfusion results in the production of agent(s) in the placenta, which injures or activates endothelial cells. Smarason et al demonstrated that trophoblast products can cause the maternal syndrome of pre-eclampsia through endothelial cell damage and endothelial dysfunction through deported microvilli (20;21). The resulting endothelial cell dysfunction increases sensitivity to normal endogenous pressors, activates the coagulation cascade, and increases vascular permeability (22;23). The clinical features of pre-eclampsia can be explained as responses to endothelial dysfunction.

The first model of the two stages was modified by Roberts & Hubel due to new knowledge (Figure 1) (18). The reduced placental perfusion is also present in pregnancies with intrauterine growth restriction, also without pre-eclampsia. Changes relevant to pre-eclampsia and other implantation disorders can be detected in the first trimester, long before the failed vascular remodelling. Increased platelet activation and markers of endothelial activation antedate clinically evident pre-eclampsia by weeks to months in groups of women who develop the disorder (18;24).

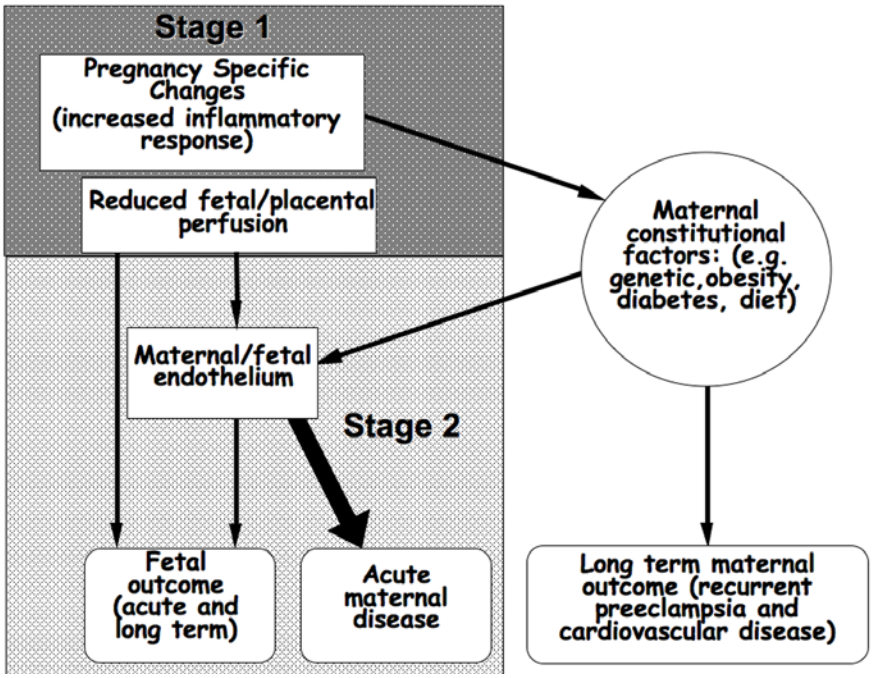

Figure 1. The modified model of the two stages by Roberts & Hubel of pre-eclampsia and the maternal and fetal interactions (18). Permission to reprint is granted through Elsevier.

This model emphasizes that reduced placental perfusion is not sufficient to cause pre-eclampsia but requires interaction with maternal constitutional factors that may be genetic, behavioural or environmental. Earlier the factor(s) released from the placenta has been considered a toxin. Roberts & Hubel suggest that what is released may be an appropriate signal from the fetal/placental unit to overcome reduced nutrient availability that cannot be tolerated by some women who develop pre-eclampsia. Further they proposed that linkage is not likely to be by one factor but several, different for different women (18).

The third review of the model was made by Redman and Sargent in 2009 (25). They argue that all the inflammatory changes of normal pregnancy are exaggerated in pre-eclampsia and that pre-eclampsia not only is an endothelial disease, but the consequence of a wider systemic inflammatory response (Figure 2).

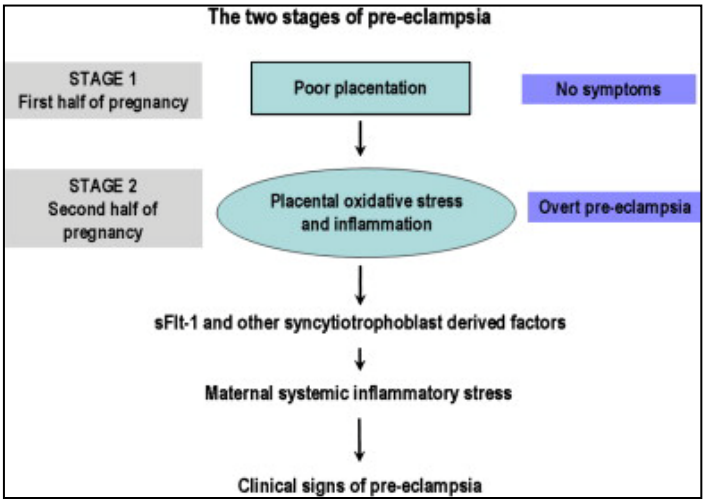

Figure 2. The third modified model of pre-eclampsia as the two stage disease including maternal inflammatory stress (25). Permission to reprint is granted through Elsevier.

Early-onset pre-eclampsia represents a considerable additional maternal risk. Von Dadelszen et al (26) proposed that gestational age is the most important variable in predicting both maternal and perinatal outcomes and subdivide pre-eclampsia into early-onset disease (< 34 + 0 weeks) and late onset disease (> 34 + 0 weeks). Vatten et al (27) argued that preterm pre-eclampsia represents a placental disease, and that term pre-eclampsia represents a mixture of conditions, ranging from mild pre-eclampsia with moderate placental involvement to hypertensive conditions without placental dysfunction or maternal reactions to the burden of pregnancy. The results of their study indicated that the heterogeneous expression of pre-eclampsia may represent separate pathogenetic entities, instead of being one fundamental process expressing varying degrees of clinical severity.

Some of the risk factors for pre-eclampsia include; nulliparity and multifetal gestation, past obstetrical history of pre-eclampsia, family history of pre-eclampsia, chronic hypertension, renal disease, autoimmune disease, antiphospholipid syndromes, obesity, insulin resistance, diabetes and thrombophilias (28). The risk factors are not highly predictive.

Pathogenesis of eclampsia

Eclampsia has been described from ancient time. In an article by Chesley he looks at different sources of the historical descriptions of eclampsia (29). Chesley sites Hippocrates (forth century BC), Celsus (first century AD) and Mauriceau (17th century). Hippocrates wrote; “It proves fatal to a woman in a state of pregnancy, if she is seized with any acute disease”. Celsus often mentioned fatal seizures in association with the extraction of dead fetuses, and much later Mauriceau had observed that the convulsions became less with delivery and in his book in 1694, he recommended prompt termination of pregnancy as the best treatment (29).

The exact cause of seizures in women with eclampsia is unknown. Sheehan and Lynch described the neurological findings in autopsies of eclamptic women, most performed within 1 to 2 hours after death (30). More than 60 percent of the eclamptic patients, who died within two days of seizures, had cerebral haemorrhages or ischaemic softening scattered throughout the brain. Cerebral venous thrombosis was common in women with postpartum eclampsia. Of the cerebral haemorrhages, petechial cortical haemorrhages involving the occipital lobe were most common. Sheehan and Lynch explained the cortical petechiae with periods of vasoconstriction which cause damage to the cortical tissue and the vessels there. When the vasoconstriction passes off some blood escapes through the injured walls of the vessels and

produces small haemorrhages. Sheehan and Lynch concluded that the theory of cerebral oedema in eclampsia could not be accepted. As opposed to this Zeeman et al examined 27 women after eclampsia with magnetic resonance imaging (MRI) (31) and found that 25 of these 27 women had reversible vasogenic oedema. Six also had areas of cytotoxic oedema consistent with cerebral infarction. The cerebral oedema involved the subcortical white and adjacent gray matter in the parieto-occipital lobes. The authors conclude that the spectrum of cerebral lesions in eclampsia as seen with MRI varies from initially reversible areas of vasogenic oedema that may progress to cytotoxic oedema and infarction in up to a fourth of women.

The difference in the findings in these two studies might be explained by the fact that the study populations were different. Sheehan and Lynch' study was based on autopsies, while Zeeman's was based on women who survived eclampsia.

These two studies demonstrate the two major hypotheses explaining eclampsia. The first is similar to the one described above by Sheehan and Lynch starting with cerebral overregulation in response to high systemic blood pressure resulting in vasospasm of cerebral arteries and localized ischemia, cytotoxic oedema and infarction. In the second eclampsia is explained by loss of autoregulation resulting in hyperperfusion, endothelial damage and vasogenic oedema. It has also been questioned whether the cerebral blood flow really is altered. The lesions might be a result of extravasations of fluid and protein across disrupted endothelium (32).

In an article by Cippola, she supports the findings of Zeeman and describes the major cerebrovascular changes in eclampsia to be similar to those for hypertensive encephalopathy, including loss of cerebral blood flow autoregulation, hyperperfusion and oedema (33). Her summary of similarities between hypertensive encephalopathy and eclampsia includes that both can arise from an acute elevation in blood pressure and the findings on MRI. There are also similar neurological symptoms with headache, vomiting, cortical blindness and seizures. Both in hypertensive encephalopathy and eclampsia the symptoms are reversible after blood pressure has been restored.

Management of pre-eclampsia

Prenatal care, history on risk factors, blood pressure and proteinuria screening are important to diagnose pre-eclampsia. Pre-eclampsia is classified according to severity of blood-pressure, extent of proteinuria in combination with laboratory tests, the woman's symptoms and gestational age at onset. The treatment of pre-eclampsia is to recognise the disease and find the right timing of delivery, to prevent maternal or fetal complications from disease progression.

Pre-eclampsia progresses through a continuum, but the rate of progression differ from one woman to another. A woman with pre-eclampsia is evaluated through maternal and fetal assessment. The time of delivery will depend on fetal gestational age, fetal status and the severity of maternal condition, were the safety of the mother is the main objective of management. Most guidelines suggest delivery rather than expectant management for women with pre-eclampsia who are ≥37 weeks of gestation with a favourable cervix (34;35).

Severe pre-eclampsia is defined with one or more of the following features; BP ≥ 160/110 mmHg, proteinuria ≥3.0 g in 24 hours (2+ or 3+ on qualitative examination) or symptoms of severe headache, visual disturbances, epigastric pain, platelet count falling below 100 x 10^9/l, increased serum creatinine (>1.2 mg/dL), elevated liver enzymes or HELLP syndrome (36). HELLP is a specific subset of signs and symptoms characterized by haemolysis (H), elevated liver (EL) enzymes and low platelet (LP) count (1).

Severe pre-eclampsia is regarded an indication for delivery regardless of gestational age, and the decision to deliver should be made once the woman is stable. Antihypertensive treatment is recommended to prevent cerebrovascular complications with blood pressure ≥160/110 mmHg (37;38), but antihypertensive drugs do not prevent the progression of pre-eclampsia. To prevent eclampsia in patient with pre-eclampsia anticonvulsants are used. C. W. Redman writes in the text book "Obstetrics": "The commonest difficulty is to identify accurately which patients are likely to have fits" (39).

In the" The Magpie Trial", Altman et al randomised 10,441 women with pre-eclampsia to magnesium sulphate ($MgSO_4$) versus placebo (40). The risk of eclampsia was more than halved amongst women with pre-eclampsia following $MgSO_4$ therapy; the overall numbers needed to treat (NNT) was found to be 91, and for a subgroup of women with severe pre-eclampsia 69. It is still questioned whether it is reasonable to treat 69 women with severe pre-

eclampsia with $MgSO_4$ therapy to save one woman from suffering eclamptic seizures. Ideally, we would seek to find better means of identifying those who are at a high risk of developing eclampsia and treat these for the benefit of the mother and her baby.

The Cochrane review by Duley et al included studies on $MgSO_4$ for women with pre-eclampsia and concluded (41); $MgSO_4$ more than halves the risk of eclampsia, and probably reduces the risk of maternal death. It does not improve (40;41) short term outcome for the baby. A quarter of women treated with $MgSO_4$ have side effects, particularly flushing.

According to RCOG's guidelines on "Management of severe pre-eclampsia/eclampsia" $MgSO_4$ should be given to women with severe pre-eclampsia once a delivery decision has been made and in the immediate postpartum period (37). In the Norwegian guideline (38) $MgSO_4$ is recommended based on careful assessment of severity of pre-eclampsia, the progression and symptoms like severe headache, epigastric pain, nausea, visual disturbances and neurological irritability.

Management of eclampsia

Initial management of eclampsia includes protecting the airways and minimizing the risk of aspiration by placing the patient on her left side. It is also important to prevent trauma from falls or violent seizure activity.

$MgSO_4$ is the therapy of choice to control and prevent recurrent seizures (42-45). The Norwegian guideline recommends diazepam administrated as rectal gel or intravenous, to treat the initial convulsion as an alternative to $MgSO_4$. Treatment with $MgSO_4$ is directed to prevent recurrent convulsions (38). Severe hypertension, if present, is treated with antihypertensive drugs.

A plan for delivery should be made for women with ante- or intrapartum eclampsia when the condition is stabilized.

Recurrence and long term maternal health risk after pre-eclampsia

The recurrence risk is dependent on the severity and time of onset of pre-eclampsia in former pregnancies. Women with severe, very early onset pre-eclampsia seem to have an increased risk of pre-eclampsia in future pregnancies (46). The recurrence risk of pre-eclampsia in

second pregnancy for women with a singleton pregnancy with pre-eclampsia the first time was 14.1% (95% CI: 13.6-14.6) in the study by Trogstad et al (47).

In the first follow-up study of women with hypertensive disorders of pregnancy, L.C.Chesley (48) followed women with eclampsia for 47 years. He concluded that eclampsia did not cause later CVD but linked diabetes and eclampsia.

Today maternal vascular, metabolic, and inflammatory complications in pregnancy such as pre-eclampsia, are increasingly linked with an increased risk of CVD in later life (49-53). Irgens et al found that the long term risk of death in women with pre-eclampsia and a preterm delivery was 2.71-fold higher (95 % CI 1.99 - 3.68) than in women who did not have pre-eclampsia and whose pregnancies went to term. The risk of death from cardiovascular causes among women with pre-eclampsia and a preterm delivery was 8.12-fold higher (95% CI 4.31 - 15.33) (54). The systematic review and meta-analysis of McDonald et al found that relative to women with uncomplicated pregnancies, women with a history of pre-eclampsia/eclampsia had an increased risk of subsequent cardiac disease in both the case-control studies (odds ratio 2.47, 95% CI 1.22-5.01) and the cohort studies (relative risk [RR] 2.33, 95% CI 1.95-2.78), as well as an increased risk of cerebrovascular disease (RR 2.03, 95% CI 1.54-2.67), peripheral arterial disease (RR 1.87, 95% CI 0.94-3.73), and cardiovascular mortality (RR 2.29, 95% CI 1.73-3.04)(51). The systematic review and meta-analysis by Bellamy et al conclude that a history of pre-eclampsia should be considered when evaluating risk of cardiovascular disease in women, and that this association might reflect a common cause or an effect of pre-eclampsia on disease development, or both (49). Despite the epidemiological evidence of increased risk for hypertension, stroke, coronary artery disease and end-stage renal disease (55-58), a clear pathophysiological explanation is not found.

4.4 Maternal mortality

Women die from a wide range of complications in pregnancy, childbirth or the postpartum period. Most of these complications develop because they are pregnant and some because pregnancy aggravates an existing disease. The four major killers world-wide are: severe bleeding, infections, hypertensive disorders in pregnancy (eclampsia) and obstructed labour (5).

The maternal mortality was around year 1900 an important cause of death among young women in Norway, and as many as 50% of deaths among women age 15-40 were related to pregnancy and birth. It has been a steady decline in the rates until now where less than one of ten deaths of women in childbearing age is related to pregnancy and birth (59). The maternal mortality ratio (MMR) of direct maternal deaths in the period 1976-1995 was 5.5 per 100,000 in Norway (60).

Improving maternal health is one of the eight Millennium Development Goals adopted by the international community at the United Nations Millennium Summit in year 2000, and the target is to reduce MMR by 75% from 1990 to 2015. The MMR in developing countries is 450 maternal deaths per 100 000 live births versus nine per 100 000 live births in developed countries (5;7-11).

Hogan et al assessed levels and trends in maternal mortality in 181 countries 1980-2008 (6), and their estimates are showing a decline in numbers of maternal deaths. Their analysis showed that although countries can achieve progress in reduction of maternal death, far too many had not done so. To reach the Millennium Development Goal they concluded that progress needs to be accelerated in many countries. Worldwide they estimated that there were 342,900 (uncertainty interval 302,100-394,300) maternal deaths in 2008, a decline from 526,300 (446,400-629,600) in 1980. The global MMR was estimated to be 422 (358-505) per 100,000 live births in 1980, 320 (272-388) in 1990 and further down to 251 (221-289) in 2008. The highest MMR was found in Afghanistan (MMR=1575), the lowest in Italy (MMR= 4). India had the largest number of maternal deaths of any country. Six countries account for over half of maternal deaths (India, Nigeria, Pakistan, Afghanistan, Ethiopia and the Democratic Republic of Congo)(61).

In the study of Hogan et al (6), Norway, together with USA, Canada, Denmark and Austria, have an apparent rise in the MMR. They explain this rise with the inclusion of late maternal deaths in the ICD 10 and that USA has made a change in their death certificate with a separate pregnancy status question. This change might explain the rise, but it also put the focus on the difficulty in registration of maternal deaths. The exact number of maternal deaths is hard to determine. Even in countries like Norway, where all deaths “need a medical certificate” the maternal deaths are frequently missed or misclassified.

When the number and cases of deaths are found, the next step is to investigate the deaths to identify the causes, the underlying causes of death and the standard of care. “Beyond the Numbers” describes five different types of review or audit that can be used in a variety of settings, among these are the following two approaches (62):

Confidential enquiries into maternal deaths are a systematic multidisciplinary anonymous investigation of all or a representative sample of maternal deaths occurring in an area, regional (state) or national level. It identifies the numbers, causes and avoidable factors associated with them.

Clinical audit has been described as a quality improvement process that seeks to improve patient care and outcomes through systematic review of aspects of the structure, processes and outcomes of care against explicit criteria and the subsequent implementation of change. Where indicated, changes are implemented at an individual, team or service level and further monitoring is used to confirm improvement in healthcare delivery.

United Kingdom has since 1952 had a national professional self-audit of maternal deaths, The Confidential Enquiry into Maternal Deaths. The most common cause of direct deaths in the Enquiry 2000-2002, was thromboembolism with pre-eclampsia/eclampsia second. The most common cause of indirect maternal deaths was psychiatric illness, with suicide as the overall leading cause (63). In the Enquiries 2003-2005 thromboembolism was the commonest cause of direct deaths, and cardiac disease was the most common indirect cause (64). In the last report, the eighth Report of the Confidential Enquiries into Maternal Deaths in the UK (2006-2008)(65), there has been a significant reduction in the overall maternal death rate from 13.95 per 100 000 maternities in the triennium 2003-2005 to 11.39 per 100 000 maternities in 2006–08. Cardiac disease remains the most common cause of indirect maternal deaths. Sepsis is in the last triennium the commonest cause of direct maternal deaths in the UK, followed by pre-eclampsia/eclampsia and thromboembolism. The number of deaths from pre-eclampsia/eclampsia has not fallen.

In the UK, France and the Netherlands, where confidential inquiries into maternal deaths have been performed, 40-70% of the direct deaths are shown to be associated with substandard care (63-68). These inquiries both look into the underlying diseases of maternal deaths and evaluate

the standard of care. The practicing consultants in obstetrics, the midwives and the general practitioners get analyses of avoidable factors and can subsequently implement changes.

5. AIMS OF THE STUDIES

To improve care we need information of the severe complications of pregnancy, childbirth and the puerperium. Through this thesis we focused on two dramatic events; women suffering eclampsia and maternal deaths. We wanted to determine the magnitude of the problems, tried to assess trends and identify risk groups. Another focus was the follow-up of women with pre-eclampsia and eclampsia, due to persisting symptoms and increased risk of CVD in later life.

5.1 Study I and II

In Scandinavian register-based studies, the incidence of eclampsia was found to be among the lowest in the world with reported incidences of 1.7-3.3/10,000 maternities (69-72). The Medical Birth Registry of Norway (MBRN) reported an incidence of eclampsia of 0.1/1000 deliveries from 1990 to 1994. In 1995 the incidence increased to 0.3/1000 deliveries and in 1996 0.4/1000 deliveries, but the incidence was still low compared to other European countries.

New guidelines in the management of eclampsia were introduced in 1998, recommending the use of $MgSO_4$ as anticonvulsant (73).

We wanted to conduct a survey to determine the incidence of eclampsia in Scandinavia, the clinical manifestation, management, current use of anticonvulsants and the outcomes of the eclamptic patients and their newborns. The study design included an evaluation of the standard of care and a follow-up interview of the women.

Aim of study I

This prospective study was designed to measure the incidence of eclampsia in Scandinavia over a two year period and to audit the clinical care for patients with eclampsia. The study aimed to analyse how many cases of eclampsia are potentially preventable by timely intervention or improved care in general and especially the systematic use of $MgSO_4$.

Aim of study II

The aim of this study was to assess the prevalence of any self-reported persisting long-term symptoms following eclampsia. The working hypothesis was that women with eclampsia would be likely to have long-term symptoms or sequelae following the severe condition eclampsia represents.

5.2 Study III

Tromsø IV is a population-based survey for risk factors associated with coronary heart disease. The forth survey included questions on former hypertensive disorders of pregnancy. We wanted to explore the associations between hypertensive diseases of pregnancy and the risk of maternal cardiovascular diseases later in life. To answer the question women reporting former pre-eclampsia and non-proteinuric hypertension were compared with women reporting normal pregnancies. Parameters like general characteristics and results of the physical examinations, current health situation, carotid intima-media thickness (IMT) and plaque in the carotid artery, and familiar disposition of coronary heart diseases were compared. The study also analysed the recurrence rate for hypertensive complications in subsequent pregnancies.

Aim of study III

The aims were to investigate the recurrence risk of hypertensive disorders in subsequent pregnancies and explore the associations between hypertensive disorders of pregnancy and maternal cardiovascular risk factor profile and development of cardiovascular diseases later in life.

5.3 Study IV

The number of maternal deaths is underestimated in most developed countries (7) and the exact number of maternal deaths is hard to determine. Information is needed to understand the events leading to death.

Aim of study IV

The aims were to identify and audit direct maternal deaths in Norway that occurred 1976-1995, to classify them according to the underlying causes of death and evaluate the standard of care and preventability.

6. MATERIALS AND METHODS

6.1 Study I

The study is a descriptive cohort study of eclampsia in Denmark, Norway and Sweden through a two-year period (mid 1998- mid 2000). Regular return letters with requests for notification of any possible case of eclampsia were sent to all maternity units in Scandinavia at 3-monthly intervals. We received photocopies of the pre-hospital and hospital case records for both mother and child. Data were further validated by cross checking cases with cases reported to the national birth registers.

Each case was evaluated according to the following predefined criteria for substandard medical care: (i) no referral to hospital if signs of pre-eclampsia (hypertension and proteinuria) or symptoms, such as intense headache or epigastric pain; (ii) if patients referred to the hospital with severe pre-eclampsia did not have their blood pressure measured nor blood samples or tests of proteinuria performed; (iii) if patients were not treated with antihypertensive drugs despite blood pressure of 160/110 mmHg on repeated measurements; (iv) when patients with severe pre-eclampsia and symptoms of imminent eclampsia were not delivered by caesarean section or had labour induced within reasonable time; or (v) when $MgSO_4$ infusion was not commenced following the first eclamptic fit. A patient case was considered as having been treated with substandard care if the case met one or more of the above criteria. Cases were categorized as substandard self-care if the woman had not followed the recommended antenatal care program, or did not accept hospital admission before eclampsia.

Eclampsia was defined as the occurrence of convulsions during pregnancy or in the first 10 days postpartum together with at least two of the following features within 24 hours after the convulsions: pregnancy-induced hypertension; proteinuria (at least 0.3 g/l in a random sample); thrombocytopenia (a platelet count of $<100x10^9$/l); or an increased plasma aspartate aminotransferase concentration (ASAT of ≥ 42 IU/l).

Pregnancy-induced hypertension was defined as a booking diastolic blood pressure of < 90 mmHg, a maximum diastolic pressure of ≥ 90 mmHg and a diastolic increment of ≥ 25 mmHg (5). This definition of hypertension made it possible to compare our findings with the similar study made in UK (3).

6.2 Study II

Native speaking women from Study I, who could be traced and consented, were followed up by a structured telephone interview between 6 and 24 months after the eclamptic episode. A structured questionnaire was used for all patients including both open and closed questions on their former obstetric history and persisting sequelae and symptoms at follow-up.

6.3 Study III

The Tromsø Study is a population-based multipurpose, single-center study with main focus on cardiovascular risk factors and disease. All inhabitants in the municipality of Tromsø, aged 25 or older (born before 1970) were invited to participate in the study, among which 14,293 were females. The screening consisted of self-administered questionnaires, clinical measurements, laboratory tests and ultrasonographic examination of the carotid artery. Risk profile for CVD was assessed using anthropometry, BP measurement, laboratory tests and ultrasonographic assessment of carotid artery intima-media thickness (IMT) and plaque in the carotid artery both linked to risk of CVD (74) and pre-eclampsia (75), was performed.

Parous women who could specify hypertension and/or proteinuria in their pregnancies, were included (n=9,974), and divided into four groups; women with pre-eclampsia, with non-proteinuric hypertension, with normotensive proteinuria and without hypertension and proteiuria in their pregnancies.

Pre-eclampsia was in this study not defined according to the ordinary classifications (1). The categorization of women in the different groups was based on their answers in the questionnaires. They were asked about hypertensive complications in their pregnancies with questions like:

- During pregnancy, have you had high blood pressure and/or proteinuria?
- If you have had high blood pressure during pregnancy, was it your first pregnancy?
- If you have had proteinuria during pregnancy, was it your first pregnancy?

6.4 Study IV

The maternal deaths were identified through the Cause of Death Registry, Statistics Norway and the MBRN. During 1976 – 1995, we identified 61 direct maternal deaths. In 51 cases we received photocopies of the hospital case records and 45 included autopsy reports.

In the study, we categorized the maternal deaths according to the underlying cause, i.e. the disease or the complication that started the cascade of events leading to death. This categorisation was made based upon the hospital case notes and the results from autopsy reports.

The quality of care was evaluated by audit by the authors based on in-depth investigation of the case records. Each case was also assessed with reference to its preventability. The deaths were categorized as unavoidable, potentially avoidable and avoidable considering the treatment, national guidelines and procedures at the time of the study (76).

7. MAIN RESULTS

7.1 Study I

The incidence of eclampsia in Scandinavia was 5.0/10,000 maternities. Eighty-six percent had a diagnosis of pre-eclampsia before the seizure and nine out of ten had at least one physical complaint before the first seizure, severe headache being the most common symptom, occurring in two thirds. By audit, 42 % were classified as having received substandard care (Table 1). In retrospect nearly half of the cases were found potentially preventable by timely intervention, improved medical care and systematic use of prophylactic treatment with $MgSO_4$.

Table 1. Cases of eclampsia in Scandinavia in a two year period (1998-2000) and the women treated with substandard care.

	Total number of births 1998-2000	Cases with eclampsia and complete data collection = cases included	Incidence of eclampsia n/10,000	Women treated with substandard care n/%
Sweden	170,189	97	5.7	39/41%
Norway	119,456	60	5.2	26/43%
Denmark	130,664	53	4.1	25/49%
Total in Scandinavia	420,309	210	5.0	90/42%

Difference in incidence in the three countries is not significant (p = 0.138)

7.2 Study II

Of the 210 eclamptic patients, 123 (59%) were followed up by structured telephone interviews. The patients were interviewed at a median time interval of eleven months following the delivery (range 6-24 months). One-hundred and eight (88%) women had attended a postpartum follow-up consultation, 84 (68%) at the hospital and 24 (20%) with their general practitioner (GP). Twenty-four women (20%) were on antihypertensive medications at discharge from the hospital; seven (6%) were still on medication at the time of follow-up. The median time for treatment with antihypertensive medications after discharge from the hospital was seven weeks (range 1-92 weeks). At the time of follow-up 51% of the women had persistent symptoms (Table 2).

Table 2. Symptoms following eclampsia reported by the patients at the time of telephone interview 6–24 months after their fit (n = 123). A total of 63 (51%) reported at least one persisting complaint.

Long-term complaints	n	%
Hemiparesis and dysarthria	2	2
Headache	22	18
Problems to concentrate	22	18
Vertigo or balance problems	12	10
Visual disturbances	13	11
Tiredness	11	9
Restlessness	9	7
Symptoms of mental depression	17	14
Amnesia for part of the hospital stay	21	17
Hypertension (requiring medical treatment)	7	6

7.3 Study III

Pre-eclampsia in the first pregnancy increased the risk of recurrence in later pregnancies 5.3 fold (95% CI 4.3-6.5) compared to a normotensive first pregnancy. A strong association between hypertensive disorders of pregnancy and future risk of CVD was demonstrated by objective assessment of risk factors that can be potentially modified. Women with a previous history of pre-eclampsia or non-proteinuric hypertension had an unfavourable cardiovascular risk profile. Hypertension was prevalent in 25% and 28% of them, respectively. We found significantly higher plaque prevalence and larger total carotid plaque area in women with previous pre-eclampsia and non-proteinuric hypertension compared to the control group. In addition the carotid artery intima-media thickness (IMT) was increased in pre-eclamptic group (Table 3).

Table 3. Age-adjusted levels of total plaque area and intima-media thickness according to previous hypertensive complications in pregnancies. The Tromsø Study.

	Group I n = 250	Group II n = 138	Group III N = 358	Group IV n = 1778	p value
Presence of carotid plaques (n/%)	127/51%	74/53%	154/43%	751/42%	0.018
Total carotid plaque area (mm^2) (95% CI)	10.00 (8.24-11.77)	10.70 (8.05-13.36)	8.18 (6.67-9-69)	7.09 (6.50-7.67)	0.0001
Mean intima-media-thickness (mm)	0.86 (0.84-0.89)	0.84 (0.81-0.88)	0.82 (0.80-0.84)	0.82 (0.81-0.83)	0.001

Group I; previous pre-eclampsia, Group II; non-proteinuric hypertension in previous pregnancy, Group III; normotensive proteinuria in previous pregnancy, and Group IV; no hypertension and no proteinuria in previous pregnancies. Contrast test of variances are made between group I and group IV (control group), and group II and Group IV (control group).

7.4 Study IV

The MMR of direct maternal deaths in the period 1976-1995 was 5.5 per 100,000. The leading underlying causes of deaths were hypertensive disease of pregnancy and thromboembolism. Substandard care was delivered in 21 (21/49) of the cases, and mainly in the hospitals (18/21). The substandard care was due to inadequate surveillance and treatment of the hypertensive disease, inadequate thromboprophylaxis and complications due to clearly inappropriate actions taken by the staff. Among the 45 women who gave birth, 32 were delivered by a caesarean, and in 17 of these, the death of the mother was directly ascribed to the operation (Table 4).

Table 4. The relation between underlying cause of death in 49 cases and substandard care, avoidable and potentially avoidable cases and caesarean delivery.

Underlying cause of death	Total (n = 49)	Substandard care (n = 21)	Avoidable and potentially avoidable cases (n = 27)	Caesarean section (n = 32)	Deaths due to caesarean section (n = 17)
Hypertensive disease of pregnancy	11	6	5	11	3
Thromboembolism	9	5	7	7	6
Other direct deaths	7	1	1	6	3
Amniotic fluid embolism syndrome	6	0	0	3	
Complications related to anaesthesia	4	3	4	4	4
Haemorrhage	3	3	3		
Genital tract sepsis	3	2	2	1	1
Early pregnancy death	6	1	5		

8. DISCUSSION

8.1 Study I and II

In developing countries the incidence of eclampsia varies widely with 6-100 cases per 10.000 live births (77). In the Western countries the incidence of eclampsia has decreased over the past century and is now stabilised with 4-6 per 10.000 live births (3;78;79). The MBRN reported a low incidence of eclampsia compared to other European countries, and this low incidence might depend on a serious underreporting of eclampsia to MBRN during these years. In study I we found the incidence of eclampsia in Scandinavia to be 5.0/10,000 deliveries (2) and in Norway 5.2/10,000 deliveries, comparable to the incidence in other developed countries.

In a study of eclampsia in the Netherlands, from 2004-2006, they found a marked increased incidence (6.2 per 10,000 deliveries) compared with other Western European countries (79). The incidence of eclampsia has been halved in the UK from 1992 to 2005/2006, from 4.9/10.000 to 2.75/10,000 maternities, presumably as a result of the widespread use of MgSO4, following publication of the Magpie trial (65).

Eclampsia is associated with increased risks of maternal morbidity and mortality. The reported maternal mortality after eclampsia in a study from the National Hospital, Norway in the period 1959-1978 was 3%. Almost 50% had three or more eclamptic seizures, and one third developed severe complications (80). Based on later studies is seems that the outcome among women with eclampsia is less severe. In the study by Douglas et al in the UK from 1992 nearly one in 50 women (1.8%) died, and 35% of all women had at least one major complication (3). In our study, including 210 women with eclampsia in Scandinavia (1998-1999), three women had a cerebrovascular accident (1.4%) and there were no maternal deaths. In the study from the Netherlands the case fatality rate was 1 in 74 (1.4%) and 3.3% had a cerebrovascular accident (79).

In study I the prodromal symptoms of eclampsia were high-lighted. The subjective symptoms like severe headache, visual disturbances and epigastric pain or vomiting, are important when diagnosing severe pre-eclampsia and should lead to careful clinical assessment to prevent complications. In the interviews 6-24 month after the eclamptic fit many women were still overwhelmed by the experience of the intense, frontal headache that preceded eclampsia and described it as ‘the most intense pain ever experienced’ and ‘a pain worse than the most

intense uterine contractions'. Many women reported having experienced a severe fear of death after the eclamptic fit and many had persistent symptoms consistent with post-traumatic stress disorder (problems to concentrate, tiredness, restlessness). The information about sequelae for a selected group of women with eclampsia is sparse, especially regarding subjective symptoms and minor health problems. Our study with follow-up interviews adds new information about this group (81). At the time of follow-up, 63 women (51%) had at least one persistent symptom; two patients had severe neurological sequelae (hemiparesis and dysarthria), 11% had visual disturbances, 22% had problems concentrating or recalling phone numbers and messages, 18% reported frequent headaches and 10% had vertigo or balance problems.

Chesley followed 270 women surviving eclampsia though a period of more than twenty years, with focus on hypertension and hypertensive diseases and genetics (82;83). The Magpie Trial was a randomised trial comparing $MgSO_4$ with placebo for pre-eclampsia (42). In a two-year follow-up study of these patients (mainly by mail), two thirds of the surviving women in both groups reported at least one health problem. Ninety-five of 3,375 women (2.8%) had persisting serious morbidity, severe hypertension (2.4%), 8% were still on antihypertensive drugs, renal problems (0.4%) or sequelae after stroke (0.1%)(84). In our Scandinavian study, 6% of women with eclampsia were still on antihypertensive medication at the time of follow-up and 2% had severe morbidity. The number of women reporting complications or persistent symptoms after eclampsia in the Scandinavian countries is lower than reported in the two two-year follow-up of the Magpie Trial. The result may be regarded as reassuring according to the low frequency of severe neurological sequelae following eclampsia. Since the Magpie follow-up addressed women with pre-eclampsia and our study addressed women with eclampsia, we had expected to find a higher rate of complications, assuming that eclampsia is a more severe form of pre-eclampsia.

Based on the findings in study I and II we suggested a need for routine clinical follow-up of patients with eclampsia. Although few women suffer from severe sequelae, many women have persisting symptoms indicating a need for follow-up. This is also important due to the epidemiological evidence of increased risk for CVD as hypertension, stroke, coronary artery disease and end-stage renal disease (55-58;85).

8.2 Study III

In the study of hypertensive disorders of pregnancy and long term maternal health risk the women suffering pre-eclampsia and non-proteinuric hypertension had an unfavourable risk profile based on history, physical examination, blood tests and carotid artery ultrasound. Women with previous history of pre-eclampsia had doubled risk of hypertension and coronary artery disease compared to controls. They had carotid plaques more often, had larger total carotid plaque area and intima-media thickness compared to controls. We find an association between pregnancy-related hypertensive disorders and plaque burden. Compared to early IMT changes, plaque formation may represent a later, manifest stage of atherosclerosis and a closer relationship to clinical vascular disease

In a systematic review and meta-analysis by Bellamy et al including both retrospective and prospective studies, they found an increased risk of cardiovascular disease (49). The relative risks for hypertension were 3.70 (95% CI 2.70 - 5.05) after 14.1 years weighted mean follow-up, for ischaemic heart disease 2.16 (95% CI 1.86 - 2.52) after 11.7 years, for stroke 1.81 (95% CI 1.45 - 2.27) after 10.4 years, and for venous thromboembolism 1.79 (95% CI 1.37 - 2.33) after 4.7 years. No increase in risk of any cancer was found. Another systematic review and meta-analysis by McDonald et al concludes that women with a history of pre-eclampsia/ eclampsia have approximately double the risk of early cardiac, cerebrovascular, and peripheral arterial disease, and cardiovascular mortality (51). They suggest further research to determine the mechanisms underlying these associations and to identify effective prevention strategies.

Although pre-eclampsia and CVD share many of the same constitutional risk factors (85) and endothelial dysfunction may persist following a pre-eclamptic pregnancy (53;86-89), no study has demonstrated that the risk profile is altered by pre-eclampsia. Furthermore, whether and how long the impaired vascular function persists after a pre-eclamptic pregnancy remains controversial. A recent study showed that the vascular dysfunction persists 6-24 months postpartum only in women with early-onset pre-eclampsia, but not in women who had late-onset disease (89), whereas the risk of CVD is increased in both.

Hopefully the epidemiological association between hypertensive disorders of pregnancy and CVD will result in a routine follow-up of women with hypertensive disorders of pregnancy.

The follow-up should primarily encourage the women to modify their life-style to minimise avoidable risks and also allow early intervention as medical prophylaxis.

8.3 Study IV

Even in countries like Norway, where all deaths "need a medical certificate", maternal deaths are frequently missed or misclassified (6;90), and we do not know the exact number of maternal deaths in Norway. The death may occur at different places and departments of hospitals that do not report routinely to the MBRN. As a consequence of the imprecise figures reported, the method applied by WHO in order to estimate the rate of maternal mortality in Norway, imply the reported value is multiplied by 1.5 (5). To obtain valid information on all direct maternal deaths, we need data from multiple sources, including medical birth registers, patient registers, civil registers and cause of death registers (5;11;65;90).

During the work with this study it was difficult to indentify the maternal deaths in Norway, and as a consequence only direct maternal deaths are included in the study. Using the medical birth registers and cause of death registers we realised that the indirect maternal deaths were impossible to identify, and even within the direct maternal deaths the number of identified cases might not be correct.

An evaluation of the quality of care found that substandard care was delivered in 21/49 of the cases. An important factor associated with direct maternal deaths in Norway 1976-1995, was mode of delivery. The estimated fatality rate was 0.27/1000 for caesarean deliveries, and 0.01/1000 for vaginal deliveries. In addition, more than half of the deaths (17/32) were in the audit, judged to be directly attributable to the operation in mothers delivered by caesarean section. In the enquiries in UK, "Saving Mothers' Lives, 2003-2005", the majority (61%) were delivered by caesarean section (64). The steady raise in the caesarean section rate should therefore be a matter of concern.

8.4 Standard of care

It is important that management of pregnancy, labour and delivery meets required standards and follows national guidelines. We assume that obstetricians and midwives use evidence-based guidance for management and decisions made during pregnancy, labour and delivery. Contrary to this, it is difficult to implement new guidelines and change or improve physicians practice (91). The challenge is illustrated in study I. A new guideline was introduced

recommending prevention of recurrent convulsions in eclampsia with $MgSO_4$ (43;73). Despite this, substandard care was mainly due to patients not receiving $MgSO_4$ following their first seizure. This matter of changing the practice of physicians is commented by John Thorp (91): “There is no proof that evidence, no matter how clearly it is formulated and spoon-fed to clinicians, will change their practice.”

The standard of care was evaluated through audit in the articles of eclampsia and maternal deaths. Substandard care was observed in 42% and 43% of the cases. Studies and enquiries from UK, France and the Nederland on maternal mortality and severe morbidity find that many women are treated with substandard care and not treated according to the national guidelines (63;64;66;67;79;92). In the study of eclampsia in the Netherlands (79), substandard care was judged to be present in 83% of the cases. In a study in France they tried to determine what factors related to health services that might explain substandard care of severe morbidity due to obstetric haemorrhage (92). The lack of a 24-hour on-site anaesthetist at the hospital and a low volume of deliveries (<500 births per year) were the factors associated with substandard care. Overall, 62% of the cases received appropriate care, 24% received totally inadequate care and 14% mixed care.

The Norwegian Board of Health centrally and the Norwegian Board of Health in the counties handled in the period 2003–2006, 47 cases within the area of pregnancy- and birth care. In a recent study the cases are reviewed (93). Several conditions caused the adverse events but they were able to classify the events into four main categories: communication- and cooperation failure, uncertain lines of responsibility, lack of qualification, and weaknesses in the organisation. The examination of the material disclosed that at least 2/3 of the adverse events could be traced back to organisation of the facility and uncertain lines of responsibility although the definition of systemic failure is unclear.

In the Confidential Enquiry “Saving mothers lives 2003-2005” (64) the assessors classified 64% of direct deaths and 40% of indirect deaths as having some degree of substandard care. The major concerns in the Enquiries have been lack of inter-professional and/or inter-agency communications. There were a number of cases in which crucial clinical information, which may have affected the outcome, was not passed from the general practitioner to the midwifery or obstetric services at booking or shared between consultants in other specialties, including staff in accident and emergency departments and the obstetric team.

In the Confidential Enquiry “Saving mothers lives 2006-2009” another aspect is discussed (65). A lack of clinical knowledge and skills among some doctors, midwives and other health professionals was one of the leading causes of potentially avoidable cases. One of the commonest findings was the initial failure by the clinical staff to immediately recognise and act on the signs and symptoms of potentially life-threatening conditions.

8.5 Methodological considerations and limitation of the present study

This thesis includes observational studies trying to identify patterns of practice related to the management of eclampsia and maternal deaths.

The study “Eclampsia in Scandinavia” was a prospective study including all women giving birth in a two-year period (mid 1998 – mid 2000) in Scandinavia. Notifications of eclampsia cases were obtained from all obstetric units at 3 monthly intervals, including 210 women with eclampsia. All patient files were reviewed, and systematic audit was carried out to identify potentially preventable cases using predefined criteria. One hundred and twenty-three women (59%) were followed up with a structured telephone interview, 6-24 months (median 11) after their eclamptic fit.

Some limitations of Study II, “Follow-up interviews after eclampsia”, should be noted. First, there was no control group. The control group could have been women with normotensive pregnancies or with pre-eclampsia without eclampsia. The follow-up rate was only 59%, and although we did not find any evidence that the non-interviewed women differed from the interviewed subjects, we cannot be certain that the interviewed group is representative of all women with eclampsia. Second, the study was based on telephone interviews without any clinical investigation and the results reflect the subjective experiences of the women rather than objectively registered parameters. Telephone interview was chosen because this was a study including all obstetric units in Denmark, Norway and Sweden. Since the present study was descriptive and did not follow a case-control study design, it is not possible to draw any firm conclusions on the causal relationship between eclampsia and the reported symptoms at follow-up.

The management of individual deaths and eclampsia was evaluated by audit by the authors, based on in-depth investigation of the case records. Each case was evaluated according to

predefined criteria for substandard care. In general, the audit as method can provide evidence of where problems may lay and identify areas of required recommendations and improvements.

The maternal deaths were also assessed with reference to its preventability. The deaths were categorized as unavoidable, potentially avoidable and avoidable considering the treatment, national guidelines and procedures of today (38;76).

In the report “Why Mothers Die 2000-2002” (63) the limitation of randomised trials dealing with rare events, like many of the causes of maternal death, is discussed. The authors argue that randomised trials, unless they are very large, provide little information about rare complications of treatments and that safety issues are better illuminated by observational studies. Through audit the management is evaluated according to predefined evidence based guidelines. They state that treatment options for the rare events will rely on lesser levels of evidence and frequently on “expert opinions”. Criterion-based audit has been used in obstetrics to improve quality from the midwives/doctors' perspective and in a systematic review 95% of studies showed significant improvement in at least one standard measured (94). Audits of severe complications and maternal death allow development of strategies to prevent morbidity and mortality associated with pregnancy. Since maternal deaths are rare in developed countries severe acute maternal morbidity is considered a new indicator of the quality of obstetric care and audit can be used to indentify substandard care (95). The best result of the audit relates to the action it stimulates in the health system (96), thus the audit gives the obstetricians and midwives the possibility to review the complications.

In Study III, “Recurrence and long-term maternal health risks of hypertensive disorders of pregnancy: a population based study” there was no strict definition of the level of the blood pressure considered pathological during the pregnancy. The occurrence of hypertensive diseases in pregnancy is based on self-reporting by women years after their pregnancy (36% > 50 years old). The recall bias might be a valid concern both concerning maternal-recall of self-reported pre-eclampsia (97) and their family history of cardiovascular diseases (98).

8.6 Perspectives

Eclampsia complicates one in 2000 pregnancies in Scandinavia. The exact cause of eclampsia is unknown. Pregnancy is associated with significant cardiovascular adaptation of the circulation. As pointed out by Cippola (33) it is important to understand how the cerebral circulation is altered during gestation and in response to pre-eclampsia and how this might contribute to the development of eclampsia. The understanding of the cerebral circulation adaption during pregnancy with the endothelial dysfunction and oxidative stress in pre-eclampsia in combination with loss of cerebral blood flow autoregulation, and the disruption of blood-brain barrier might be important to the treatment and prevention of eclampsia (33).

In the follow-up interviews with women 6-24 months after eclampsia, we found the majority of women to have persisting symptoms, indicating a need for further clinical investigations of the long-term consequences of eclampsia. A case-control study might provide the answer to whether symptoms like headaches, depression, tiredness, and failure to concentrate are more frequent among women who have suffered from pre-eclampsia or eclampsia than after uncomplicated pregnancies.

Most eclamptic convulsions occur in hospitals in women with diagnosed pre-eclampsia. Nine out of ten had warning signs or symptoms heralding the seizure. Of the women with eclampsia 42% were treated with substandard care. It is important to analyse the factors leading to substandard care and identify methods to reduce substandard care. In the "Confidential Enquiries into Maternal Deaths in the United Kingdom 2006-2008" the most important challenge identified was the need to improve clinical knowledge and skills (65). The need for continuous education and training must be taken seriously and every obstetric unit would benefit from having an audit on all serious events in the unit and established protocols for coping with severe events like eclampsia.

Women who had pre-eclampsia, have an increased risk of cardiovascular diseases in later life. If greater awareness of this association could lead to earlier diagnosis and improved management, it might be possible to reduce the morbidity and mortality of CVD. Women with hypertensive disorders of pregnancy might benefit from counselling and appropriate follow-up providing the opportunity for early life-style interventions and primary prevention strategies. The findings of the studies of eclampsia and pre-eclampsia and long-time maternal health risk both indicate a need for follow-up of women with eclampsia and pre-eclampsia.

Hopefully clinical practice is applying the knowledge that has been gained through research and implements new guidelines for follow-up of these women.

The main findings in this thesis are based on audit of severe complications in obstetrics. It is important to remember that even in Norway the correct numbers of maternal deaths are unknown. Hopefully it will be possible to establish a better system for registration and audit of all maternal deaths. Through clinical audit with review of patient care against standards, it will be possible to improve quality of obstetric care (94). Detailed assessment of individual women through audit by the Confidential Enquiry into Maternal Deaths in the United Kingdom has been acknowledged as a major contributor to the decline of maternal deaths in the UK over the past 50 years (95).

We need a Nordic Confidential Inquiry with recent, not historical data, every two or three years in order to survey this rare and very serious outcome. This will offer an alternative to the medicolegal processes often pursuing these cases. An open audit performed by health care professionals will lead to a quality improvement for the benefit of the women.

9. CONCLUSIONS

The incidence of eclampsia in Scandinavia was 5.0/10,000 maternities. Eclampsia occurred mainly in hospital and the majority of women had symptoms heralding the seizure. In retrospect, nearly half of the cases were found potentially preventable by timely intervention, improved medical care and systematic use of prophylactic treatment with $MgSO_4$. Although few women suffer from severe sequelae, many women had persisting symptoms following eclampsia.

A strong association between hypertensive disorders of pregnancy and increased risk of atherosclerosis and CVD was demonstrated by objective assessment. Previously pre-eclamptic women had significantly larger carotid artery intima-media thickness and total carotid plaque area.

The direct maternal mortality ratio in Norway was 5.5/100,000 births in 1976-1995. A majority of the cases was considered potentially avoidable and associated with caesarean delivery.

Patient safety and implementation and use of guidelines are important to reduce maternal and neonatal morbidity and mortality.

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APPENDIX

REGISTRERINGSSKJEMA - EKLAMPSI

1 Studienummer ☐☐☐

2 Helseregion ☐
1 = I
2 = II
3 = III
4 = IV
5 = V

SOSIALE OG DEMOGRAFISKE DATA

		Ja	Nei
3	Journal fra sykehus der eklampsi skjedde	☐	☐
4	Journal fra andre sykehus	☐	☐
5	Helsekort for gravide	☐	☐
6	Anne informasjon, telefon osv	☐	☐

7 Fødselsdato (mor) ☐☐☐☐☐☐ ☐☐☐☐☐

8 Alder (år) ☐☐

9 Etnisitet (definer fødeland) ☐
1 = Norge
2 = Andre europeiske/Nord-Amerika
3 = Asia
4 = Afrika
5 = Latin-Amerika
6 = Annet

10 Sivilstatus ☐
1 = enslig *2 = samboer*
3 = gift *4 = annet (skilt, enke)*

11 Postkode ☐☐☐☐

12 Yrke . . . . . .

13 Utdannelse ☐
1 = Grunnskole *3 = Høyere utdanning*
2 = Videregående skole *4 = Annet*

14 Tidligere sykdommer

	Ja	Nei
Ingen signifikant sykehistorie	☐	☐
Insulinkrevende diabetes	☐	☐
Epilepsi	☐	☐
Nyresykdom (kjent strukturell eller biospi verifisert)	☐	☐
Autoimmun sykdom	☐	☐
Hypertensjon utenom graviditet	☐	☐
Behandlingstrengende hypertoni utenom graviditet	☐	☐
Hypertoni på p-piller	☐	☐

Annet (spesifiser) . . . . . .
. . . . . .

15 Tidligere viabel graviditet ☐

0 = Ingen
1 = 1 viabel graviditet (>20 uker)
2 = 2 viable graviditeter
3 = 3 viable graviditeter
4 = ≥viable graviditeter

Første barns fødselsvekt (g) ☐☐☐☐ Gestasjonsalder (uker) ☐☐
Andre barns fødselsvekt (g) ☐☐☐☐ Gestasjonsalder (uker) ☐☐
Tredje barns fødselsvekt (g) ☐☐☐☐ Gestasjonsalder (uker) ☐☐
Spesifiser (død, morbiditet osv) . . . . . .
. . . . . .

16 Tidligere provosert abort ☐

0 = Ingen tidligere provosert abort
1 = provosert abort x 1 < 20 uker
2 = provosert abort x 2 < 20 uker

17 Tidligere spontan abort ☐

0 = Ingen tidligere spontan abort
1 = spontan abort x 1 < 20 uker
2 = spontan abort x 2 < 20 uker

18 Tidligere preeklampsi ☐

1 = Ingen tidligere graviditet
2 = Ingen preeklampsi i tidligere graviditet
3 = Preekampsi i tidligere graviditet
Hvis Ja på nr 3, når debutuke . . . . . .

19 Tidligere eklampsi ☐

1 = Ingen tidligere graviditet
2 = Ingen tidligere eklampsi
3 = Tidligere eklampsi

20 Antall sigaretter ved 1. kontroll i nåværende graviditet ☐☐

21 Faste medikamenter før graviditet ☐

0 = Ingen
1 = Antikonvulsiva
3 = Steroider
4 = Andre (spesifiser). . . . . . .

SVANGERSKAPSOMSORG

22 Termin Naegele (NL) ☐☐☐☐☐☐

23 Termin ultralyd (TUL) (<20 uker) ☐☐☐☐☐☐

24 Antall uker ved 1. kontroll ☐☐

25 Høyde (cm) ☐☐☐

26 Pregravid vekt (kg) ☐☐☐

27 Vekt (kg) ved 1. kontroll ☐☐☐

28 Antall fostre ☐

29 Antall kontroller før 20. svangerskapsuke ☐☐

30 Antall kontroller etter 20. svangerskapsuke ☐☐

		Ja	Nei
31	Henvist spesialavdeling før eklampsi	☐	☐
32	Overflyttet fra ett sykehus til et annet (høyere nivå)	☐	☐
33	Aksepterte ikke innleggelse før eklampsi	☐	☐
34	Skrevet seg ut mot råd	☐	☐

FUNN OG SYMPTOMER

35 Vektøkning under svangerskapet ☐☐

36 Siste vekt før eklampsi ☐☐

37 Antall dager fra siste vekt til eklampsi ☐☐

38 Systolisk BT, 1. svangerskapskontroll (mmHg) ☐☐

39 Diastolisk BT, 1. svangerskapskontroll ☐☐☐

40 Proteinuri ved 1. svangerskapskontroll ☐
0 = Ingen *3 = ++*
1 = Spor *4 = +++*
2 = +

41 Maks systolisk BT før eklampsi ☐☐☐

42 Maks diastolisk BT før eklampsi ☐☐☐

43 Siste systolisk BT før eklampsi ☐☐☐

44 Siste diastolisk BT før eklampsi ☐☐☐

45 Tid mellom siste BT og eklampsi (første krampeanfall)
Hvis < 1 døgn, angi timer ☐☐
Hvis ≥ 1 døgn, angi dager ☐☐

46 Tid mellom siste undersøkelse på proteinuri og eklampsi
Timer
Dager ☐☐
☐☐

47 Første systoliske BT etter eklampsi ☐☐☐

48 Første diastoliske BT etter eklampsi ☐☐☐

49 Tid mellom eklampsi og første BT etter anfallet
Timer ☐☐
Dager ☐☐

50 Maks systolisk BT etter kramper ☐☐☐

51 Maks diastolisk BT etter kramper ☐☐☐

52 Intervall mellom kramper og første test med proteinuri etter kramper
Timer ☐☐
Dager ☐☐

53 Maks proteinuri <u>før</u> kramper ☐
0 = Ingen *3 = ++*
1 = Spor *4 = +++*
2 = +

54 Maks proteinuri <u>etter</u> kramper ☐
0 = Ingen *3 = ++*
1 = Spor *4 = +++*
2 = +

55	Antenatal hypertensjon uansett tidspunkt (*hypertensjon er første BT i svangerskap <90 mmhg diastolisk, maks diastolisk BT >90 mmHg og en økning i diastolisk BT ≥25 mmHg)*	Ja ☐	Nei ☐
56	Antenatal proteinurisk preeklampsi uansett tid (definisjon 300 mg/d eller + på protein)	Ja ☐	Nei ☐
57	Svangerskapsvarighet første gang hypertensjon ble registrert (uker)		☐☐
58	Antall uker første gang kriterier for proteinurisk preeklampsi er nådd		☐☐
59	Tid fra første gangs proteinurisk preeklampsi er diagnostisert til første krampeanfall *Timer* *Dager*		☐☐ ☐☐

60	Diagnose som finnes i journal/helsekort for gravide	Ja	Nei
	Ingen	☐	☐
	Hypertensjon eller økt BT	☐	☐
	Pregnancy induced hypertension	☐	☐
	Preeklampsi	☐	☐
	Kronisk hypertensjon	☐	☐
	Superimposed preeklampsi	☐	☐
	Annet (spesifiser)		

61	Symptomer beskrevet av pasientene før første krampe	Ja ☐	Nei ☐
	Ingen	☐	☐
	Hodepine	☐	☐
	Synsforstyrrelser	☐	☐
	Epigastrie/høye costalbuesmerter	☐	☐
	Irritabel/uro	☐	☐
	Annet (spesifiser).		

62	Medikasjon før kramper	Ja	Nei
	Ingen	☐	☐
	Aspirin	☐	☐
	Metyldopa	☐	☐
	Nifedipin	☐	☐
	Labetalol	☐	☐
	Hydralazin	☐	☐
	β-blokker	☐	☐
	Diuretika	☐	☐
	Fragmin	☐	☐
	Diazepam	☐	☐
	Mg. sulfat	☐	☐
	Klorpromazin	☐	☐
	Phenytoin	☐	☐

Generell anestesi ☐ ☐
Morfin/petidin ☐ ☐
Annet (spesifiser). . . . . . ☐ ☐

63 Komplikasjoner i svangerskapet

	Ja	Nei
Ingen	☐	☐
Anemi (Hb <9 g/dl)	☐	☐
Truende abort	☐	☐
Antepartum blødning	☐	☐
Abruptio placentae	☐	☐
IUGR (÷ 2 SD)	☐	☐
Hemokons (Hb > 14 g/dl)	☐	☐

Annet (spesifiser). . . . . . .

64 Høyeste målte Hb før 12 uker *(reell verdi)* ☐☐☐

65 Høyeste målte Hb mellom 12-28 uker *(reell verdi)* ☐☐☐

66 Laveste målte Hb mellom 12-28 uker *(reell verdi)* ☐☐☐

67 Høyeste målte Hb etter 28 uker ☐☐☐

68 Serum ferritin målt før 20. svangerskapsuke *(reell verdi)* ☐☐☐

69 Har pasienten fått jernbehandling

Ja	Nei
☐	☐

70 Maks serum kreatinin før kramper ☐☐☐

71 Maks serum ASAT før kramper ☐☐☐☐

72 Laveste trombocytter før kramper ☐☐☐

73 Serum fibrinogen før kramper *(reell verdi)* ☐☐☐

74 Kefotest undersøkt før kramper ☐
0 = ikke målt
1 = Normal
3 = Forlenget

75 Undersøkt fibrin degraderingsprodukter *(FDP eller D-dimer)* før kramper ☐
0 = ikke undersøkt
1 = Normal
3 = Økt

Høyeste urat verdi ☐☐☐
Laveste albumin ☐☐☐
Høyeste LDH ☐☐☐☐
Høyeste bilirubin ☐☐☐

EKLAMPSI

76 Dato for første krampe ☐☐☐☐☐

77 Tidspunkt på dagen *(klokkeslett)* ☐☐☐☐

78 Svangerskapsuke ved første krampe, om post partum angis uker ved fødsel ☐☐

79 Type av eklampsi

	Ja	Nei
Antepartum	☐	☐
Intrapartum	☐	☐
Postpartum	☐	☐
Ukjent	☐	☐

80 Hvor skjedde første krampeanfall ☐

0 = Hjemme
1 = Transport
2 = Kvinneklinikk (<1500 fødsler)
3 = Fødeavdeling (500-1500 fødsler)
4 = Fødeavdeling (<500 fødsler)
5 = Fødestue
6 = Annet (spesifiser). . . . . .

		Ja	Nei
81	Krampeanfall i sykehus (uansett tidspunkt)	☐	☐

82 Total antall krampeanfall ☐☐

83 Antall krampeanfall <u>før</u> behandling (*antikonvulsiva)* ☐☐

84 Antall krampeanfall <u>etter</u> behandlingsstart ☐☐

85 Lengde på sykehusopphold før første krampeanfall *(dager)* ☐☐☐

86 Medikamenter brukt ved behandling av krampeanfall

	Ja	Nei
Ingen	☐	☐
Diazepam	☐	☐
Mg. sulfat	☐	☐
Phynytoin	☐	☐
Metyldopa	☐	☐
Hydralazin	☐	☐
Labetalol	☐	☐
Nifedipen	☐	☐
β-blokker	☐	☐
Diuretika	☐	☐
Babitural	☐	☐
Generell narkose	☐	☐

Annet (spesfiser). . . . . .

87 Profylakse mot nye kramper etter første anfall — Ja ☐ Nei ☐
Ingen ☐ ☐
Mg. sulfat ☐ ☐
Diazepam ☐ ☐
Hemineverin ☐ ☐
Fenytoin ☐ ☐
Andre (spesifiser). . . . . . .

88 Antall kramper etter start av profylakse ☐

89 Blodtransfusjon under behandling ☐
0 = Nei
1 = Ja

90 Antall transfusjoner (SAG) (*reell verdi)* ☐☐

91 Platetransfusjon ☐
0 = Nei
1 = Ja

92 Antall enheter med platetransfusjon ☐☐

93 Maks serum kreatinin etter kramper ☐☐☐

94 Maks serum bilirubin ☐☐☐

95 Maks serum ASAT etter kramper ☐☐☐

96 Laveste platetall etter kramper ☐☐☐

97 Kefotest etter kramper ☐
0 = Ikke målt
1 = Normal
2 = Forlenget

98 Fibrinogen etter krampeanfall *(verdi)* ☐☐☐

99 FDP eller D-dimer etter kramper ☐
0 = Ikke målt
1 = Normal
2 = Økt

100 Haptoglobin etter kramper ☐
0 =Ikke målt
1 = Normal
2 = Lav

FØDSEL

101 Dato for fødsel ☐☐☐☐☐☐

102 Tidspunkt på dagen ☐☐☐☐

103 Antall uker ved fødsel ☐☐

104 Sted for forløsning ☐
0 = Hjemme
1 = Transport
2 = Kvinneklinikk (<1500 fødsler)
3 = Fødeavdeling (500-1500 fødsler)
4 = Fødeavdeling (<500 fødsler)
5 = Fødestue
6 = Annet (spesifiser). . . . . .

105 Tid mellom første krampe og forløsning
Timer (<1 dag) ☐☐
Dager (≥1 dag) ☐☐

106 Induksjon av fødsel	Ja	Nei
Ingen induksjon	☐	☐
Amniotomi	☐	☐
Oxytocin	☐	☐
Prostaglandin	☐	☐

Annet (spesifiser). . . . . .

107 Forløsningsmåte	Ja	Nei
Uforløst	☐	☐
Spontan hodeleie	☐	☐
Tang	☐	☐
Vakuum	☐	☐
Vaginal	☐	☐
Elektiv sectio	☐	☐
Akutt sectio før fødsel	☐	☐
Akutt sectio under fødsel	☐	☐

108 Anestesitype	Ja	Nei
Ingen	☐	☐
NO_2	☐	☐
Opiater	☐	☐
Epidural	☐	☐
Spinal	☐	☐
Generell narkose	☐	☐

Annet (spesifiser) . . . . . .

MATERNELT UTKOMME

109 Komplikasjoner til forløsning ☐

0 = Ingen
1 = Maternell feber ≥38°C
2 = Blødning ≥500 ml – angi antall ml ☐☐☐☐
3 = Andre (spesifiser) . . . . . .
. . . . . .

110 Komplikasjoner til eklampsi

	Ja	Nei
Ingen	☐	☐
UVI	☐	☐
Lungeinfeksjon	☐	☐
DVT	☐	☐
PE	☐	☐
Cerebrovas. ulykke	☐	☐
Retinaløsning	☐	☐
Cortikal blindhet	☐	☐
DIC	☐	☐
Nyresvikt (kreatinin ≥150)	☐	☐
Lunegødem	☐	☐
Hjertestans	☐	☐

Annet (spesifiser). . . . . . .
. . . . . .

111 Varighet av hospitalisering etter kramper *(dager)* ☐☐

112 Lå pasienten på intensivavdelingen ☐☐

113 Maternell død ☐

0 = Ja
1 = Nei

114 Tid for maternell død ☐

0 = Antenatal
1 = Intra partum
2 = Post partum
3 = Usikker

115 Dato for morens død ☐☐☐☐☐

116 Årsak til død ☐

0 = Ukjent
1 = Cerebrovasc. ulykke
2 = Lungeemboli
3 = Blødning
4 = Sepsis
5 = Respirasjonssvikt
6 = Annet (spesifiser). . . . . . .

117 Obduksjon foretatt ☐
0 = Nei
1 = Ja
Resultat . . . . . .
. . . . . .

118 Ble CT tatt Ja ☐ Nei ☐
Spesifiser resultat . . . . . .
. . . . . .

119 Ble MR tatt Ja ☐ Nei ☐
Spesifiser resultat . . . . . .
. . . . . .

120 Maternell morbiditet etter utskriving

	Ja	Nei
Ingen	☐	☐
Feber	☐	☐
Lungeinfeksjon	☐	☐
UVI	☐	☐
Sårinfeksjon	☐	☐
Hypertensjon	☐	☐
Hodepine	☐	☐
Hukommelsestap	☐	☐
Neurologisk utfall	☐	☐
Depresjon	☐	☐
Psykose	☐	☐

Annet (spesifiser) . . . . . .
. . . . . .

FØTALT UTKOMME

121 Utkomme barn 1 ☐
0 = Intrauterin død
1 = Intrapartumm død
2 = Nenonatal død (0-7 dager)
3 = Død senere (< 7 dager)
4 = Overlevet . . . . . .

122 Apgar 1 min *(angi verdi)* ☐☐

123 Apgar 5 min *(angi verdi)* ☐☐

124 Kjønn barn ☐
0 = gutt
1 = pike

125 Fødselsvekt *(g)* ☐☐☐☐

126 Centile (vekt) ved fødsel ☐☐

127 Lengde *(cm)* ☐☐

128 Hodeomkrets *(cm)* ☐☐

129 Tid for barn i intensivavdeling *(dager)* ☐☐

130 Morbiditet barn 1

	Ja	Nei
Ingen	☐	☐
Respirasjonsproblemer	☐	☐
Utviklingsforsinkelse	☐	☐
Spesifikk neurologisk utfall	☐	☐
Retinopati	☐	☐

Annet (spesifiser) . . . . . .

131 Barnets helstilstand ved 6 måneder *(frisk)*

	Ja	Nei
Hvis nei, spesifiser	☐	☐

. . . . . .

132 Årsak død barn 1

	Ja	Nei
Ikke kjent	☐	☐
Misdannelser	☐	☐
Isoimmun	☐	☐
Antepartum asfyksi	☐	☐
Intrapartum asfyksi	☐	☐
Fødselstraume	☐	☐
Lungeumodenhet	☐	☐
Hyaline membraner	☐	☐
Intrakraniell blødning	☐	☐
Infeksjon	☐	☐

Annet (spesifiser) . . . . . .

133 Dato for død barn 1 ☐☐☐☐☐☐

134 Utkomme tvilling 2 ☐

0 = Intrauterin død
1 = Intrapartum død
2 = Neonatal død (0-7 dager)
3 = Død senere (7 dager)
4 = Overlevet

135 Apgar 1 min tvilling 2 ☐☐

136 Apgar 5 min tvilling 2 ☐☐

137 Kjønn tvilling 2 ☐

0 = gutt
1 = pike

138 Fødselsvekt tvilling 2 *(g)* ☐☐☐☐

139 Tid for barn i intensivenhet tvilling 2 *(dager)* ☐☐

140 Morbiditet tvilling 2

	Ja	Nei
Ingen	☐	☐
Respirasjonsproblemer	☐	☐
Utviklingsforsinkelse	☐	☐
Spesifikk neurologisk utfall	☐	☐
Retinopati	☐	☐
Annet (spesifiser)		

141 Årsak død barn 2

	Ja	Nei
Ikke kjent	☐	☐
Misdannelser	☐	☐
Isoimmun	☐	☐
Antepartum asfyksi	☐	☐
Intrapartum asfyksi	☐	☐
Fødselstraume	☐	☐
Lungeumodenhet	☐	☐
Hyaline membraner	☐	☐
Intrakraniell blødning	☐	☐
Infeksjon	☐	☐
Annet (spesifiser)		

142 Forløsning av tvilling 2

	Ja	Nei
Mor uforløst	☐	☐
Spontan hodefødsel	☐	☐
Tang	☐	☐
Vakuum	☐	☐
Vaginalt sete	☐	☐
Elektiv sectio	☐	☐
Akutt sectio før fødsel	☐	☐
Akutt sectio under fødsel	☐	☐

143 Klassifisering av tilfelle ☐

0 = Klassisk eklampsi
1 = Eklampsi, men bare hypertensjon
2 = Eklampsi, men bare proteinuri
3 = Epilepsi
4 = Andre årsaker til kramper (hypoglykemi, besvimelse, vasovag.)
5 = Ukjent årsak til kramper

144

	Ja	Nei
Spontan graviditet	☐	☐
IVF	☐	☐
Assistert befruktning	☐	☐
AID	☐	☐
Eventuelt spesifiser		

MOMENTER TIL INNLEDNING VED TEL. INTERVJU 8- 12 UKER POSTPARTUM

- Presentasjon av oppringer
- Info. om eklampsi- studie i Norge / Skandinavia
- Påminnelse om at hun ved fødselen og komplikasjoner til denne ble informert om denne studie
- Nå kontakt for å høre hvordan forløpet har vært for deg og barnet ditt

MOMENTER TIL AVSLUTNING VED TEL. INTERVJU 8-12 UKER POSTPARTUM

- Informasjon og forespørsel om å få ringe igjen når barnet er 6 mnd.

MOMENTER TIL INNLEDNING VED TEL. INTERVJU 6MÅNDER POSTPARTUM

- Presentasjon av oppringer
- Påminnelse om eklampsi studie og forrige samtale
- Nå på nytt kontakt for å høre forløpet videre for deg og barnet ditt

MOMENTER TIL AVSLUTNING VED TEL. INTERVJU 6MÅNDER POSTPARTUM

- Forespørsel om å ta blodprøve og informasjon om denne, blant annet for å forsøke å finne fellestrekk i enkelte blodverdier for kvinner med eklampsi
- Avtale praktisk gjennomføring med sending av rekvisisjon og hvordan prøven skal tas (fastende). Blodprøve tas ved legekontoret hjemme hos kvinnen

REGISTRERINGSSKJEMA — EKLAMPSI

TELEFONINTERVJU ETTER 8 – 12 UKER

1. Studie nr. --------

2. Tel.nummer: _____

3. Dato for samtale:_____

4. Antall uker postpartum --------

SVANGERSKAPET

5. Svangerskapskontroller gjennom ført hos:
   - Ingen ____
   - Allmennpraktiker ____
   - Spesialist ____
   - Allmennpraktiker/ jordmor _____
   - Annet (spesifiser) _____ (……)

6. Brukte du noen form for jern-preparater under svangerskapet? J/N
   Type preparat:…….

   Varighet av behandling (uker / dager) ____/_____

7. Brukte du noen form for antihypertensiva i svangerskapet? J/N
   Type preparat:…….

   Når ble dette evt. seponert?
   Svangerskapsuke:……
   Uker / dager postpartum:……/…….

OPPFØLGING, BEHANDLING OG KONTROLLER ETTER EKLAMPSI

8. Antall kontakter med allmennlege etter fødsel --------

9. Har du vært til vanlig etterkontroll etter fødsel? J / N

10. Evt. påviste funn du kjenner til fra disse kontrollene:
    - 1 - Ingen J / N
    - 2 - Forhøyet BT J / N
    - 3 - Nevrologiske utfall J / N
    - 4 - Annet J / N

    Spesifiser.....

11. Bruker du noen medisiner nå?

1 - Ingen J / N
2 - Antihypertensiva J / N
Spesifiser type:.....
3 - Antidepressiva J / N
Spesifiser type:.....
4 - Andre medikamenter J / N
Spesifiser type:.....

SYMPTOMER OG KOMPLIKASJONER FØR OG ETTER EKLAMPSI

12. Husker du om du hadde noen av følgende symptomer før du fikk kramper på sykehuset?

1 - Ingen J / N
2 - Hodepine J / N
3 - Synsforstyrrelser J / N
4 - Epigastrie / hø. costalbuesmerter J / N
5 - Irritabilitet / irritasjon / uro J / N
6 - Annet J / N
Spesifiser:.....

13. Har du hatt noen av disse symptomene i tiden etter krampene?

1 - Ingen J / N
2 - Hodepine J / N
3 - Synsforstyrrelser J / N
4 - Epigastrie / hø. costalbuesmerter J / N
5 - Irritabilitet / irritasjon / uro J / N
6- Svimmelhet J / N
7 – Konsentrasjonsvansker J / N
8 – Bevegelses /gangvansker J / N
9 - Annet J / N
Spesifiser:.....

14. Er noen av symptomene fortsatt til stede?

1 - Ingen J / N
2 - Hodepine J / N
3 - Synsforstyrrelser J / N
4 - Epigastrie / hø. costalbuesmerter J / N
5 - Irritabilitet / irritasjon / uro J / N
6- Svimmelhet J / N
7 – Konsentrasjonsvansker J / N
8 – Bevegelses /gangvansker J / N
9 - Annet J / N
Spesifiser:.....

15. Har det vært andre komplikasjoner i forløpet etter fødselen og eklampsien?

1 - Ingen J / N

2 - UVI J / N
3 - lungeinfeksjon J / N
4 - DVT J / N
5 - Lungeemboli J / N
6 - Hjerneblødning / cerebral trombose J / N
7 - Synsutfall J / N
8 - Svikt i nyrefunksjonen J / N
9 - Feber J / N
10 Sårinfeksjon J / N
11 Hukommelsestap J / N
12 Nevrologiske utfall J / N
13 Depresjon J / N
14 Psykose J / N
15 Annet J / N
Spesifiser: .....

OM BARNET

16. Ble barnet utskrevet fra sykehuset samtidig med deg? J / N

17. Barnet fortsatt inneliggende i sykehus J / N

18. Ble ditt opphold på sykehuset forlenget på grunn av. barnets tilstand J / N

19. Lå barnet noen gang på barneavdeling. J / N

20. Antall dager barnet var på barneavdeling. -------

21. Har barnet vært til vanlig 6 ukers kontroll? J / N
Evt. bemerkninger ved undersøkelse av barnet
ved denne kontrollen: .....

22. Opplever dere barnet som friskt? J / N
Om nei, spesifiser mor bemerkninger om avvik:.....
.....

23. Er barnet under utredning hos barnelege / allmennpraktiker? J / N
Om ja; spesifiser for hva:.....
.....

24. Ernæring av barnet nå:
1 - Ammer J / N
2 - delvis amming J / N
3 - Morsmelk tillegg J / N

25. Barnets vekt ved 6 uker: _____

REGISTRERINGSSKJEMA — EKLAMPSI

TELEFONINTERVJU ETTER 6 MÅNEDER

1. Studienr. --------

2. Tel.nummer _____

3. Dato for samtale: _____

4. Antall uker postpartum --------

Oppfølging, behandling og kontroller etter eklampsi

5. Antall konsultasjoner ved sykehuset etter fødsel --------

6. Antall kontakter med allmennlege etter fødsel --------

7. Evt. påviste funn du kjenner til fra disse kontrollene:
   - 1 - Ingen J / N
   - 2 - Forhøyet BT J / N
   - 3 – Siste målte BT: _____/_____
     ca.dato for denne målingen:_____

   Proteinuri J/N
   Om ja tidspunkt for siste kontroll _____

   - 3 – Nevrologiske utfall J / N
   - 4 – Annet J / N
     Spesifiser….....

8. Bruker du noen medisiner nå?
   - 1 – Ingen J / N
   - 2 – Antihypertensiva J / N
     Spesifiser type:….....
     Evt. når seponert om tidl. brukt etter fødsel _____
   - 3 – Antidepressiva J / N
     Spesifiser type:….....
   - 4 – Andre medikamenter J / N
     Spesifiser type:….....

SYMPTOMER OG KOMPLIKASJONER EKLAMPSI

9. Er noen av symptomene fortsatt tilstede?

1 – Ingen	J / N
2 – Hodepine	J / N
3 – Synsforstyrrelser	J / N
4 – Epigastrie / hø. kostalbuesmerter	J / N
5 – Irritabilitet / irritasjon / uro	J / N
6- Svimmelhet	J / N
7 – Konsentrasjonsvansker	J / N
8 – Bevegelses /gangvansker	J / N
9 - Annet	J / N

Spesifiser:.....

10.Har noen av følgende komplikasjoner oppstått i forløpet etter fødselen og eklampsien?

1 – Ingen	J / N
2 – UVI	J / N
3 – lungeinfeksjon	J / N
4 – DVT	J / N
5 – Lungeemboli	J / N
6 – Hjerneblødning / cerebral trombose	J / N
7 – Synsutfall	J / N
8 – Svikt i nyrefunksjonen	J / N
9 – Feber	J / N
10 Sårinfeksjon	J / N
11 Hukommelsestap	J / N
12 Nevrologiske utfall	J / N
13 Depresjon	J / N
14 Psykose	J / N
15 Annet	J / N

Spesifiser: ….....

Om barnet

11. Har du vært til vanlige kontroller på helsestasjonen med barnet? J / N

Evt. bemerkninger ved undersøkelse av barnet
ved disse kontrollene: ….....

12. Opplever dere barnet som friskt? J / N

Om nei, spesifiser mor bemerkninger om avvik:….....
….....

13. Utvikler barnet seg normalt synes du? J / N

14. Har barnelege/allmennpraktiker /helsesøster sagt noe om avvik i barnest utvikling? J/N

Om ja spesifiser…….
……..

15. Er barnet under utredning hos barnelege / allmennpraktiker? J / N

Om ja; spesifiser for hva:….....
….....

16. Siste vekt av barnet : _____

Dato for vektmåling: _____

Barnets alder ved veiingen: _____

17. Amming nå J/N

18. Er menstruasjonen kommet tilbake? J/N

Dato for siste mens.:_____

OM EGEN HELSE FØR DETTE SVANGERSKAPET / FØDSELEN

19. Ved evt. tidligere svangerskap, var det noen av følgende komplikasjoner i dette?

Høyt blodtrykk	J/N
Preeklampsi	J/N
Glukosuri	J/N
Vekstavvik hos barnet	J/N

20.Har du tidligere hatt tromboembolisk sykdom? J/N

Om ja spesifiser:……
…….

21. Har noen i din familie hatt tromboembolisksykdom? J/N
(mor/ far/ søsken før 60 års alder)

Om ja spesifiser hvem og type sykdom……..
…….

22. Har noen i din familie behandlingstrengende hypertensjon før 60-års-alder? J / N

Om ja spesifiser hvem og evt. alder ved debut:…
……..

23. Har noen i din familie hatt hjerteinfarkt før de ble 60 år? J / N

Om ja spesifiser hvem og evt. alder ved debut:…
……..

24. Har du tidligere fått påvist for høyt blodtrykk? J/N

Grenseblodtrykk……J/N
Hypertoni (ubehandlet)….J/N
Hypertoni, med.behandlet J/N

Evt. spesifiser medikamenter , alder ved debut og ikke-medikamentelle tiltak
…….
……..

25. Har du fått påvist kronisk nyresykdom før dette svangerskapet? J/N

Evt. spesifiser:……..

26. Lider du av andre kroniske sykdommer? J/N

Evt. ja spesifiser:……..

27. Vet du om noen i din familie har hatt
Eklampsi: J / N
Om ja hvem (mor, søster) …….
Preeklampsi J / N
Om ja hvem (mor, søsken)…….

28. Mors egen fødselsvekt: _____g.

MANGLER I TIDLIGERE UTFYLT SKJEMA

Før avslutning be kvinnen om manglende opplysninger i tidligere utfylte skjema.

Informasjon om blodprøvetaking og praktiske aspekter ved dette.

PROSJEKT: MATERNELLE DØDSFALL

Pasientens alder: ☐☐ Pasientnr: ☐☐☐

TIDLIGERE SYKDOM

Hypertensjon Ja ☐ Nei ☐
Evt. beskriv (behandling etc) ……...

Nyresykdom Ja ☐ Nei ☐
Evt. beskriv
……..…….

Diabetes Ja ☐ Nei ☐
Evt. beskriv
……..…….

Autoimmunsykdom Ja ☐ Nei ☐
Evt. beskriv
……..…….

Epilepsi Ja ☐ Nei ☐
Evt. beskriv
……..…….

Lungesykdom Ja ☐ Nei ☐
Evt. beskriv
……..…….

Tromboemboli Ja ☐ Nei ☐
Evt. beskriv (når, hvordan, behandling, disposisjon, faktorer)
……..……..……
……..
……...

Annet Ja ☐ Nei ☐
Evt. beskriv
……..…….

Ingen signifikant sykdom Ja ☐ Nei ☐

TIDLIGERE SVANGERSKAP

Antall svangerskap ☐☐
Antall aborter ☐☐
Antall fødsler ☐☐☐
Beskriv (når, svangerskapsuke, fødselsvekt osv)……..
……..

AKTUELT SVANGERSKAP

Siste menstruasjon ……Syklus: ……/……
Termin Naegle ☐☐☐☐☐☐
Termin UL ☐☐☐☐☐☐
Antall svangerskapskontroller: ☐☐
Siste svangerskapskontroll (dato) ☐☐☐☐☐☐
Fødselsdato ☐☐☐☐☐☐
Antall svangerskapsuker ☐☐
Fødselsvekt (g) ☐☐☐☐
Apgar score 1 min ☐☐ 5 min ☐☐

BARNET

Perinatalt dødsfall Ja ☐ Nei ☐
Intrauterin død Ja ☐ Nei ☐
Neonatal død Ja ☐ Nei ☐
Antall dager etter fødsel ☐☐☐
Årsak……
Komplikasjon barn Ja ☐ Nei ☐
Beskriv…….
……...

Opphold i barneavdelingen(dager) ☐☐☐

FORLØSNINGSMETODE

Spontan fødsel Ja ☐ Nei ☐
Indusert fødsel Ja ☐ Nei ☐
Indikasjon..……

Sectio Ja ☐ Nei ☐
Akutt Ja ☐ Nei ☐
Indikasjon..……

Elektiv Ja ☐ Nei ☐
Indikasjon..……

Tang Ja ☐ Nei ☐
Vakum Ja ☐ Nei ☐
Indikasjon.……

Sete Ja ☐ Nei ☐
Indikasjon……..

Komplikasjon til fødsel Ja ☐ Nei ☐
Beskriv…….
……..
…….
……...

KOMPLIKASJON I AKTUELT SVANGERSKAP

Hypertensjon	Ja ☐	Nei ☐
Preeklampsi	Ja ☐	Nei ☐
Eklampsi	Ja ☐	Nei ☐
HELLP	Ja ☐	Nei ☐
Tromboemboli	Ja ☐	Nei ☐
Blødning	Ja ☐	Nei ☐
Uterusruptur	Ja ☐	Nei ☐
Amnionvæske emboli	Ja ☐	Nei ☐
Anestesikomplikasjon	Ja ☐	Nei ☐
Sepsis	Ja ☐	Nei ☐
Annet	Ja ☐	Nei ☐

Beskriv……..
……...
……..
……...

MATERNELL DØD

Dato ☐☐☐☐☐☐

Klinisk diagnose ……..
Obduksjon Ja ☐ Nei ☐
Diagnose.……

Beskriv hendelsesforløp og behandling gitt før dødsfall:
……
……
……
……
……
……..

MATERNELT DØDSFALL

Under graviditet	Ja ☐	Nei ☐
Under fødsel	Ja ☐	Nei ☐
Postpartum (<42 dager)	Ja ☐	Nei ☐
Sent dødsfall ≥42 dager og < ett år J	Ja ☐	Nei ☐

DØDSSTED

Sykehus	Ja ☐	Nei ☐
Fødestue	Ja ☐	Nei ☐
Hjemme	Ja ☐	Nei ☐
Annet	Ja ☐	Nei ☐

Beskriv.……
……...

KATEGORISERING AV DØDSFALL

Direkte maternelt dødsfall Ja ☐ Nei ☐

Diagnose..……

Indirekte maternelt dødsfall Ja ☐ Nei ☐

Diagnose..……

Tilfeldig maternelt dødsfall Ja ☐ Nei ☐

Diagnose..…….

Sent maternelt dødsfall Ja ☐ Nei ☐

Diagnose.…….

VURDERING AV BEHANDLING

Adekvat Ja ☐ Nei ☐
Substandard Ja ☐ Nei ☐
Inadekvat Ja ☐ Nei ☐

Beskriv ……

Forslag til forbedring ……...
……
……
……...

VURDERING AV FORLØP TOTALT

Uunngåelig (unavoidable) Ja ☐ Nei ☐
Mulig unngåelig (potentially avoidable) Ja ☐ Nei ☐
Unngåelig (avoidable) Ja ☐ Nei ☐

STUDY I-IV

STUDY I

Andersgaard AB, Herbst A, Johansen M, Ivarsson A, Ingemarsson I,
Langhoff-Roos J, Henriksen T, Straume B, Øian P.
Eclampsia in Scandinavia: incidence, substandard care, and potentially preventable cases.
Acta Obstet Gynecol Scand 2006;85:929-36.

STUDY II

Andersgaard AB, Herbst A, Johansen M, Borgström A, Bille AG, Øian P.

Follow-Up Interviews after Eclampsia.

Gynecol Obstet Invest 2009;67:49-52.

Study III

Andersgaard AB, Acharya G, Ellisiv Mathiesen, Stein Harald Johnsen, Straume B, Øian P.

Recurrence and long-term maternal health risks of hypertensive disorders of pregnancy: a population based study**.**

Submitted.

Study IV

Andersgaard AB, Langhoff-Roos J and Øian P. Direct maternal deaths in Norway 1976-1995. Acta Obstet Gynecol Scand 2008;87:856-61.

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