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Project thesis

Preeclampsia rates and maternal mortality in high- and low-income countries

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Abstract

Objectives

The aim of this project thesis is to describe the global incidence of preeclampsia and eclampsia, and the consequences in the form of maternal mortality caused by preeclampsia. Also, identification, prevention, and treatment of preeclampsia in low-income countries is evaluated.

Methods

This thesis is written as a targeted literature review, based on a non-systematic search in MEDLINE (PubMed) and google. Review articles and original papers were selected based on title and abstract. Some of the literature included was suggested by my supervisor, and some papers were included from the reference lists while reading.

Results

Preeclampsia rates varied considerably in the papers included, and showed no consistent pattern of higher incidences in any regions. Severe consequences of preeclampsia such as eclampsia and fatal outcome are much more common in low- and middle-income countries. Preeclampsia rates seem to have been increasing in the 19th century, and then decreasing since the turn of the millennium, in studies carried out in high-income countries. Low-income countries are lagging behind on diagnosis and treatment of preeclampsia. Factors contributing to this are less use of or access to antenatal care, lack of qualified health personnel, and lack of resources such as essential medicines.

Conclusion

More research is needed on the global burden of preeclampsia, especially in low-income countries where true incidence rates are largely unknown and where the burden of severe disease is unacceptably high. Such intervention is essential for policy makers to be able to implement appropriate measures to tackle the problem of preventable maternal deaths caused by preeclampsia.

Introduction

Preeclampsia is a common syndrome of pregnancy, affecting the present and future health of both the mother and fetus. In this project thesis I wanted to explore how the incidence and burden of disease is distributed globally, and how preeclampsia contributes to maternal mortality. Maternal mortality is a problem with large regional variations, which is deeply unfair. As a medical student in Norway, I am rarely confronted with this issue, as maternal mortality is low in our part of the world, but in some part of the world being pregnant and giving birth must be considered high-risk conditions. This project thesis was written as part of my medical studies at the University of Oslo.

I would like to thank my supervisor Annetine Staff, first of all for leading me on to this very interesting subject. It has been enlightening to write this thesis and get a better understanding of preeclampsia in a global health context. I would also like to thank her for her guidance and help during the process, in everything from forming the aims of this thesis, to giving me feedback on my writing.

Background

Preeclampsia is defined by the International Society for The Study of Hypertension in Pregnancy (ISSHP) as new onset hypertension (defined as at least 140 mmHg in diastolic blood pressure and/or at least 90 mmHg in diastolic blood pressure) after 20 weeks of gestation, combined with new-onset (after 20 weeks gestation) proteinuria or other signs of organ dysfunction such as acute kidney injury, liver involvement or neurological or hematological complications (1). Preeclampsia belongs to the group of hypertensive disorders of pregnancy (HDP), which include gestational hypertension, preeclampsia/ eclampsia, chronic hypertension, and chronic hypertension complicated by preeclampsia/eclampsia.

Preeclampsia is a heterogenous syndrome and is often divided into an early-onset form and a late-onset form, based on whether the woman is delivered before or after 34 weeks of pregnancy. Other studies use the cutoff at term, namely early-onset preeclampsia as preeclampsia with delivery prior to week 37 (2). Early-onset preeclampsia is associated with fetal growth restriction and will often have a more severe development for the mother and fetus, including more often fetal growth restriction. Late-onset preeclampsia is rarely associated with fetal growth restriction at birth. Both forms are usually asymptomatic in the beginning, but when subjective symptoms occur (e.g. severe headache and reduced fetal movements), they may be due to the development of an impending terminal crisis that is potentially deadly for both the mother and the fetus (e.g. eclampsia and fetal death) (3). Subjective symptoms include headache and visual disturbances, nausea and vomiting, epigastric pain and dyspnea/breathlessness, and less fetal movements (4). Objective signs may include eclampsia, rapidly developing edema and hypertension, as well as proteinuria and biochemical findings (e.g. HELLP: hemolysis, elevated liver enzyme, low platelets).

Preeclampsia can develop into many life-threatening syndromes, including eclampsia and HELLP (2). Both can occur antenatally (before or after term), intrapartum and postpartum. The HELLP syndrome complicates 20-30% of all cases of severe preeclampsia. Other severe features of preeclampsia include increased risk of abruptio placentae (putting both the mother and fetus at risk due to severe maternal hemorrhage), disseminated intravascular coagulation, pulmonary edema, acute renal failure, and eclampsia. Eclampsia complicates 1-2% of cases of severe preeclampsia and presents as tonic-clonic seizures in a pregnant or recently pregnant woman. Eclampsia rates vary however globally, as will be

discussed in this thesis. Similar symptoms to those described above (in particular severe headaches and visual disturbances/flashing lights) often occur beforehand (5).

Maternal risk factors for preeclampsia include nulliparity, age over 40 years, a body-mass index of 35 or higher and a family history of preeclampsia. Preconceptional chronic diseases like hypertension, diabetes and kidney disease in the mother is associated with increased risk. There are also several risk factors related to the pregnancy itself such as in-vitro fertilization, multiple pregnancies and gestational diabetes (2). Paradoxically, smoking in pregnancy is associated with reduced risk of developing preeclampsia, the mechanism for this is poorly understood. Differences in placental production of angiogenic factors is one mechanism that has been proposed, suggesting that a lower level of antiangiogenic proteins in smokers result in an epidemiologically lower risk of developing preeclampsia. Importantly, smoking is associated with a high risk of fetal growth restriction, intrauterine fetal death, as well as cot death and asthma development in the surviving offspring. Smoking is therefore never recommended as a preventive strategy for preeclampsia (2, 6).

Pathophysiology

Preeclampsia has been labeled “The disease of theories” (7), as the detailed pathophysiological processes leading to the development of the clinical syndrome are not all clear. There are likely multiple pathological processes leading to a common pathway consisting of maternal endothelial cell activation, intravascular inflammation and syncytiotrophoblast cell stress within the placenta, with the release of inflammatory cytokines and the pro- and anti-angiogenic factors soluble fms-like tyrosine kinase-1 (sFlt-1) and placenta growth factor (PlGF) (2). The placenta plays a crucial role in the development of the syndrome; therefore, we can call it a placental syndrome. Redman introduced the two-stage placental model of preeclampsia in 1991(8), which has later been reviewed and expanded as our understanding of the pathology of preeclampsia has increased. The two-stage model of preeclampsia suggests preeclampsia to be a consequence of placental dysfunction with release of inflammatory factors, (stage 1), which again gives rise to the clinical maternal syndrome (stage 2) (2).

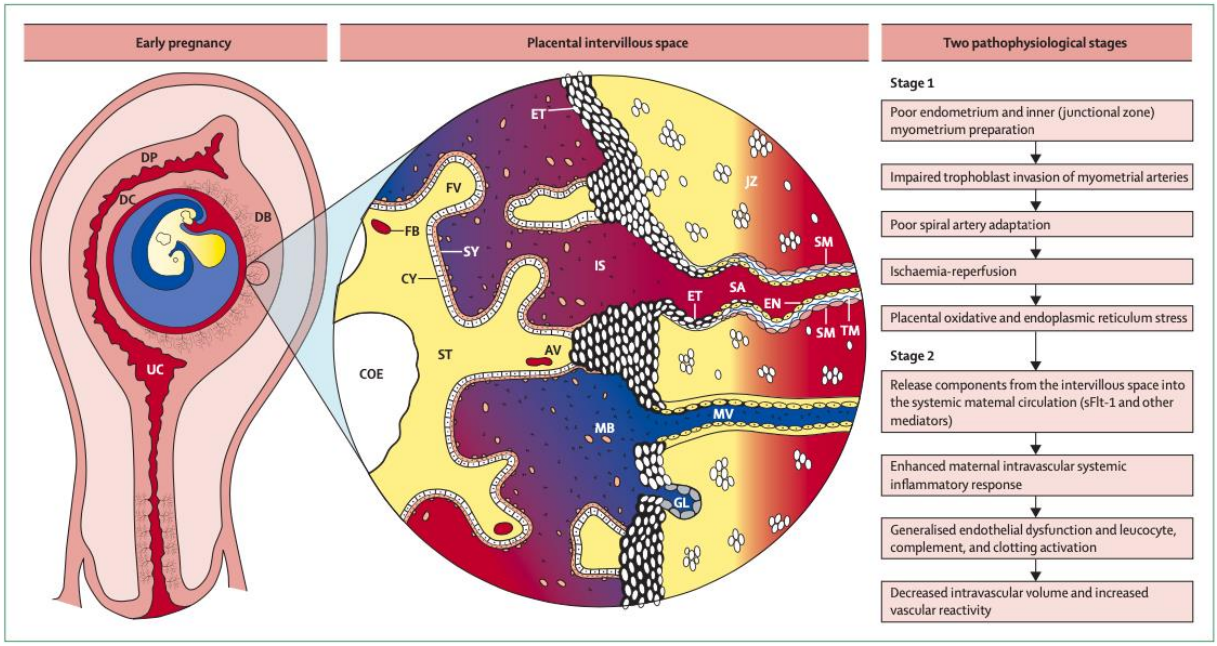

Figure 1: Possible pathophysiological processes in preeclampsia. Reprinted from The Lancet, Steegers, AP et al., Pre-eclampsia, 2010, with permission from Elsevier (5).

There are many pathways leading to placental dysfunction: Placental malperfusion is often observed in early-onset preeclampsia. It is caused by failure of the physiologic transformation of the spiral arteries, leading to uteroplacental malperfusion and cellular stress in the placental syncytiotrophoblasts. Other contributing factors to placental dysfunction are maternal infection, autoimmune and endocrine disorders and diseases like diabetes, obesity, sleep apnea, periodontal disease and intestinal dysbiosis. Other etiological factors are pregnancies with a hydatidiform mole, placental ageing, and breakdown of the maternal-fetal immune tolerance (7). All these pathways are illustrated in figure 2.

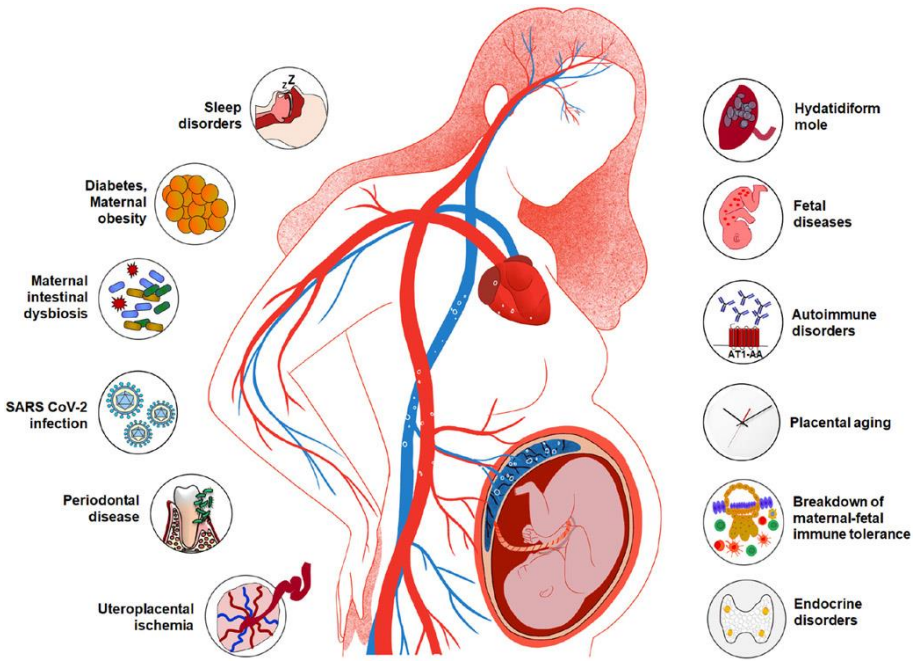

Figure 2: Reprinted from American Journal of Obstetrics and Gynaecology, Jung, E. et al., The etiology of preeclampsia, 2022, with permission from Elsevier (7).

Prevention and treatment of preeclampsia

The only treatment available today of the maternal signs of preeclampsia and HELLP syndrome is to remove the placenta, after delivery of the child. In preeclampsia occurring before term, this requires a discussion of the risks for the child by being born prematurely, and the risk for the mother by continuing pregnancy. From pregnancy week 37 an induction of delivery is indicated (if vaginal delivery is possible) in women with preeclampsia, regardless of severity, in order to avoid the development of severe and potential lethal complications of eclampsia and HELLP. This recommendation is included in many guidelines, including the ones from Norway and NICE (4, 9). Antihypertensive treatment is indicated in preeclamptic women with a systolic blood pressure from 150 mmHg and/or a diastolic blood pressure from100 mmHg, with the main goal of reducing the risk of cerebral vascular complications. In Norway, Labetalol (alfa- and betablocker) and Nifedipin (calcium antagonist) are the first choices for antihypertensive treatment in pregnancy. Treatment of severe preeclampsia and eclampsia include monitoring and stabilization of the woman, and treatment with magnesium sulphate for seizures, prior to delivery, when needed (4).

Low-dose aspirin has been shown to reduce the risk of preeclampsia in high-risk pregnancies (10), when used every day, and starting before gestational week 16. In Norway, assessment of the woman's risk of developing preeclampsia is by mapping her risk factors in the medical history. A new approach of screening women for elevated preeclampsia risk is to use an algorithm at gestational week 11-14 where also blood pressure, measuring of the blood flow to the placenta by ultrasound Doppler and measuring of maternal circulating PlGF is included, which increases the predictive accuracy of the risk of preeclampsia (11). Aspirin treatment should ideally be started from 11-14 weeks of gestation, at doses of 150 mg daily until week 36. Norwegian guidelines previously recommended 75 mg daily, that has been shown to be safe to use until delivery at any gestational age, without increasing risk of severe hemorrhage (4). The current Norwegian guideline recommends the clinician to either suggest 75 mg until delivery, or 150 mg until week 36. Other preventive measures include calcium supplements to women with a low dietary intake of calcium, and optimalisation of maternal health before pregnancy, by reducing overweight, treating underlying disease and pursuing a healthy lifestyle (4).

Maternal health as a human right

In 1990 the United Nations defined a set of eight goals to end poverty by 2015, the Millennium Development Goals (MDGs). The fifth goal was to improve maternal health reducing maternal mortality by 75% and achieving universal access to reproductive health. After 2015, the MDGs have been replaced by the Sustainable Development Goals, which are considerably more comprehensive than the MDGs, and apply to all UN member states, not only low-income countries. Maternal health is still a priority in the SDGs, and one of the goals is to reduce the maternal mortality rate (MMR) to 70 by 2030. MMR is defined as the number of maternal deaths in a given time period per 100.000 live births in the same period (12).

Between 1990 and 2015 the MMR fell globally by 44%, from 385 to 216 (13). Yet in 2020 the MMR had risen to 223, illustrating stagnating progress in most countries. Alarmingly, eight countries showed a substantially increase in MMR. Three sub-Saharan African countries had a MMR over 1000; South Sudan (1223), Chad (1063) and Nigeria (1047). In the USA, considered a high-income country, the MMR also increased from 20.1 in

2020 to 32.9 in 2023, and the increase and rate was much higher for Black women than for White and Hispanic women (14). By comparison, the MMR in Norway was 2 in 2020 (15).

We are thus a long way from achieving the goal of reducing the global MMR to 70 by 2030, and it is likely that this goal will not be achieved, as was the case with the MDG goal of a 75% reduction of MMR globally within 2015. Most of maternal deaths (95%) occur in low- and middle-income countries (16), making it clear that this is both a preventable and deeply unfair problem. The map below illustrates how the MMR differs globally.

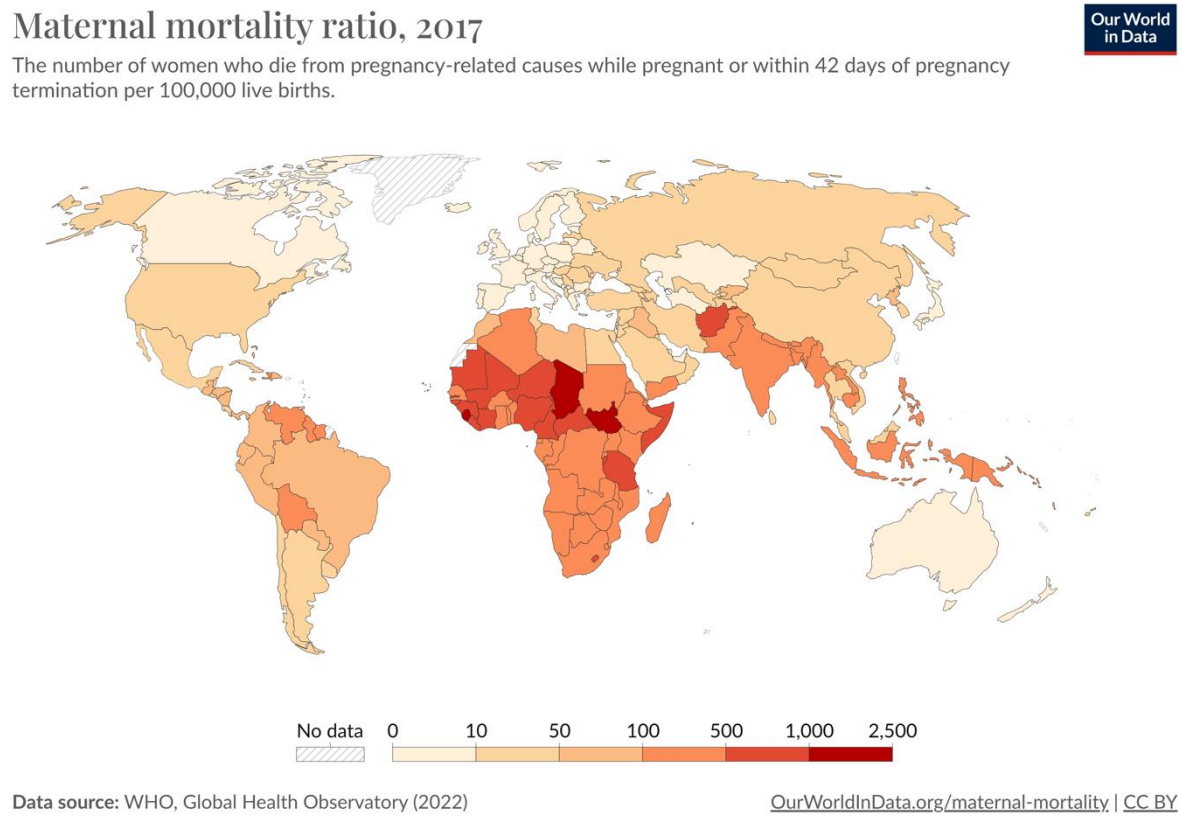

Figure 3: Gapminder (2010), WHO (2019) and OECD (2022) – processed by Our World in Data

Aim

This project thesis aims to review the incidence and consequences of hypertensive disorders of pregnancy in a global health perspective, with a special focus on preeclampsia. I will investigate how the burden of disease is distributed globally and if there is a difference in

incidence and mortality between low and high-income countries. Finally, I will have a look at some possible explanations as to why these differences arise and discuss what can be done to minimize them.

Methods

This project thesis is written as a targeted literature review, where I have tried to make an understandable and thorough review of the literature and what is already known on the topic of my research question. Relevant research articles on the incidence and consequences of preeclampsia globally are found through non-systematic search in MEDLINE (PubMed) in January and June 2023.

The following search terms were employed in MEDLINE: (global health[MeSH Terms]) AND (preeclampsia[MeSH Terms]), which gave 23 results, and Google: global incidence of preeclampsia.

I also included articles that seemed relevant from the reference list of articles while reading, as well as articles suggested by my supervisor professor Annetine Staff, who is an international expert within the field of placental syndromes and preeclampsia.

Review articles and original papers on the incidence and mortality of preeclampsia and eclampsia globally, in different regions, and in specific countries, were included. I also included several articles focusing on the trends in incidence over time. While doing the literature search, I found that the literature on the global incidence of preeclampsia is sparse and decided to expand the search to include hypertensive disorders of pregnancy. I have also included articles on the prevention and treatment of hypertensive disorders of pregnancy in low- and middle-income countries.

Results

Global estimates of preeclampsia and trends in preeclampsia rates

Abalos et al. published a systematic review on the global incidence of preeclampsia and eclampsia in 2013 (17). This is the only systematic analysis included in this thesis that provides estimates of preeclampsia and eclampsia globally. It included 74 studies from 40 countries that had available data reporting on preeclampsia and eclampsia (figure 4), and only seven had data on national coverage. The authors used a statistical model to calculate preeclampsia rates in the regions where data were lacking. The model showed a slightly higher incidence than the crude rates in their study, with a global incidence of preeclampsia of 4.6% of all deliveries. The paper also calculated rates for the individual WHO (World health Organization) regions, where the authors found wide variations ranging from 1.0% in the Eastern Mediterranean region to 5.6% in the African region. The incidence for the other regions were 3.0% in America, 5.3% in Europe, 5.1% in South-East Asia and 3.9% in the Western Pacific.

The paper's statistically modeled global incidence rate of eclampsia was 1.4% of all deliveries, this was also slightly higher than the calculated crude rate. The incidence rate of eclampsia varied more than preeclampsia, from 0.1% in the European and Western Pacific region, to 2.9% in the African region. The eclampsia rate was 0.7% in America, 1.9% in the Eastern Mediterranean, and 1.1% in Southeast Asia.

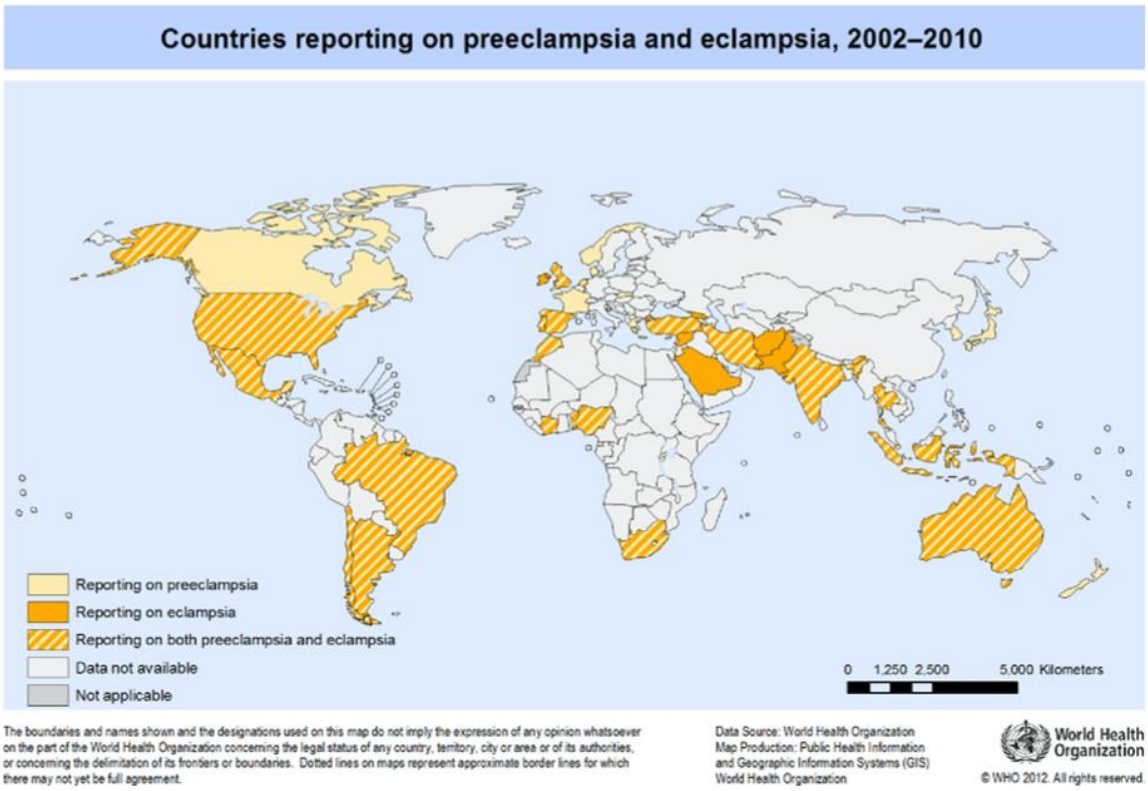

Figure 4: Reprinted from European Journal of Obstetrics and Gynaecology and Reproductive Biology, Abalos et al., Global and regional estimates of preeclampsia and eclampsia: a systematic review, Copyright (2013), with permission from Elsevier (17).

A WHO multi-country survey on maternal health published in 2013 by Souza et al. (18) collected data from 357 health facilities in 29 countries in Africa, Asia, Latin America, and the Middle East. Only health facilities dealing with minimum of 1000 deliveries a year and that had the capacity to perform cesarean section were included. The paper found a frequency of preeclampsia of 2.2% and of eclampsia of 0.3% of all deliveries. In a secondary analysis to this survey by Abalos et al. (19), the participating countries were grouped into low, lower middle, higher middle, and high income. The upper middle-income and high-income countries had the highest incidence of preeclampsia of 2.99% and 2.63%, compared to the lower middle and low-income countries with incidences of 2.27% and 1.14%. The low-income, lower middle-income and upper middle-income countries had incidences of eclampsia of 0.26%, 0.35%, and 0.23%, respectively. The high-income countries had the lowest eclampsia incidence, namely 0.05%.

Results on the global incidence of preeclampsia and eclampsia are summarized in the Table below:

Reference	Study design	Main findings
Abalos et al. (2013)	Systematic review article using a statistical model calculating rates of preeclampsia globally based on reports from 40 countries	Global incidence of preeclampsia: 4.6% (Eastern Meditarranean (1.0%), America (3.0%), in Western Pacific (3.9%), in South-East Asia (5.1%), in Europe (5.3%), in Africa (5.6%)) Global incidence of eclampsia: 1.4% (Europe and Western Pacific (0.1%), America (0.7%), Southeast Asia (1.1%), Eastern Mediterranean (1.9%), Africa (2.9%))
Souza et al. (2013)	Multi-country survey from 357 secondary and tertiary health facilities in 29 countries	Global incidence of preeclampsia: 2.2% Global incidence of eclampsia: 0.3%
Abalos et al. (2014)	Secondary analysis to Souza et al., grouping countries based on income	Incidence of preeclampsia and (eclampsia) for: Low-income countries: 1.14%, (0.26%) Lower-middle income countries: 2.27%, (0.35%) Upper-middle income countries: 2.99%, (0.23%) High-income countries: 2.63%, (0.05%)

In Scandinavia, all deliveries are registered in a national birth registry. A descriptive cohort study conducted across all maternity units in Norway, Sweden and Denmark in a two-year period from 1998 to 2000, found a total incidence of eclampsia of 0.05%. There were no maternal deaths, but several cases of severe maternal morbidity. 93% of the women with eclampsia were treated in an intensive care unit, 16% were complicated by HELLP syndrome

and three women suffered persistent sequelae from cerebrovascular hemorrhage or hypoxia. In the study period, magnesium sulphate was not routinely used in severely affected preeclampsia patients to prevent eclampsia, and the author states that about half of the cases could have been prevented by this, referring to the Magpie trial (20, 21). The median number of antenatal visits per woman in the study group was ten.

Several studies have explored the trends of preeclampsia rates in different regions, all of them in the global north. A large cohort study from the US including 120 million births described the changes in preeclampsia rates between 1980 and 2010. Preeclampsia rates increased in the study period from 3.4% in 1980 to 3.8% in 2010, which was mostly driven by severe preeclampsia rates (22). A similar study was performed in Quebec, Canada between 1989 and 2010. The total incidence of preeclampsia in the study period was 3.6%. The incidence increased from 2.6% to 5.1% the study period, but this increase was not associated with an increase in maternal morbidity and mortality (23).

In a population-based study in Australia, Canada, Denmark, Norway, Sweden, Scotland and the USA (Massachusetts) in the time period 1997-2007, preeclampsia and pregnancy hypertension rates were declining in all regions except from Massachusetts, where preeclampsia rates increased by 2.4% (24). This is in line with the results from a large register study from Norway by Klungsøyr et al., comparing secular trends in the epidemiology of preeclampsia in the period 1967-2008, covering more than two million women giving birth. The authors found an overall prevalence of preeclampsia of 3%, which increased from around 2% in 1967-1974 to 3.5% in 1985 where it remained stable until 1998. In 1999 a new birth notification form to the registry was introduced, and that year the preeclampsia rate increased to 4.4%, whereafter it decreased to 3.6% in 2008 (25).

Sole et al. published a population-based cohort study from Norway in 2022, showing that the prevalence of preeclampsia in Norway decreased from 4.3% in the period 1999-2002 to 2.7% in the period 2015-2018. This decrease happened despite the proportion of pregnant women with risk factors for preeclampsia like advanced maternal age, nulliparity and assisted reproduction increased in the same period. The rates of gestational hypertension did not change significantly, but had an increasing trend in the first decade, followed by a decreasing trend. The authors also found an increase in aspirin prescription to women under 40 years of age in the same period, and a doubling of labor induction from 10.9% to 22.2% (26), suggesting that these antenatal and obstetric measures may have contributed to the lower rates

of preeclampsia despite the increase in maternal risk factors. The authors also referred to increasing focus on healthy diet, more physical activity and a general lowering blood pressure level, as contributing factors to the observed trend in preeclampsia reduction.

The Global Burden of Disease (GBD) study is a global observational epidemiological study led by the University of Washington, the largest of its kind, covering 204 countries. The study has collected data on hypertensive disorders of pregnancy (HDP) but does not differentiate between gestational hypertension, preeclampsia, and eclampsia. Wang et al. used the GBD study to calculate age standardized incidence rates (ASIR) of HDP between 1990 and 2019. In this period the ASIR of HDP decreased globally from 579 to 463 per 100.000 population. The authors found higher 2019 incidence and death rates from HDP in regions with low and middle socio-demographic index (SDI) than in countries with high socio-demographic index. Chad, Niger, and Somalia had the highest incidence rates, and a respective SDI of 0.24, 0.16 and 0.08. Korea, Canada and Luxembourg had the lowest estimates and a respective SDI of 0.88, 0.87, and 0.90 (27). Jiang et al. also used the GBD study to describe the global burden of HDP. The authors found that Africa, Southeast Asia, and the Eastern Mediterranean had the highest incidence of HDP, whereas the Western Pacific region, Europe and North America and the Caribbean had the lowest incidence. The authors also stratified the disease burden measured as incidence, disability-adjusted life years and deaths by SDI, and found, in consistency with the findings of Wang et. Al., that the countries with lower SDI generally had a higher disease burden of HDP (28).

Global differences in mortality and morbidity linked to preeclampsia (and/or hypertensive diseases of pregnancy)

Hypertensive disorders of pregnancy is the second most important cause of maternal deaths worldwide after hemorrhage, accounting for 14% of all maternal deaths (29), and it is the leading cause of maternal deaths in Latin America and the Caribbean (30). Other important causes of maternal mortality are sepsis, complications of abortions and thromboembolism (31). Most HDP related deaths were in 1992 registered as caused by eclampsia (32).

Most (95%) of maternal deaths occur in low- and middle-income countries (33). However, the proportion of deaths due to hypertensive pregnancy complications do not differ much between low- and middle-income countries, and high-income countries. In a WHO

analysis, hypertensive disorders of pregnancy was found to cause 16.1% of maternal death in high-income countries, 9.1% in Africa and Asia and 25.7% in Latin America and the Caribbean (30).

There is a significant difference in the risk of a severe outcome in women with HDP depending on where they live. As an example, the mortality rate from eclampsia is 3-5% in low-income countries (34), compared to high-income countries where it is close to zero (35, 36). Where maternal mortality is high, eclampsia is a more common cause of death. As maternal mortality rate falls in a country, a higher proportion of deaths can be attributed to preeclampsia than eclampsia (37).

Assessment of preeclampsia in low- and middle-income countries

The presence of skilled health personnel at birth is an important target in reducing maternal mortality. A milestone in reaching the sustainable development goals is that 90% of all births should be attended by skilled personnel by 2025 (38). In Europe almost all (99%) births are attended by trained personnel such as a midwife or doctor, compared to 70% in Sub-Saharan Africa and 89% in South Asia (39). Other targets defined by the WHO in support of the SDG milestones are that 90% of women should have four or more antenatal care contacts within 2025, and that 60% of the population should be able to access a health facility with Emergency Obstetric Care within two hours.

An important part of routine antenatal care is serial measurement of blood pressure and proteinuria to screen for preeclampsia. One study carried out in 27 countries in Sub-Saharan Africa, the region with the highest MMR, found that antenatal care utilization was greater in urban than rural areas (34.7% against 22.4% receiving antenatal care). No education, having a husband with no education and unemployment were all factors associated with lower rates of the use of antenatal care (40). In contrast to this, more than 99% of Norwegian women receive antenatal care (41).

There are two well founded interventions to reduce the risk of preeclampsia in high-risk patients: Low dose aspirin, and calcium supplements in populations with low dietary calcium intake (37, 42). Low dietary intake of calcium is more common in the low- and middle-income countries, whereas Northern European countries have the highest calcium

intake. A study from Ecuador's Andean area showed that women in this area only consumed 60% of the WHO's recommended calcium intake (43).

For eclampsia, magnesium sulfate is well documented in preventing and controlling eclamptic seizures and is preferred over other anti-convulsant drugs such as benzodiazepines (21, 34). A WHO multi-country study showed that the 357 hospitals in 29 countries studied had a high coverage of essential interventions including magnesium sulphate, and only 18% of the study population had a "missed opportunity" in the form of not receiving the essential intervention. However, this did not seem to influence maternal mortality (18). In a review study from 2022, the authors found that magnesium sulphate is often unavailable in some facilities, particularly in rural areas of low- and middle-income countries. There were also more frequent stock-outs, contributing to the limitation of access to the drug (44). In contrast, access to magnesium sulphate is not an issue of concern in high-income countries (45).

In order to treat women with severe preeclampsia with magnesium sulphate, it is crucial to intervene early, and women with severe preeclampsia features need to be admitted to a hospital for observation and treatment. This poses a significant challenge in low- and middle-income countries, as most women in these settings are often not diagnosed early, and eclampsia often develops at home or during transport to healthcare facilities (46). Even if the woman receives healthcare in a lower-level medical facility, barriers to treatment include lack of possibility to refer to hospital or simply no place to refer to, problems with transportation to hospital and costs (44). Studies in Bangladesh, Nigeria, Pakistan, Ethiopia and Kenya also found that a lack of community awareness around warning signs for preeclampsia and eclampsia were important factors and that common symptoms of preeclampsia such as severe headache and blurred vision was often misinterpreted as malaria. Rapidly developing large edema in the form of swollen ankles was misdiagnosed as a normal phenomenon of pregnancy (47).

Discussion

There is a significant degree of variation in the reporting of preeclampsia and eclampsia incidence rates from different countries and regions, which poses a challenge when examining the global rates of these conditions. In the referred study by Abalos et al. (17), only seven countries had data on national coverage of the occurrence of preeclampsia and eclampsia, and a minority of countries had any data reporting on preeclampsia and eclampsia. The Global Burden of Disease (GBD) study examined the incidence and burden of various diseases globally and included data from 204 countries, including hypertensive disorders in pregnancy (HDP) (27, 28). However, it does not distinguish between different hypertensive disorders and does not specify how many cases are attributed to gestational hypertension, preeclampsia, or eclampsia. Different routines for reporting preeclampsia rates in different countries and varying cut-offs and definitions of preeclampsia are also potential limitations here.

The various studies included in this thesis present somewhat conflicting results regarding the incidence of preeclampsia. The papers by Wang et al. and Jiang et al. were both based on the Global Burden of Disease study (27, 28), and both papers found a reverse linear relationship between socio-demographic index (SDI) of a region and the incidence of HDP in that region. I assume that the majority of HDP cases are preeclampsia or gestational hypertension. This would indicate that preeclampsia may occur more frequently in low-income countries, which aligns with the understanding that low socioeconomic status is a significant risk factor for developing preeclampsia.

Two studies included in this thesis provided global incidence figures for preeclampsia (Table 1). One was a systematic review where the authors used a statistical model to calculate incidence, based on reports from 40 countries by Abalos et al. (17). The other was a WHO multi country survey from 29 countries by Souza et al. (18). These two studies found an overall global incidence of preeclampsia of 4.6% and 2.2% respectively, illustrating the uncertainty of the true rates. Abalos et al. found the highest calculated incidence of preeclampsia in the African region and Europe, the regions with the lowest and highest SDI. This could indicate that the incidence of preeclampsia in a region is not dependent on the economic and developmental status of the given region. However, I also included a secondary analysis to the WHO study by Souza et al. (19), which found that upper-middle and high-income countries had the highest incidence of preeclampsia, while low-income countries had

a much lower incidence at only 1.14%. This stands in contradiction to what was found by Wang et al. and Jiang et al. from the GBD study, which indicated a higher incidence in low-income countries, as mentioned above.

However, the studies mentioned in the previous paragraph have weaknesses to consider: Souza et al. (18) collected data only from secondary and tertiary hospitals in 29 countries, and the numbers may not be representative of community settings or smaller healthcare institutions. This could explain the seemingly much lower incidence of preeclampsia in low-income countries, as many women in these countries may be treated outside these large healthcare institutions. Another indicator that this number may be an underestimate is the fact that the authors found an incidence of eclampsia of 0.26%, which would mean a much higher proportion of women with preeclampsia would develop eclampsia than what is normally expected. The low incidence in low-income countries may contribute to the totally reported lower global incidence of 2.2% and could partly explain the gap between the global incidences found in these two studies. The calculated incidences by Abalos et al. (17) are based on existing reports of preeclampsia, which were only available for a limited number of countries. Also, their calculated preeclampsia rates were slightly higher than the crude rates, this again could indicate that their global estimate of 4.6% is too high. The authors acknowledge the problem of the lack of primary data, and suggest that more data and a global survey are needed for a reliable picture of the actual incidence rates.

As mentioned earlier, preeclampsia is a heterogeneous condition with multiple mechanisms influencing its development, and there are many risk factors. Different incidence rates in various regions may be attributed to variations in the prevalence of these risk factors. It has been proposed that the etiological processes leading to preeclampsia are differently distributed in high- and low-income countries, with immunological and genetic risk factors being more important in high-income countries, while nutritional, metabolic, and infectious factors play a more significant role in low-income countries (43).

When it comes to eclampsia, the studies were more consistent and showed a much larger difference in incidence across different regions. A large cohort study from Scandinavia found an incidence of eclampsia at 0.05% (20), which is in line with the figures from WHO, which also found an incidence in high-income countries at 0.05% (19), and similar to the calculated incidence from Abalos et al. in Europe at 0.1% (17). In the same article by Abalos et al., the incidence of eclampsia in the African region was 2.9%. Thus, in their study, the

European and African regions had a similar incidence of preeclampsia, but the African region had a significant higher incidence of eclampsia. The WHO study also found a much higher incidence of eclampsia in low- and middle-income countries (19). There could be many reasons for this, including better screening, prevention, and treatment of preeclampsia in high-income countries, preventing further clinical development into eclampsia.

All studies on trends in preeclampsia rates were based on data from high-income countries. These studies show a similar pattern of increasing incidences from the earliest study periods in the 1960's, 70's and 80's, until the turn of the millennium, whereafter the incidence has been declining in Norway, Denmark, Sweden, Scotland, Canada, and Australia (22-25). The only population studied where the incidence seemed to increase was in Massachusetts, USA (24). This is interesting, because factors positively associated with preeclampsia are increasing: Women giving birth are older, more obese and have more comorbidities. Assisted reproduction rates and multiple births are also increasing, while the proportion of pregnant women who smoke is going down. On the other hand, we see increased rates of planned delivery and fewer pregnancies reaching beyond 40 weeks. In addition, greater use of intervention to reduce risk or prevent progression from gestational hypertension to preeclampsia has been proposed as an explanation (24). Most cases of preeclampsia develop at the end of pregnancy, and increased planned delivery rates could therefore explain why fewer pregnancies are affected.

Hypertensive disorders of pregnancy was the second leading cause of maternal mortality, causing between 9.1% and 25.7% of maternal deaths across different regions, and 14% of total deaths globally (29, 30). The majority of these deaths were in low-income countries, and women in these countries had a much higher risk of death from eclampsia than women in high-income countries. This shows that most maternal deaths that are due to preeclampsia are also preventable with correct measures for detection and treatment, as many high-income countries have largely succeeded in eliminating preeclampsia related maternal deaths.

It has been proposed that adequate antenatal care is the only effective way to detect and prevent preeclampsia (43), and it is one of the targets from WHO to reduce maternal mortality, together with presence of skilled health personnel at birth and access to health facilities with emergency obstetric care. However, antenatal care use differed considerably between high- and low-income countries, and within low-income countries between urban

and rural areas. Possible reasons are socioeconomic factors like educational status and employment, access to health care facilities offering high quality antenatal care services and the presence of qualified health care personnel. Inadequate training of healthcare personnel and poor equipment could also play a role.

Interventions for risk reduction and treatment of preeclampsia like magnesium sulphate were often unavailable in rural areas in low- and middle-income countries (44). In hospital settings it was most often available, but for some reason this did not seem to influence mortality (18). This could point to problems other than just the availability of the drug being a barrier to efficient treatment, for example lack of knowledge and skills among providers, or delayed referral and start of treatment.

To be able to implement measures like the use of low-dose aspirin regimens to women with increased risk of preeclampsia, early identification of increased risk is vital. Calcium supplements could be recommended routinely in line with iron and folic acid to all pregnant women in areas with low dietary intake. A Randomized Clinical trial published in January 2024 suggests that 500 mg daily dose of calcium is equivalent in preventing preeclampsia to the traditionally recommended high dose of 1500-2000 mg calcium by the WHO (48). Treatment with magnesium sulphate also requires that women with severe preeclampsia to be identified and referred to correct health institution. All of this requires antenatal care and follow-up, and this should be adapted to the conditions women are living under. Even though maternal health has been a priority in the WHO for decades, many countries are lagging behind on implementing policies to actually address and solve the problem.

During the COVID-19 pandemic, there was a reduced use of antenatal care in both high- and low-income countries. In the period from March to December 2020, the utilization of antenatal care decreased by 32%, and the rate of institutional births decreased by 16%, coinciding with an increase in maternal mortality (14). This increase is likely attributed not only to mortality from COVID-19 disease, but also to the effects of the pandemic on healthcare services for pregnant women. This effect was more pronounced in low-income countries, highlighting the importance of high-quality antenatal care to prevent maternal mortality. Interestingly, a negative trend in maternal mortality was seen in groups with restricted socioeconomic status, also after removing covid-related deaths, in high-income countries like the US (49). This finding suggests that the pandemic exacerbated existing

socioeconomic differences in health, and challenges whether equity of care is applied even in regions with enough resources.

A promising intervention that has been shown to increase the use of antenatal care is mobile health (mHealth) (50). mHealth uses mobile devices to send out reminders, educate women and help them monitor their health during pregnancy. This could represent an accessible and cheap solution to strengthening antenatal care in regions with limited resources, including in low- and middle-income countries, giving pregnant women knowledge and resources to make them able to take care of their own health, in that way empowering women to seek help when needed.

Conclusion

Although some of the studies in this thesis indicated a trend of higher preeclampsia rates in low-income countries, the variability in findings does not support such a correlation. It must be concluded that the burden of preeclampsia is high in most regions, and more targeted data collection and research on the incidence of preeclampsia and eclampsia is needed, especially in low-income countries. Women in low- and middle-income countries had substantially greater risk of developing eclampsia and also of a fatal outcome. There were large disparities between high- and low-income countries in preventive measures and programs for detection of preeclampsia, such as antenatal care services and use, and treatment, like magnesium sulphate availability and use. Policies need to be implemented to improve this situation.

The large difference in MMR is a good example of inequality and the great injustice a large part of the world is faced with, lacking access to fundamental human rights such as reproductive and maternal health. Improving maternal health globally should continue to be a priority, especially in regions where limited progress on this front have been achieved to date. In high-income countries there is a need to critically review their options for equity in antenatal care. To conclude, preeclampsia is an important cause of preventable maternal death, especially in low- and middle-income countries, and needs to continue to be a priority in global health.

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