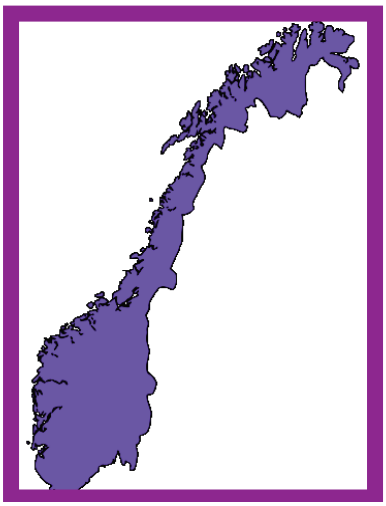
Exploring Hypertensive Disorders of Pregnancy
Risk factors, Prevalence and Time Trends

Kristina Baker Sole, MD, MPH



PhD Thesis 2022

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UNIVERSITY OF OSLO

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-348-0068-9

Cover: Hanne Baadsgaard Utigard.
Print production: Graphics Center, University of Oslo.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

The present PhD thesis was carried out at Oslo University Hospital and the Faculty of Medicine at the University of Oslo between 2016 and 2021. I am thankful that the University of Oslo provided direct financial support from August 2016 to October 2017 and continued to cover all indirect costs during my entire PhD studies.

And now, personal messages of thanks to those who got me through this…

Dr. Katariina Laine, principal supervisor extraordinaire and co-author of all three Papers, I am forever indebted to you. You taught me SPSS on Day 1 and shared your tiny office with me for almost a year. Time and again you helped me see the forest for the trees. When I made a very unpopular decision, you stood by me and were unfailingly understanding. You believed in me when I did not. Miraculously, you were always available, even at odd hours of the day and night. When you put the fear of God in me – and you did that only once – it helped me see the light at the end of tunnel. Thank you for respecting me as a colleague and treating me like a friend.

Dr. Annetine Staff, co-supervisor and co-author of all three Papers, I am truly grateful for your support and feedback. I credit you for starting me on this journey: At our first meeting you handed me a turnkey research project and put me in contact with Dr. Laine. Words cannot truly express my gratitude for your generosity. During my studies, you went through every manuscript draft I wrote with a fine-toothed comb and challenged me over and over again, accepting nothing less than excellent. Thank you for helping me understand the connection between pathophysiology and epidemiology.

Dr. Sari Räisänen, co-author of Paper III, thank you for your wonderful ideas, thoughtful questions, constructive criticism and manuscript editing.

Dr. Jan Petter Odden, former *fylkeslege*, thank you for finding a creative solution that allowed me to continue my PhD studies. You saved the day when all hope was lost.

Dr. Marte Myhre Reigstad, thank you for volunteering in the midst of a global pandemic to be my opponent for the midpoint evaluation. You were kind and encouraging, and you challenged me to start thinking about The Big Picture.

Benjamin and Sebastian, thank you for putting up with a chronically overworked, stressed out and sleep-deprived mother who then brought a PhD into our lives. I'm truly sorry you had to eat First Price spaghetti and *kneippbrød* for an entire year.

Arne, *min kjære*, there is no doubt that this PhD has been the hardest on you. You allowed me to prioritize the PhD above all else, gave me ample time and space to work, listened to my endless complaining and did your best to manage my stress and anxiety. You made countless dinners for me. You spent many evenings, weekends and warm summer days alone. You brought me potato chips and wine while I was writing. You rubbed the burning knot in my back. Thank you for being my rock.

An eminent Oxford don once told me to "pinch my nose and swallow it". This was the best PhD advice ever. Rest in peace, John. You are sorely missed.

I would not be where I am today without the love and support of my late husband. Fair sails and following winds, Jim, until we meet again.

LIST OF PAPERS

I. Sole KB, Staff AC, Laine K. The association of maternal country of birth and education with hypertensive disorders of pregnancy: A population-based study of 960 516 deliveries in Norway. Acta Obstet Gynecol Scand. 2018 Oct;97(10):1237-1247. doi: 10.1111/aogs.13393. Epub 2018 Aug 2. PMID: 29873810.

II. Sole KB, Staff AC, Laine K. Maternal diseases and risk of hypertensive disorders of pregnancy across gestational age groups. Pregnancy Hypertens. 2021 May 14;25:25-33. doi: 10.1016/j.preghy.2021.05.004. Epub ahead of print. PMID: 34022624.

III. Sole KB, Staff AC, Räisänen S, Laine K. Substantial decrease in preeclampsia prevalence and risk over two decades: A population-based study of 1 153 227 deliveries in Norway. *under review.*

ABBREVIATIONS

aCL	Anti-cardiolipin antibodies
ACOG	American College of Obstetricians and Gynecologists
aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
aRR	Adjusted relative risk
ART	Assisted reproductive technology
anti-β_2GPI	Anti-β_2 glycoprotein I antibodies
BMI	Body mass index
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
DIC	Disseminated intravascular coagulation
EEA	European Economic Association
FGR	Fetal growth restriction
FIGO	International Federation of Gynecology and Obstetrics
FMF	Fetal Medicine Foundation
HELLP	Hemolysis, elevated liver enzymes and low platelets
ISSHP	International Society for the Study of Hypertension in Pregnancy
IUFD	Intrauterine fetal death
LA	Lupus anticoagulant
LMP	Last menstrual period
MAP	Mean arterial pressure
MBRN	Medical Birth Register of Norway
MoBa	Norwegian Mother and Child Cohort
NICE	National Institute of Health and Care Excellence
NICU	Neonatal intensive care unit
NGF	Norsk gynekologisk forening (Norwegian Society of Gynecology and Obstetrics)
NorPD	Norwegian Prescription Database
NS	Non-significant
OR	Odds ratio
PAPP-A	Pregnancy-associated plasma protein-A
PCr	Urine protein/creatinine ratio

PlGF	Placental growth factor
PRES	Posterior reversible encephalopathy syndrome
RR	Relative risk
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SLE	Systemic lupus erythematosus
sENG	Soluble endoglin
sFlt-1	Soluble fms-like tyrosine kinase-1
SGA	Small for gestational age
SSB	Statistisk sentralbyrå (Statistics Norway)
USPSTF	United States Preventative Services Task Force
UtA-PI	Uterine artery pulsatility index
WHO	World Health Organization

ENGLISH SUMMARY

Hypertensive disorders of pregnancy include gestational hypertension, chronic hypertension, preeclampsia and preeclampsia superimposed on chronic hypertension. Gestational hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg arising on or after 20+0 weeks of gestation without proteinuria or maternal organ dysfunction. Preeclampsia is currently defined as sustained de novo hypertension after 20+0 weeks of gestation accompanied by proteinuria and/or other signs of maternal organ dysfunction and/or uteroplacental dysfunction. For over one hundred years, preeclampsia was thought to be caused by toxins from fetal waste products crossing the placenta into the maternal circulation. It is now understood to be the result of an abnormal interaction between placental and maternal vasculature.

The revised two-stage model of preeclampsia pathogenesis proposes that both early and late-onset preeclampsia results from placental malperfusion and syncytiotrophoblast stress but that the causes and timing of placental malperfusion differ. This model fits with the clinical heterogeneity of preeclampsia as well as gestational hypertension. The threshold liability model proposes that all women are at risk of preeclampsia, but that due to underlying biologic variability some women are more susceptible due to additional exposures. The competing risk model assumes that all women will develop preeclampsia if their pregnancies had an infinite gestational length. The clinical appearance of preeclampsia signs and symptoms is dependent on whether a woman is delivered before or after her personalized threshold for the disease.

Hypertensive disorders of pregnancy affect 10% of pregnancies worldwide and are associated with increased maternal, fetal and neonatal morbidity and mortality, and increased risk of metabolic and cardiovascular diseases later in life for both mother and child. Preeclampsia develops in 3-5% of pregnancies, mostly at term or late preterm gestation, but early-onset preeclampsia often presents with severe organ affection and is associated with higher adverse maternal and neonatal outcomes. Approximately 25% of women with chronic hypertension will develop superimposed preeclampsia.

There are many reported risk factors for preeclampsia. Socioeconomic risk factors include immigrant status, minority race or ethnicity, low education and low income. Maternal characteristics such as advanced maternal age, nulliparity, antiphospholipid syndrome,

chronic hypertension, chronic renal disease, pre-gestational diabetes, and high pre-pregnancy body mass index (BMI) are associated with an increased risk of preeclampsia. Obstetric risk factors for preeclampsia include multifetal pregnancy, assisted reproductive technology, prior stillbirth, prior placental abruption and prior preeclampsia. First-trimester smoking is protective against preeclampsia, but increases the risk of other adverse pregnancy outcomes such as fetal growth restriction.

Recent screening strategies using a combination of maternal characteristics, mean arterial blood pressure, mean uterine artery pulsatility index and biomarkers can identify high-risk women that may benefit from aspirin, which reduces the risk of preterm preeclampsia by approximately 60%. Effective prophylaxis for late-onset preeclampsia has yet to be found. Once preeclampsia develops, there is no treatment other than the use of magnesium sulfate to prevent maternal seizures (eclampsia), antihypertensive medication to prevent adverse maternal cardiovascular outcomes such as cerebral hemorrhage and delivery to stop the disease.

This thesis was a population-based retrospective (historical) cohort study using data from the Maternal Birth Register of Norway, Statistics Norway and the Norwegian Prescription Database. The main aims of the thesis were to assess the prevalence of and risk factors for hypertensive disorders of pregnancy in Norway over two decades, and to test if the findings fit with established and more recent models of preeclampsia pathogenesis. More specifically, the thesis aimed to assess overall prevalence of preeclampsia and chronic hypertension in both nulliparous and parous women, and the prevalence of early, intermediate and late-onset preeclampsia in nulliparous women. Socioeconomic (maternal country of birth and education) and biologic (diabetes, chronic hypertension and BMI) exposures were investigated to estimate their association with hypertensive disorders of pregnancy. Lastly, secular trends of risk factor prevalence and preeclampsia prevalence and risk were observed. Univariate and multivariable regression was used to analyze the associations between risk factors and hypertensive disorders of pregnancy, and the data were limited, stratified and adjusted for possible confounders in order to minimize the risk of bias. The epidemiologic findings were interpreted using the revised two-stage model of preeclampsia, the threshold liability model and the competing risk model.

Paper I included 907 048 deliveries between 23+0 and 43+6 weeks of gestation from 1999 to 2014 after excluding multifetal gestations and pregnancies with major congenital

anomalies. In the study group, 382 618 deliveries were to nulliparous women and 524 430 deliveries were to parous women. The overall prevalence of preeclampsia and gestational hypertension were 3.4% and 1.8%, respectively. Hypertensive disorders of pregnancy were almost two-fold higher among nulliparous than parous women (7.2% vs 3.7%). The prevalence of preeclampsia was 5.0% in nulliparous women and 2.3% in parous women. Gestational hypertension was present in 2.2% of nulliparous deliveries and 1.4% of parous deliveries. Compared to women with secondary education (high school or equivalent) women with low education had no increased risk of preeclampsia or gestational hypertension, regardless of parity. Women with higher education had lower risks of hypertensive diseases of pregnancy. Foreign-born women had the same or lower risks of preeclampsia or gestational hypertension compared to women born in Norway, regardless of parity. These findings remained mostly unchanged after adjustment for maternal age, diabetes, consanguinity and 1st-trimester smoking.

For Paper II, the study population included all singleton deliveries by nulliparous women between 1999 and 2014 at gestational age 23+0 to 43+6 weeks (n = 382 618) after excluding pregnancies with major congenital anomalies. Three quarters (76%) of the preeclampsia deliveries were at 37+0 to 43+6 weeks of gestation (late-onset), whereas 14% were at 34+0 to 36+6 weeks (intermediate-onset) and 10% were at 23+0 to 33+6 weeks (early-onset). The proportion of early-onset preeclampsia was 28.0%, compared to 14.1% in the intermediate gestational age group and 4.1% at term. Superimposed preeclampsia developed in 23% of women with chronic hypertension. The prevalence of gestational hypertension was relatively stable across the three gestational age groups (2.1-2.7%), and the majority (93.0%) of women with gestational hypertension delivered at term. There was a positive association between pre-gestational and gestational diabetes, chronic hypertension, pre-pregnancy BMI and preeclampsia in all three gestational age groups. The risk for preeclampsia in all gestational age groups remained high after adjusting for possible confounders (model 1), including BMI (model 2). Gestational diabetes and BMI were independent risk factors for gestational hypertension. However, BMI confounded the risk of gestational hypertension in women with pre-gestational diabetes.

Paper III included all women with singleton or twin deliveries (n = 1 153 227) between 22+0 and 44+6 weeks of gestation from the start of 1999 to the end of 2018. Preeclampsia prevalence decreased by 37% (from 4.3% to 2.3%) and gestational hypertension increased

by 6.7% (from 1.5% to 1.6%) between the first and last four-year time periods. This trend was observed concurrent with an increasing proportion of high-risk parturients with advanced maternal age, type 2 diabetes, gestational diabetes and assisted reproduction. First-trimester smoking decreased. Nulliparity, twin gestations, type 1 diabetes and chronic hypertension remained fairly stable, whereas the proportion of foreign-born women nearly doubled over the study period. Observed population changes in risk factors could not fully explain the 44% decreased risk of preeclampsia over the study period. During the study period, there was an increase in low-dose aspirin prescriptions among all women < 40 years old (population-level data) as well as an increase in labor inductions (individual-level data).

This thesis explored socioeconomic and biologic risk factors for hypertensive disorders of pregnancy according to parity, gestational age group at delivery, and time period. Unlike other studies showing a higher risk of hypertensive disorders among immigrants and women with low socioeconomic status, this thesis found no social inequalities for preeclampsia in foreign-born women or women with low education. Possible reasons for this are the healthy immigrant effect and readily accessible free prenatal care. Chronic maternal diseases of diabetes, chronic hypertension and obesity increased the risk of hypertensive disorders of pregnancy at all gestational ages of viability in nulliparous women. The findings support the concept of multifactorial pathways to the heterogeneous group of hypertensive disorders of pregnancy. This is particularly relevant as nulliparous women have an elevated risk of preeclampsia as compared to parous women, likely due to immunological and anatomical factors related to uteroplacental artery remodeling and other placentation processes. Lastly, the decreased prevalence and risk of preeclampsia over the past 20 years, despite an increasing prevalence of high-risk women, may be due to changes in obstetric care with increased use of low-dose aspirin and labor induction, improved baseline health in the general population, or potential alterations in genetic polymorphisms or epigenetic variations yet to be determined. The findings in this thesis support the revised two-stage model of preeclampsia, as well as the threshold liability model and competing risk model.

NORSK SAMMENDRAG (NORWEGIAN SUMMARY)

Hypertensive svangerskapskomplikasjoner utvikles hos cirka 10% av gravide og inkluderer kronisk hypertensjon, svangerskapshypertensjon og preeklampsi. Svangerskapshypertensjon defineres som nyoppstått hypertensjon uten proteinuri eller maternell organaffeksjon etter 20. svangerskapsuke. Definisjonen av preeklampsi har nylig blitt endret til nyoppstått og vedvarende hypertensjon etter 20. svangerskapsuke kombinert med ett eller flere nyoppståtte tegn på maternell organaffeksjon (for eksempel proteinuri) og/eller veksthemming hos fosteret. Opptil 25% gravide med svangerskapshypertensjon utvikler preeklampsi.

Preeklampsi skyldes en dysfunksjonell interaksjon mellom maternell sirkulasjon og placentasirkulasjon. Ufullstendig fysiologisk remodellerte uteroplacentære spiralarterier i tidlig svangerskap fører til placentadysfunksjon. Senere i svangerskapet kan placentadysfunksjon oppstå på grunn av manglende plass i livmoren, ut fra en nylig revidert to-trinns modell for preeklampsi. Begge tilstander fører til fysiologisk stress i syncytiotrofoblast og økt produksjon av proinflammatoriske stoffer som kommer over i den gravides sirkulasjon. Dette skaper økt systemisk inflammasjon og endotelial dysfunksjon hos den gravide og det kliniske syndromet som inkluderer maternell hypertension og organaffeksjon. Gravide med høy risiko for preeklampsi bør tilbys lavdose acetylsalisylsyre for å forebygge tidlig preeklampsi-utvikling. Preeklampsi kan bare kureres med forløsning av barnet. Magnesiumsulfat brukes for å stoppe og forebygge kramper (eklampsi), mens antihypertensiv terapi er indisert ved høye blodtrykk for å redusere risiko for maternell hjerneblødning,

Denne avhandlingen er en befolkningsbasert observasjonsstudie med bruk av data fra Medisinsk fødselsregister (MFR), Statistisk sentralbyrå (SSB) og Reseptregisteret. Formålet var å vurdere risikofaktorer for preeklampsi over 20 år og studere funnene i sammenheng med biologiske modeller for preeklampsi. Sosioøkonomiske (fødselsland, utdanning) og biologiske (diabetes, kronisk hypertensjon, kroppsmasseindeks) risikofaktorer for preeklampsi og svangerskapshypertensjon ble undersøkt i henhold til paritet, gestasjonsalder og tidsperiode. Selv om andre studier har funnet høyere risiko for hypertensive svangerskapskomplikasjoner blant innvandrere og kvinner med lav sosioøkonomisk status fant denne avhandlingen ingen slike sosiale ulikheter for preeklampsi hos utenlandsfødte kvinner eller kvinner med lav utdanning. Mulige årsaker til dette er at innvandrere har bedre

helse enn kvinner født i Norge og at det er lett tilgang til gratis svangerskapsomsorg i Norge.

Kroniske sykdommer som diabetes, kronisk hypertensjon og fedme økte risiko for hypertensive lidelser hos gravide i alle gestasjonsaldersgrupper hos førstegangsfødende. Funnene i avhandlingen er forenlig med modellen om multifaktorielle årsaker til preeklampsi og svangerskapshypertensjon. Dette er spesielt relevant hos førstegangsfødende som har en forhøyet risiko for preeklampsi sammenlignet med flergangsfødende, sannsynligvis på grunn av immunologiske og anatomiske faktorer knyttet til remodellering av spiralarterier, placentering og placentafunksjon.

Forekomsten av preeklampsi gikk ned 37% i de siste 20 årene i Norge til tross for en økende andel av høyrisikogravide. Dette kan skyldes endringer i svangerskapsomsorg med økt bruk av lavdose acetylsalicylsyre og fødselsinduksjon. Andre mulige årsaker er bedre helse generelt i befolkningen eller andre endringer i genetiske polymorfismer eller epigenetiske variasjoner som ennå ikke er avklart.

Funnene i denne avhandlingen støtter tre forskjellige biologiske modeller for preeklampsi.

1 INTRODUCTION

Hypertensive disorders of pregnancy include preeclampsia and eclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension and gestational hypertension (1). These disorders may range from asymptomatic to life-threatening with major impact on maternal, fetal or neonatal morbidity or mortality (2-4). Preeclampsia is the second leading cause of maternal mortality worldwide (5), with the burden of disease greatest in low and middle-income countries (6). Hypertensive disorders of pregnancy have potential long-term health consequences for both mother and child (7, 8).

1.1 Gestational hypertension

1.1.1 Definition

Gestational hypertension is defined as new-onset hypertension in a pregnancy of 20+0 weeks of gestation or more (1, 7, 9). The American College of Obstetricians and Gynecologists (ACOG) defines gestational hypertension as two blood pressure readings at least four hours apart with systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-109 mmHg in a previously normotensive woman; blood pressures ≥ 160/110 are defined as preeclampsia (10). The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines gestational hypertension as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on or after 20+0 weeks of gestation using a crystal liquid sphygmomanometer or other appropriate blood pressure device (1). In Norway, gestational hypertension is also defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on or after 20+0 weeks of gestation, and without proteinuria or maternal organ dysfunction (9). Approximately 25% of women with gestational hypertension to developing preeclampsia in the same pregnancy (1).

Transient gestational hypertension, according to ISSHP, is new-onset hypertension (blood pressure ≥ 140/90 mmHg) that arises at any point during the pregnancy and resolves during the pregnancy without treatment (1). Women with transient gestational hypertension have a 20 percent risk of gestational hypertension and a 20 percent risk of preeclampsia in the same pregnancy (1).

1.2 Preeclampsia

1.2.1 Definition

There has long been controversy about the exact definition of preeclampsia (11), which is not surprising in the light of its heterogeneous clinical presentation . For many years, preeclampsia was defined as new-onset hypertension with proteinuria or edema, or both, after 20+0 weeks of gestation in a previously normotensive woman (12). Edema was later removed from the diagnostic criteria, but the presence of proteinuria was still required to make the diagnosis of preeclampsia (13). In 2013 the ACOG Task Force on Hypertension in Pregnancy revised the definition of preeclampsia (14). In 2018, the ISSHP published a similar updated definition (1), which has also been adopted by the International Federation of Gynecology and Obstetrics (FIGO) (15) and slightly revised by the Norwegian Society of Gynecology and Obstetrics (NGF) (9). Preeclampsia is currently defined as de novo hypertension after 20+0 weeks of gestation accompanied by proteinuria and/or maternal organ dysfunction and/or uteroplacental dysfunction (1, 9, 14, 16). Maternal organ dysfunction may include acute renal insufficiency, impaired liver function, pulmonary edema, neurologic complications and/or hematologic disturbances (1, 14, 16, 17). Uteroplacental dysfunction may include fetal growth restriction (FGR) (18), abnormal umbilical artery Doppler wave form, or intrauterine fetal death (IUFD) (1, 16).

Preeclampsia can be superimposed on chronic hypertension. In women with chronic hypertension, defined as elevated blood pressure before 20+0 weeks of gestation, blood pressure elevation is not sufficient for the diagnosis of superimposed preeclampsia, but instead, maternal organ dysfunction must be present (1). In women with chronic hypertension and proteinuric renal disease, worsening of proteinuria is not sufficient to make the diagnosis (1). However, in women with chronic hypertension without pre-existing proteinuria, a rise in blood pressure coinciding with new-onset proteinuria is diagnostic for superimposed preeclampsia (1). Since FGR can be a complication of maternal chronic hypertension, it is not used as a diagnostic criteria for superimposed preeclampsia (1).

1.2.2 Pathophysiology

In normal pregnancy, the blastocyst, containing the inner cell mass and the trophoblast, implants in the uterus and invades the maternal endometrium/decidua (Figure 1) (19). Extravillous trophoblasts migrate through the decidua to the lower-third of the myometrium and, along with decidual immune cells, facilitate removal of smooth muscle from maternal

spiral arterial walls, thus transforming them from thick-walled vessels with narrow lumina to thin-walled fibrinoid vessels with luminal diameters 5-10 times larger than in the non-pregnant state (20, 21). This physiological remodeling of the maternal vasculature results in the formation of a healthy placenta with a fetal side, a maternal side and a high-capacitance low-resistance intervillous space where chorionic villi, lined with the syncytiotrophoblast, are bathed in maternal blood (Figure 2) (19, 20, 22). The multinucleated syncytiotrophoblast plays a central role in gas exchange, nutrient transfer, waste elimination, hormone synthesis, maternal-fetal communication and fetal programming (22).

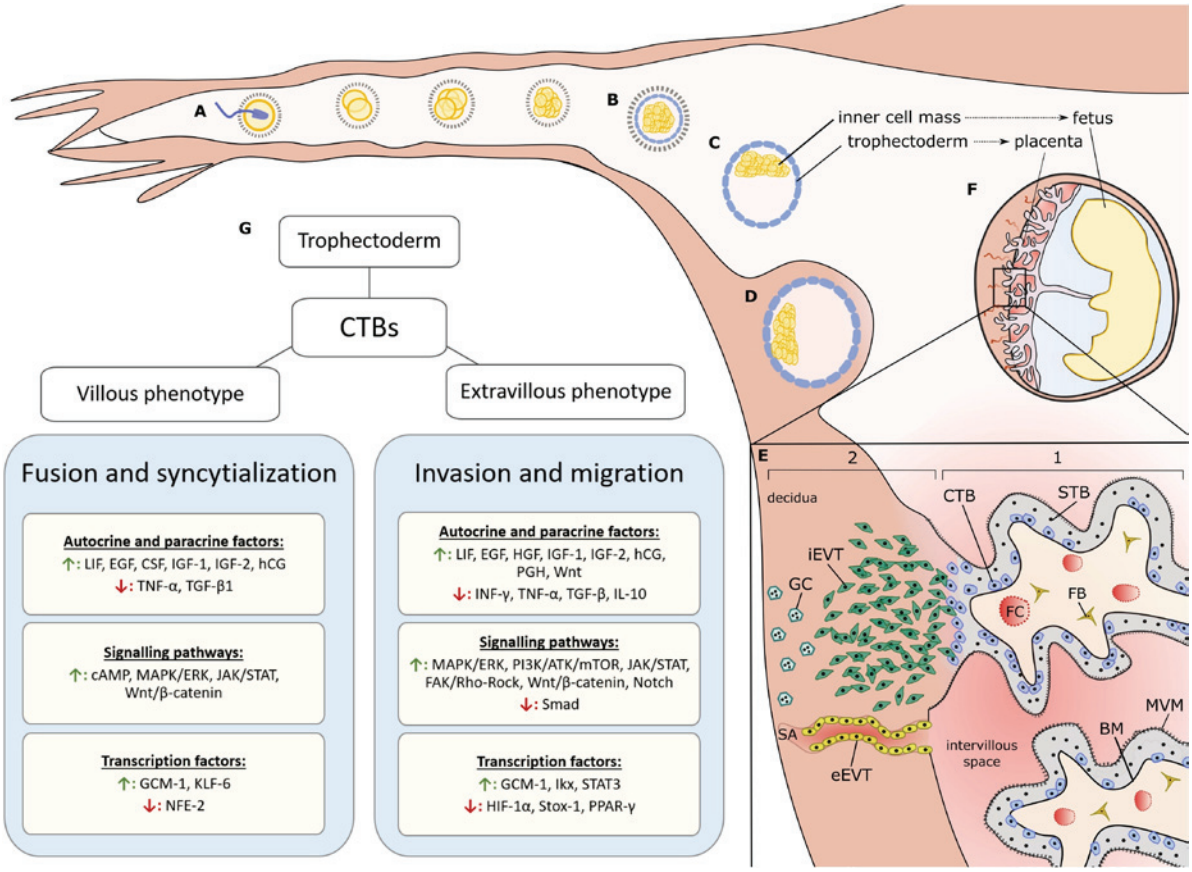


Figure 1. Schematic depiction of human embryogenesis, placenta formation and main regulatory pathways involved. A) Upon fertilization by a sperm, the egg becomes a zygote and starts dividing. B) Following multiple stages of division, the cells start differentiating into trophectoderm (blue) and inner cell mass (yellow). C) At this point the inner cell mass clusters at one end, leaving a cavity at the other, and this structure is now called a blastocyst. D) The endometrial lining starts proliferating and makes direct contact with the CTBs. E1) Proliferation and differentiation by fusion gives rise to multinucleated STB layer, bordered by maternal-facing MVM and fetal-facing BM. Structurally it covers the floating villi bathed in maternal blood and creates the crucial part of placental barrier. E2) Proliferation by detachment from the basal membrane and migration to the decidua gives rise to EVTs. One type of EVTs, the iEVTs, invade the maternal decidua and are thought to establish interactions with uterine cell types, important for attachment and immunological acceptance. Fusion of iEVTs forms GCs as the final differentiation step of the invasive pathway. The second type of EVTs is of endothelial nature, eEVTs, and in the beginning of the pregnancy form a plug in the maternal spiral arteries to prevent premature blood flow. Upon blood circulation establishment they replace the endothelial cells in the spiral arteries and convert them to low-resistance, high-capacity arteries. The reduced

contractility and pressure of blood flow ensures proper oxygen and nutrient delivery to the fetus. F) Upon successful placentation, the differentiated cells give rise to the placenta and the fetus. G) Main autocrine and paracrine factors, signalling pathways and transcription factors regulating the trophoblast fusion and invasion/migration. Reprinted from *Staud F, Karahoda R. Trophoblast: The central unit of fetal growth, protection and programming. Int J Biochem Cell Biol. 2018;105:35-40* with permission from Elsevier Science & Technology Journals.

Abbreviations: ATK - protein kinase B; BM - basal membrane; CSF - colony-stimulating factor; CTB - cytotrophoblast; eEVT - endovascular extravillous trophoblasts; EGF - epidermal growth factor; ERK - extracellular signal-regulated kinase; FAK - focal adhesion kinase; FB - fibroblast; FC - fetal capillary; GC - giant cell; GCM - glial cells missing; hCG - human chorionic gonadotropin; HGF - hepatocyte growth factor; HIF - hypoxia-inducible factor; iEVT - interstitial extravillous trophoblasts; IGF - insulin-like growth factor; Ikx - ikaros receptor; IL - interleukins; INF - interferon; JAK - janus kinase; KLF - kruppel-like factor; LIF - leukemia inhibitory factor; MAPK - mitogen-activated protein kinases; mTOR - mammalian target of rapamycin; MVM - microvillous membrane; NFE - nuclear factor erythroid-derived; PGH - placental growth hormone; PI3K - phosphoinositide 3-kinase; PPAR - peroxisome proliferator-activated receptor; Rock - Rho-associated protein kinase; SA - spiral artery; STAT - signal transducer and activator of transcription protein; STB - syncytiotrophoblast; Stox-1 - storkhead box; TGF - transforming growth factors; TNF - tumor necrosis factor.

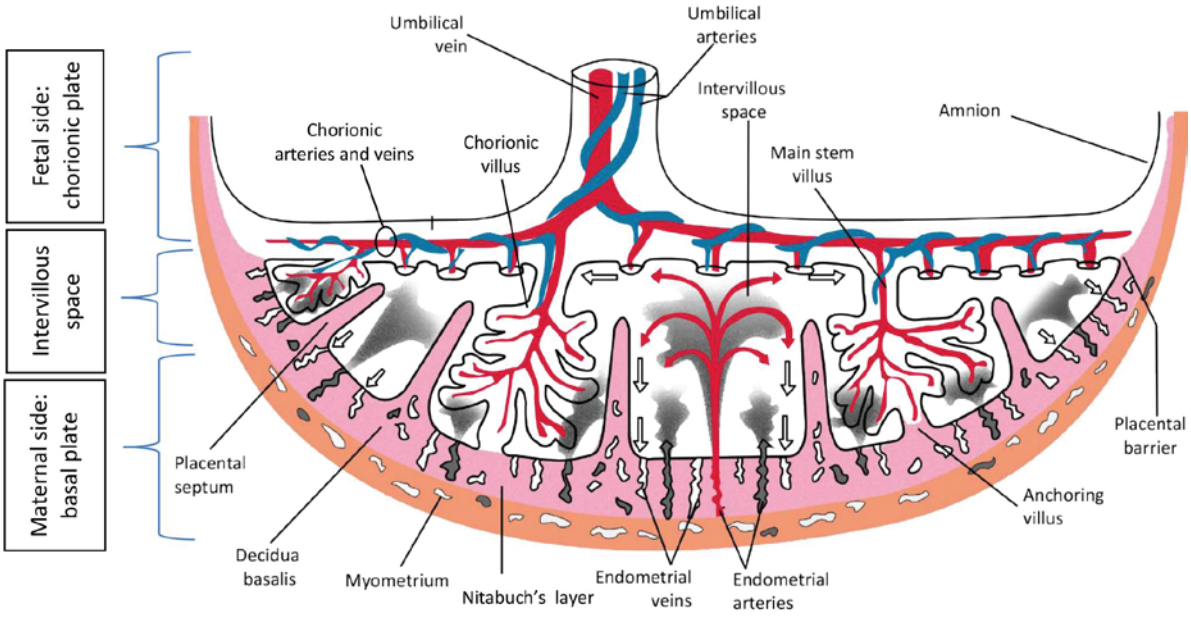


Figure 2. Schematic drawing of the fetal side and maternal side of the placenta in the second half of pregnancy. Fetal side: Chorionic plate that contains the amnion and main stem villi (chorionic villi). Maternal side: Basal plate that contains placental septa and decidua basalis. Red, fetal veins: Umbilical vein, chorionic veins and venules; maternal arteries: endometrial arteries. Blue, fetal arteries: Umbilical arteries, chorionic arteries and arterioles. Pink, decidua basalis, Nitabuch's layer, placental septa. Brown, myometrium. Reprinted from *Jansen C, Kastelein AW, Kleinrouweler CE, Van Leeuwen E, De Jong KH, Pajkrt E, et al. Development of placental abnormalities in location and anatomy. Acta Obstet Gynecol Scand. 2020;99(8):983-93* with permission from John Wiley & Sons.

The pathogenesis of hypertensive disorders of pregnancy is thought mainly to be related to an abnormal interaction between placental and maternal vasculature, of which one or both may be dysfunctional, resulting in an exaggerated maternal systemic inflammatory response

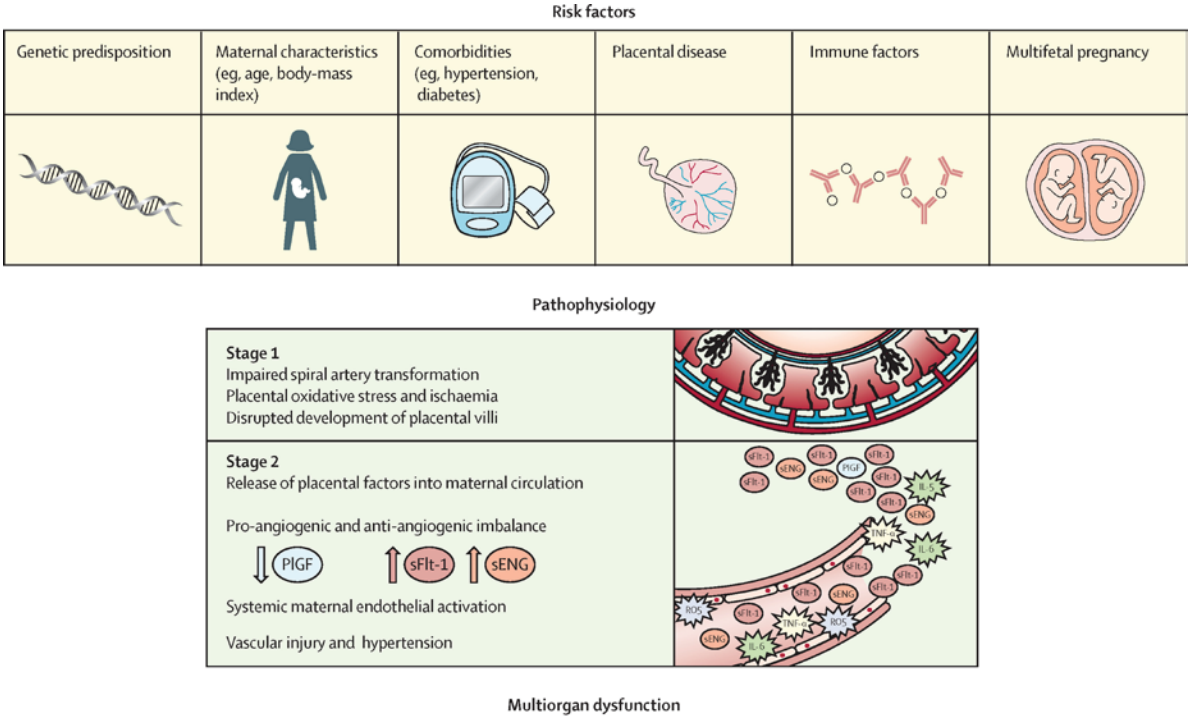
and clinically presenting as multi-organ dysfunction (Figure 3) (23, 24). Previous models of preeclampsia have suggested that early-onset preeclampsia may arise predominantly from placental dysfunction, whereas late-onset preeclampsia may be due to exaggerated maternal response to inflammatory or metabolic stress from underlying disorders such as diabetes, chronic hypertension and obesity with or without poor placentation (23, 25, 26). An alternative two-stage model (Figure 4) proposes that both early and late-onset preeclampsia result from placental malperfusion and syncytiotrophoblast stress, but that the causes and timing of placental malperfusion differ (27-30). In early-onset preeclampsia, the first stage is malplacentation, whereas in late-onset preeclampsia, the first stage is declining placental function. The common second stage for both early and late-onset preeclampsia is synctiotrophoblast stress (30). This model fits better with the clinical heterogeneity of preeclampsia as well as gestational hypertension.

Impaired or inadequate maternal spiral arterial remodeling, resulting in poor placentation and maternal vascular malperfusion, is characterized by high-velocity turbulent blood flow causing ischemia-reperfusion injury and placental oxidative stress (21). Placental malperfusion results in infarction, retroplacental hemorrhage, abnormal development of villi and/or decidual arteriopathy, including atherosis, perivasculitis, fibrinoid necrosis and arterial thrombosis (21, 31). Malplacentation, as a cause of the first stage of early-onset preeclampsia, is due to the combination of incomplete spiral artery modeling, impaired placental growth and placental malperfusion (30). The process may also arise as a result of chronic maternal inflammatory states such as obesity, which may promote activation of decidual immune mediators and anti-angiogenic factors (32).

Declining placental function arises as placenta mass increases within the limited confines of the uterus, resulting in chorionic villous crowding and reduced intervillous space. This results in increased fetoplacental vascular resistance, as seen by increasing umbilical artery pulsatility indices, and possibly decreased placental perfusion (30). The first stage of late-onset preeclampsia is thus secondary to intraplacental (intervillous) malperfusion and hypoxia due to mechanical restrictions as the growing placenta reaches its size limit (27-29).

Placental malperfusion and declining placental function lead to synctiotrophoblast stress (30). The synctiotrophoblast produces and releases placenta-derived cytokines, clinically referred to as biomarkers, such as soluble fms-like tyrosine kinase-1 (sFlt-1), also known as vascular endothelial growth factor receptor-1 (VEGFR-1), soluble endoglin (sENG) and

vascular placental growth factor (PlGF) (23). Excessive production of sFlt-1 due to synctiotrophoblast stress binds and reduces free levels of VEGF and PlGF, both of which are necessary for normal vascular endothelial function (30). Changes in maternal circulating placenta-derived biomarkers, such as decreased angiogenic PlGF and increased antiangiogenic sFlt-1 and sENG promotes generalized maternal endothelial dysfunction (vascular inflammation), leading to the clinical syndrome of preeclampsia with hypertension and end-organ dysfunction (21, 23, 33-40).



		Symptoms	Signs	Investigations	Complications
	Neurological	Headache and visual disturbances	Brisk reflexes and clonus	..	Eclampsia, posterior reversible encephalopathy syndrome, and intracranial haemorrhage
	Renal	..	..	Proteinuria and raised serum creatinine	Acute kidney injury
	Hepatological	Epigastric pain	Right upper quadrant tenderness	Elevated serum liver enzymes	Hepatic haematoma or rupture
	Haematological	..	Dark brown urine and petechiae	Low platelets, abnormal clotting tests, and haemolysis	Coagulopathy
	Uteroplacental and fetal	Vaginal bleeding and reduced fetal movements	Hard uterus and reduced fundal height	Fetal growth restriction	Placental abruption and intrauterine fetal death
	Cardiorespiratory	Breathlessness, chest pain, and confusion	Tachypnoea	Decreased oxygen saturation and diastolic dysfunction	Pulmonary oedema

Figure 3. Pathophysiology of preeclampsia. Reprinted from *Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. Lancet. 2021;398(10297):341-54* with permission from Elsevier Science & Technology Journals.

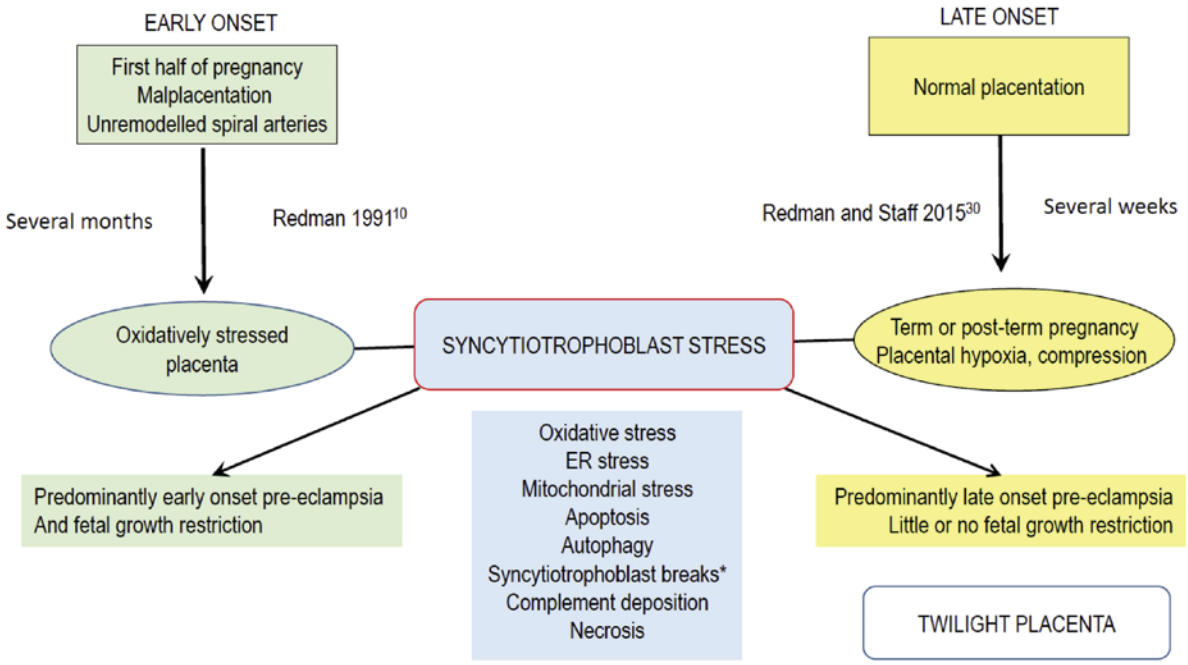


Figure 4. Two-stage model of preeclampsia: early and late placental dysfunction
Early-onset disease is characterized by a long first stage and more severe placental and fetal sequelae. Late-onset disease has a shorter first stage and less severe sequelae if delivery supervenes normally. They both cause syncytiotrophoblast stress, associated with the specific stresses as listed. Early-onset preeclampsia is based predominantly on spiral artery dysfunction that causes focal oxidative stress in the relevant territory of the artery. Late-onset disease is more diffuse and affects syncytial health in a less focused way. Adapted from Redman (41) and Redman and Staff (29).
Reprinted from *Redman. Syncytiotrophoblast stress in preeclampsia. Am J Obstet Gynecol 2020* with permission from Elsevier Science & Technology Journals.

1.2.3 Clinical measures

Hypertension in pregnancy is diagnosed as sustained systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, with subsequent blood pressure readings taken after several hours (1). Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 110 mmHg is considered a severe clinical feature, and blood pressure readings should be confirmed after 15 minutes (1). Blood pressure is taken with a liquid crystal sphygmomanometer or an appropriately calibrated automated device, validated for pregnancy (1). A screening blood pressure should ideally be taken pre-pregnancy or at least in early pregnancy to establish a baseline reading and exclude chronic hypertension. Blood pressure self-monitoring is a feasible alternative to office readings (42).

The gold standard for diagnosing proteinuria in pregnancy is a 24-hour urinary protein ≥ 300 mg, but collecting a 24-hour urine specimen is impractical and time-consuming (1). Proteinuria is instead pragmatically diagnosed clinically by ≥ 1+ (30 mg/dL) on a urine

dipstick, confirmed by a spot urine protein/creatinine ratio (PCr) ≥ 30 mg/mmol (0.3 mg/mg) (1, 10). Random spot urine PCr correlates well with 24-hour urinary protein (43-45). Urine albumin/creatinine is another alternative to PCr (46-48), as assessment of urinary albumin may better reflect glomerular damage (49, 50). A urine dipstick of ≥ 2+ (100 mg/dL) can be used if 24-hour urinary protein or PCr are not available (1, 10). Automated dipstick reading is preferred over visual assessment (1).

Maternal organ dysfunction is diagnosed by one or more of the following:

- Creatinine ≥ 90 μmol/L (1), 1.1 mg/dL (10) or a twice normal concentration (10), as a sign of acute kidney injury and renal insufficiency
- Liver transaminase ALT or AST > 40 IU/L (1) or twice normal concentration (10), as a sign of impaired liver function
- Platelets < 150,000/μL, as a sign as thrombocytopenia (1, 10)
- Other hematologic complications, such as disseminated intravascular coagulation (DIC) or hemolysis (1)
- Headache unresponsive to treatment (1, 10) or other neurological impairment such as seizure (eclampsia), altered mental status, blindness, stroke, clonus, persistent visual scotomata (1)
- Pulmonary edema (10)

Ultrasound evidence of uteroplacental dysfunction reflects malplacentation, abnormal uterine spiral artery remodeling and increased placental vascular resistance (30). End-diastolic umbilical artery Doppler flow is reduced, reversed or absent (51). Uterine artery pulsatility index is > 95th percentile for gestational age (52). FGR (Figure 5) < 10th percentile for gestational age as a result of poor placental perfusion and chronic fetal hypoxia is also a sign of uteroplacental dysfunction (53-57).

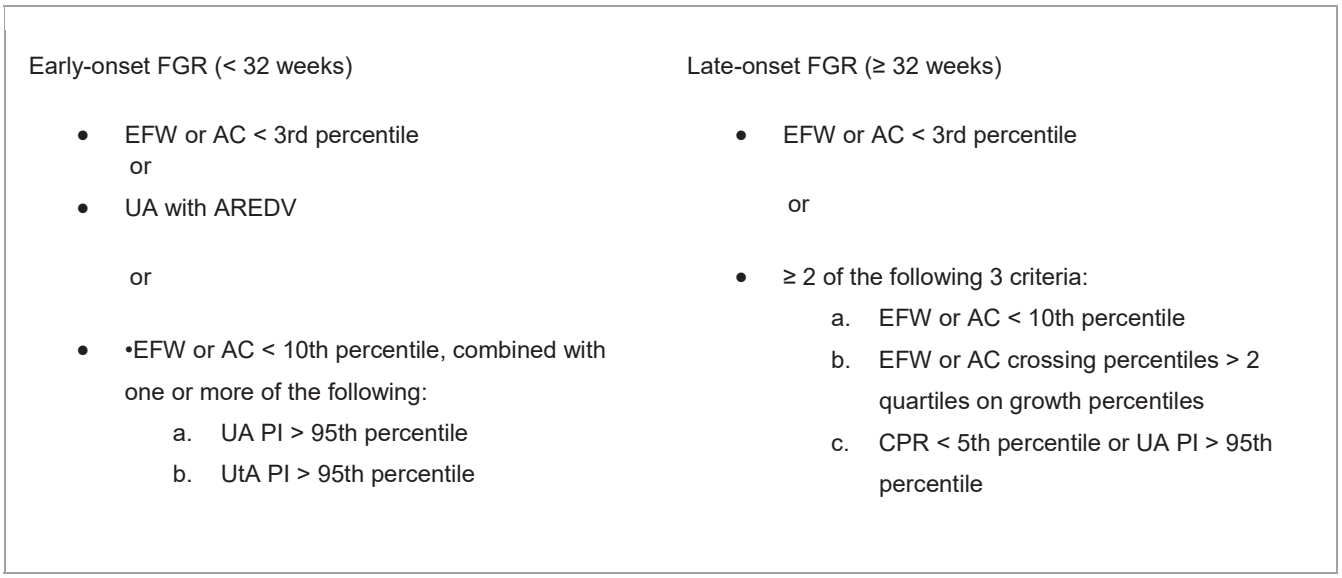


Figure 5. FIGO consensus-based definitions for early and late fetal growth restriction. Reprinted from *Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, et al. FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet. 2021;152 Suppl 1(Suppl 1):3-57* with permission from John Wiley & Sons.
Abbreviations: AC, fetal abdominal circumference; AREDV, absent or reversed end-diastolic velocity; CPR, cerebroplacental ratio; EFW, estimated fetal weight; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery. Adapted from Gordijn et al.(52).

1.2.4 Classification

Preeclampsia has historically been classified as either mild or severe (13), however current internationally accepted definitions have eliminated this dichotomous classification (1) or use the terminology "preeclampsia with or without severe features" (1, 10). Traditionally, "mild" preeclampsia was defined as a blood pressure ≥ 140/90 mmHg and 24-hour urinary protein ≥ 0.3 grams. "Severe" preeclampsia was defined having one or more of the following: ≥ 160/110 mmHg on two occasions greater than six hours apart, 24-hour urinary protein ≥ 5 grams (or urine dipstick ≥ 3+ at least four hours apart), oliguria (< 500 mL/24 hours), cerebral or visual abnormalities, pulmonary edema or cyanosis, epigastric or right upper-quadrant pain, liver function impairment, thrombocytopenia or FGR (13).
ACOG's current classification of "preeclampsia with severe features" is similar to the traditional classification of "severe preeclampsia", but it does not include FGR (10). Mild preeclampsia can progress to severe disease (58).

Preeclampsia is also classified by gestational age at onset. As the time of onset is most often less reliably recorded than time of delivery, preeclampsia "onset" is for simplicity often

dichotomized according to delivery, either preterm (< 37+0 weeks of gestation) or term (≥ 37+0 weeks of gestation), or into very preterm delivery (< 34+0 weeks gestation) or not (28, 29, 59, 60). Preeclampsia is also classified by either early (< 34+0 weeks of gestation) or late (≥ 34+0 weeks of gestation) in onset (61, 62).

HELLP syndrome is considered a serious variant or complication of preeclampsia (1, 63, 64). The syndrome, first described in 1985 (65), is a multisystem disease characterized by maternal hemolysis, elevated liver enzymes and low platelets (66). Hypertension and/or proteinuria is not always present (64, 67). The diagnosis is based on laboratory evidence of microangiopathic hemolytic anemia, hepatic dysfunction, and thrombocytopenia (67). Right upper quadrant pain is a common presenting symptom, but women may also present with non-specific symptoms as malaise, headache, nausea, vomiting and flu-like symptoms (63, 67). The complete form of HELLP has all three biochemical abnormalities of the disease triad, while partial or incomplete HELLP encompasses only one or two abnormalities (66). HELLP arises usually in the third-trimester, and may have a rapid disease progression with serious clinical deterioration, including DIC, hepatic rupture or cerebral hemorrhage (63, 68).

The Mississippi classification of HELLP (69) includes hemolysis accompanied with the following laboratory abnormalities:

- Class 1 HELLP: Platelets ≤ 50 000/μL, AST or ALT ≥ 70 IU/L, Total LDH ≥ 600 IU/L
- Class 2 HELLP: Platelets 50 000-100 000/μL, AST or ALT ≥ 70 IU/L, Total LDH ≥ 600 IU/L
- Class 3 HELLP: Platelets 100 000-150 000/μL, AST or ALT ≥ 40 IU/L, Total LDH ≥ 600 IU/L
- Partial HELLP syndrome: Evidence of severe preeclampsia-eclampsia in association with 2 of 3 laboratory criteria for HELLP syndrome

An alternative diagnostic criteria for HELLP is based on the Tennessee classification: Hemolysis, platelets ≤ 100 000/μL, AST ≥ 70 IU/L, LDH ≥ 600 IU/L (66).

1.2.5 Prevalence

Hypertensive disorders of pregnancy affect 10% of pregnancies worldwide and is associated with increased maternal, fetal and neonatal morbidity and mortality (4, 70-73). Gestational hypertension is a less severe hypertensive disorder of pregnancy, but it can progress to preeclampsia in 25% of cases (16). Preeclampsia affects 3-5% of pregnancies worldwide (74, 75), with the greatest burden of the disease seen in low-resource countries (76-78). Regional variations in national preeclampsia prevalence have been reported (79). Late-onset preeclampsia is more prevalent than early-onset disease (80). HELLP syndrome affects 0.5% to 0.9% of pregnancies, and is a considered a serious variant of preeclampsia (1, 63, 64). Secular trends of chronic hypertension among partituents increased in the United States from 1995-2008, specifically from 0.90% to 1.52% for primary hypertension and from 0.07% to 0.24% for secondary hypertension (72). Approximately 25% of women with chronic hypertension will develop superimposed preeclampsia (1, 81).

Preeclampsia prevalence varies by parity, with a higher prevalence of disease among nulliparous women (82). Preeclampsia prevalence is approximately three times higher in twin pregnancies than singleton pregnancies (83). Single country and multinational observational studies report increased risk of preeclampsia among specific immigrant groups delivering in industrialized countries (84-92). A systematic review and meta-analysis of epidemiologic studies, however, found a lower risk of hypertensive disorders of pregnancy among immigrant populations (93).

Hypertensive disorders of pregnancy increased globally by almost 11% between 1990 and 2019 (94). Preeclampsia and gestational hypertension increased by 25% and 184%, respectively, in the United States from 1986 to 2004 (95). European studies reporting population-level temporal trends in the prevalence of hypertensive disorders of pregnancy are lacking or outdated, and it is unclear how demographic changes or new clinical practices may impact preeclampsia prevalence (96). Older MBRN data show an increase in preeclampsia prevalence from 1967 to 1999 followed by a decreasing trend to 2008 (97). Preeclampsia prevalence in non-European countries with high socioeconomic indices and comprehensive national healthcare systems observe conflicting results. A Canadian study observed a doubling of preeclampsia prevalence from 1989 to 2012 (98). An Australian study, however, found a decreasing prevalence of preeclampsia between 2000 and 2008, but an increase in eclampsia over the same time period (99).

1.2.6 Global health perspective

The global incidence of hypertensive disorders of pregnancy increased by approximately 10% from 16.30 million in 1990 to 18.08 million in 2019, but the age-standardized incidence of hypertensive disorders of pregnancy decreased by 0.68% [95% confidence interval (CI) -0.49 to -0.86] and maternal mortality due to hypertensive disorders of pregnancy decreased 30.05% over the same time period (94). Age-standardized incidence rates were higher in low-resource countries compared to high-resource countries (94). Globally, approximately 70 000 women and 500 000 babies die each year due to preeclampsia/eclampsia (15).

A 2013 World Health Organization (WHO) systematic review of 74 studies comprising approximately 39 million women from 40 countries estimated the global incidence of preeclampsia at 4.6% (95% uncertainty range 2.7-8.2%) and the global incidence of eclampsia at 1.4% (95% uncertainty range 1.0-2.0%) (75). The WHO Africa region had the highest incidence of preeclampsia incidence (5.6%) and eclampsia incidence (2.9%) (75). Data on both preeclampsia and eclampsia were available from only seven countries, including Norway; data from countries and regions outside of North America and Europe were scarce (75). The paucity of country and region-specific data on preeclampsia from low and middle-income countries means there is a serious knowledge gap in the understanding of the global burden of preeclampsia. In addition, the global, regional and country-specific variations in preeclampsia prevalence and risk are likely due the complex interplay of demographic, genetic, dietary and environmental factors (100). Preeclampsia/eclampsia is a major global health problem, and greater effort is needed to improve awareness and access to pre-conceptual counseling, as well as antenatal, intrapartum and postnatal care (15).

Preeclampsia is a known risk factor for preterm birth, but its contribution to global preterm birth is not well understood (101). A study of preterm birth in 5 industrialized nations (Czech Republic, New Zealand, Slovenia, Sweden, California USA) found that preeclampsia was the second biggest risk factor for preterm birth [odds ratio (OR) 2.8-5.7] after history of preterm birth (OR 4.6-6.0) (102). In 2010, preterm livebirth rates were approximately 5% in Europe, 12% in USA and 18% in Africa, with 60% of all preterm births occurring in sub-Sahara Africa and south Asia (103). Approximately 30 percent of neonatal deaths in low-resource countries are due to preterm birth (104).

The Global Network for Women's and Children's Health Research Maternal Newborn Health Registry found that adolescent parturients (< 15 years old and 15-19 years old) in low-resource countries had a statistically significant lower risk of hypertensive disorders of pregnancy compared to adult women (20-24 years old), but higher risk of adverse perinatal outcomes such as preterm birth and low birth weight (105). Compared to adult women, the risk of hypertensive disorders of pregnancy among mothers < 15 years old and 15-19 years old in sub-Saharan Africa and Latin America was 68% lower (OR 0.32, 95%CI 0.12-0.86) and 14% lower (OR 0.86, 95%CI 0.077-0.95), respectively. In South Asia, 15-19 year olds had a 15% lower risk of hypertensive disorders of pregnancy compared to adult women (OR 0.85, 95%CI 0.73-0.99) (105).

Although global maternal mortality decreased from 1990-2013, the percentage of deaths due to hypertensive diseases of pregnancy have remained approximately 13% (106). In general, maternal deaths were highest in older age groups, with an exponential increase in all-cause maternal mortality ratio (MMR, number of maternal deaths per 100 000 livebirths) from age 30-35 (106). Maternal morbidity has not increased among adolescent parturients (< 19 years old) from low-middle income countries compared to young adult women (20-24 years old) (105).

A 2021 cross-sectional study comparing preeclampsia in Sweden and China found similar a prevalence of preeclampsia in both countries, but severe preeclampsia accounted for two-thirds of cases in China and only one-third of cases in Sweden; the stillbirth rate among women with preeclampsia was 10 times higher in China than in Sweden (107).

1.3 Risk factors for preeclampsia

1.3.1 Socioeconomic

Immigration, ethnicity and maternal country of birth

Older national and multinational observational studies have reported increased risk of preeclampsia among specific immigrant groups delivering in industrialized countries (84-92). However, a 2010 systematic review and meta-analysis of 16 epidemiologic studies found a lower risk of hypertensive disorders of pregnancy among immigrant populations

(93). In contrast, a recent French study found that sub-Saharan immigrant women had almost double the risk of preeclampsia compared to French women (108).

A 2020 Australian multicenter study found lower risk of preeclampsia among ethnic minority groups, defined by country of birth and primary language, compared to Australian/New Zealand-born English speakers (109). A US study found a lower risk of preeclampsia among non-Hispanic black immigrant women compared to US non-Hispanic black women, but the lower preeclampsia risk disappeared after ≥ 10 years of residence in US (110). Another US study of over 100 000 low-risk women found higher risk of preeclampsia in women with ethnic discordant partners, compared to women with ethnically similar partners (87).

Several Norwegian studies have investigated the association between maternal country of birth or immigrant status and preeclampsia. One study found lower risks of preeclampsia among immigrants compared to Norwegians; a longer duration of residence in Norway narrowed the risk gap between immigrant and native women [< 5 years adjusted odds ratio (aOR) 0.64, 95%CI 0.59-0.70, ≥ 5 years aOR 0.91, 95%CI 0.84-0.99] (111). In another study, economic immigrants had a lower risk of preterm preeclampsia, whereas refugees had a higher risk of preterm preeclampsia compared to Norwegian women (112). Another study found that immigrant women from south Asia and Africa had higher prevalence of pre-gestational diabetes (mostly type 2) compared to Norwegian women, but both immigrant and Norwegians had similar increased risk of preeclampsia compared to non-diabetic immigrant and Norwegian controls (113). A fourth study found that mean systolic and diastolic blood pressures in early pregnancy (15 weeks of gestation) were lower in non-European women in Norway compared to western European women in Norway, but mean systolic blood pressure increased significantly throughout pregnancy and postpartum among non-European women compared to European women (114).

Education and income

Very few studies have investigated the association between maternal education and preeclampsia. A population-based cohort study from the Netherlands found a positive association between low education and preeclampsia, compared to women with high education (aOR 4.91, 95%CI 1.93-12.52) (115). In low and middle-income countries, women with low educational attainment had significantly higher rates of maternal mortality

at six weeks postpartum, including death due to seizures and convulsions, compared to university-educated women (76).

Unemployed women in the UK, and those with low-wage occupations may experience a higher risk of severe maternal morbidity, such as eclampsia, independent of BMI, age or ethnicity (116). The risk of severe maternal morbidity, including eclampsia, was significantly higher among women from economically disadvantaged areas in Australia (117). In Korea, lower household income was a statistically significant independent risk factor for developing preeclampsia (118). Disparities in data collection may lead to information bias regarding the association of socioeconomic factors and preeclampsia. For example, in southern California, the incidence of preeclampsia was significantly underreported on birth certificates compared to hospital data among mothers with lower educational levels, Hispanic ethnicity and public insurance (119).

1.3.2 Biologic

A 2016 systematic review and meta-analysis of 92 large cohort studies comprising a total of 25 356 668 pregnancies found that maternal age > 35 years old, nulliparity, antiphospholipid syndrome, chronic hypertension, chronic renal disease, pre-gestational diabetes, BMI > 30 kg/m^2, multifetal pregnancy, assisted reproductive technology (ART), prior stillbirth, prior placental abruption or prior preeclampsia were associated with an increased risk of preeclampsia (120).

Maternal age

Maternal age has increased over the last two decades (121), and older women account for an increased proportion of preeclampsia cases (122). Regardless of parity, risk of preeclampsia increases with maternal age, but the increased risk starts earlier in nulliparous women (123). A UK study found that increased maternal age was a risk factor for late-onset preeclampsia and gestational hypertension, but was not associated with an increased risk for early-onset preeclampsia (90). In the same study, the risk of late-onset preeclampsia and gestational hypertension increased by 4% per every year over 32 years (90). A population-based Finnish study found that preeclampsia was more frequent among women with advanced maternal age (9.4% in women > 35 years) compared to younger women (6.4% in women < 35 years) (124). An Israeli study found a higher incidence of preeclampsia in women ≥ 45

years old compared to younger parturients, with an even greater risk among women > 50 years old compared to 45-49 years old (125).

Body mass index, weight

Elevated body mass index (BMI) is associated with adverse pregnancy outcomes, including hypertensive diseases of pregnancy (126). A multicenter prospective US study found that women with 1st-trimester obesity (BMI 30.0-34.9 kg/m^2) had an approximately two-fold risk of gestational hypertension (aOR 2.5, 95%CI 2.1-30) and preeclampsia (aOR 1.6, 95% CI 1.1-2.25) compared to women with BMI < 30.0 kg/m^2; morbidly obese women (BMI ≥ 35.0 kg/m^2) had three-fold risk of gestational hypertension (aOR 3.2, 95%CI 2.6-4.0) and preeclampsia (aOR 3.3, 95%CI 2.4-4.5) (127). A recent large population-based US study of 15.8 million women found a positive linear association between obesity (BMI > 30 kg/m^2) and risk of early and late-onset hypertensive disorders of pregnancy compared to women with BMI 18.5-29.2 kg/m^2 (128). A linear correlation between 5 kg/m^2 increments in BMI and preeclampsia has been found, but only in late-onset disease (129). A Swedish study found that short stature (< 163 cm) independent of BMI was associated with both term and preterm preeclampsia regardless of severity (130).

A multicenter Chinese study found an association between elevated pre-pregnancy BMI (> 24.0 kg/m^2) and preeclampsia, both in women with and without diabetes, although this study did not adjust for possible confounders (18). A 2015 systematic review and meta-analysis of BMI and adverse pregnancy outcomes in low and middle-income countries found a positive association between BMI ≥ 25 kg/m^2 and hypertensive disorders of pregnancy, with a population-attributable risk between 14-35% (131). Other studies have not found an association between elevated BMI and early (26, 132) or intermediate-onset (34+0-36+6 weeks of gestation) preeclampsia (26).

Data from the SCreening fOr Pregnancy Endpoints study (SCOPE) showed that in nulliparous women, low maternal birth weight (< 2500 g) was associated with an approximately two-fold risk of gestational hypertension and preeclampsia compared to women with normal birth weight (3000-3499 g); a similar increase in risk was observed in women with low maternal birth weight and elevated early pregnancy (15 weeks of gestation) body mass (BMI > 25 kg/m^2) compared to women with low birth weight and lean body mass (BMI < 25 kg/m^2) (133).

Gestational weight gain is also associated with gestational hypertension and preeclampsia (132, 134-136). However, a recent meta-analysis, of which 37.9% of the study participants were from Norway, suggested that pre-pregnancy BMI, more so than gestational weight gain, is associated with adverse maternal outcomes, including preeclampsia (137). Optimal gestational weight gain during pregnancy may have a protective effect on the development of term preeclampsia (138).

Comorbidities

Diabetes

A population-based Norwegian study of over 1.1 million deliveries found the risk of preeclampsia was six times higher among women with the type 1 diabetes compared to the background population (aOR 6.0, 95%CI 5.2-6.9) (139). Nulliparity, diabetic vasculopathy, gestational weight gain, and chronic hypertension are risk factors for preeclampsia among women with type 1 diabetes (140, 141). A small Finnish study with 903 nulliparous and parous women found a positive association between type 1 diabetes and preterm preeclampsia, but no association at term (26). A population-based study in Taiwan also found a positive association between type 1 diabetes and preeclampsia and eclampsia (142).

A Swedish study of both nulliparous and parous women with pre-gestational diabetes (type 1 or type 2) showed an increased risk of both preterm and term preeclampsia (143). A Canadian study found that pre-pregnancy diabetes alone increased the risk of preterm preeclampsia (aOR 8.63, 95%CI 6.59-11.31); the risk increased substantially in women with both pre-pregnancy diabetes and chronic hypertension (aOR 65.47, 95%CI 45.47-94.27) (144). An Australian study found a nearly three-fold increased risk of preeclampsia among women with type 2 diabetes (aOR 2.75, 95%CI 1.49-5.10) (145).

In a Brazilian study, women with gestational diabetes and a prior history of gestational diabetes, advanced maternal age (> 35 years), multiparity (para ≥ 2) or maternal overweight or obesity had higher risk for hypertensive disorders of pregnancy compared to women with gestational diabetes without these comorbidities (146). Studies have investigated the association between gestational diabetes and gestational hypertension with conflicting results. A small Swedish cohort study did not find an association between the two (147), whereas a US case-control study found a positive association (148).

An independent association between type 1 or type 2 diabetes and gestational hypertension has not been observed (145).

Chronic hypertension

Approximately 23% of women with chronic hypertension develop superimposed preeclampsia (1). A US study of over 56 million deliveries found that the incidence of chronic hypertension among pregnant women increased significantly from 0.90% in 1995-1996 to 1.52% in 2007-2008, and the population attributable fraction of chronic hypertension was 11% for preeclampsia (72). A systematic review and meta-analysis of 55 studies comprising 795 221 pregnancies found that the pooled incidence of superimposed preeclampsia among women with chronic hypertension was 25.9% (95%CI 21.0%-31.5%), and the relative risk for superimposed preeclampsia was nearly 8 times that of preeclampsia in the general population [relative risk (RR) 7.7, 95%CI 5.7-10.1] (149). A population-based Dutch study of over 1 million women found an eight-fold increased risk of superimposed preeclampsia (aOR 8.0, 95% CI 7.1.9.0%) and a four-fold increased risk of eclampsia (aOR 3.9, 95% CI 1.2-12.2) among women with chronic hypertension compared to non-hypertensive women (150). A UK study found a six-fold increased risk of preterm superimposed preeclampsia (aOR 6.23, 95%CI 4.83-8.04) and a five-fold increased risk of superimposed preeclampsia at term (151).

A Canadian study found that women with chronic hypertension had 45 times increased risk of preterm birth due to preeclampsia (aOR 45.42, 95%CI 36.69 -51.99) compared to healthy controls (144). Women with chronic hypertension who were managed expectantly after 39+0 weeks of gestational age were found to have a significantly higher incidence of severe preeclampsia compared to those with planned delivery at 39+0 to 39+6 weeks (0% vs 10.3%) (152). The incidence of preeclampsia was higher in women with chronic hypertension requiring antihypertensive medication before pregnancy compared to those with a pre-pregnancy history of chronic hypertension not requiring medication (153). Cessation of antihypertensive therapy in pregnant women with mild to moderate chronic hypertension (systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-109 mmHg) did not increase the risk of preeclampsia compared with hypertensive women who remained on antihypertensive therapy during pregnancy (154).

Chronic kidney disease

Chronic kidney disease shares similar signs and symptoms of preeclampsia (155) but the use of biomarkers such as sFlt-1 and PlGF can help differentiate the two conditions (156). An Indian study of 80 pregnant women with chronic kidney disease found that women with late stage disease had nearly twice the incidence of preeclampsia compared to women with early stage disease (76.5% vs 39.1%) (157). A systematic review and meta-analysis of four studies of pregnant women with IgA nephropathy found a high incidence of preeclampsia in these women (7.3%, 95%CI 4.9-10.6%) (158).

Antiphospholipid syndrome

Antiphospholipid syndrome (Hughes syndrome) is an acquired thrombophilia, characterized by vascular thrombosis and/or obstetric complications in the setting of the persistent presence of antiphospholipid antibodies and/or lupus anticoagulant (LA) (159). Antiphospholipid antibodies include anti-cardiolipin antibodies (aCL) and/or anti-β_2 glycoprotein I antibodies (anti-β_2GPI) (160). Antiphospholipid antibodies activate endothelial cells, monocytes and platelets and induce a prothrombic state mediated by tissue factor and Thromboxane A_2 (161). In addition, antiphospholipid antibodies may interact with clotting factors resulting in decreased inactivation of procoagulants and impaired fibrinolysis (161). Other unconventional antiphospholipid antibodies such as IgM anti-phosphatidylserine/prothrombin are also associated with endothelial dysfunction (162). Approximately 80% of people with antiphospholipid syndrome have a persistently positive aCL test, 20% have a persistently positive LA test, and approximately 60% test positive for both aCL and LA (163). Less than 20% of people with antiphospholipid syndrome have a positive anti-β_2GPI test (164).

An association between LA and preeclampsia was first observed in 1985 (165). Soon after, the presence of aCL and LA was found to be associated with an increased risk of early-onset severe preeclampsia (166). A 2010 systematic review and meta-analysis of 12 studies found an increased risk of severe preeclampsia in women with aCL (pooled OR 11.15, 95% CI 2.66-46.75) (167). In a 2017 Italian multicenter retrospective cohort study with 750 pregnant women with antiphospholipid syndrome, women with > 1 antiphospholipid antibody (defined as aCL, anti-β_2GPI, and/or LA) had a higher incidence and risk of preeclampsia with and without severe features compared to women with only one antiphospholipid antibody (168). Additionally, women with anti-β_2GPI alone had a higher

incidence of preeclampsia with and without severe features compared to women with LA alone or aCL alone (168). A 2018 case-control study found that women with severe preeclampsia and/or placental insufficiency who delivered before 36+0 weeks gestation had higher risk of antiphospholipid antibodies (thus antiphospholipid syndrome) than matched controls (aOR 8.9, 95% CI 1.9-41.4) (169).

Systemic Lupus Erythematosus

Preeclampsia incidence among women with systemic lupus erythematosus (SLE) is 15-30% and may be due to lupus nephritis, use of cortisone or the presence of antiphospholipid antibodies (170). A case-control study found that sFlt-1 concentrations were significantly higher among pregnancies with SLE and preeclampsia compared to matched controls with SLE and without preeclampsia (171). A 2020 systematic review and meta-analysis of 10 studies comprising over 6000 women with SLE found a three-fold increased risk of preeclampsia compared to healthy controls (pooled OR 2.99, 95%CI 2.31-3.88) (172). A Swedish study found an eight-fold higher risk of early-onset preeclampsia among women with SLE compared to healthy pregnant controls [adjusted relative risk (aRR) 7.8, 95%CI 4.8-12.9] (173).

Smoking

Smoking has long been known to have a protective effect against the development of preeclampsia. A 2015 systematic review and meta-analysis of 17 studies comprising over 1.8 million pregnant women found a one-third decreased risk of preeclampsia among women who smoke compared to women who do not (pooled aOR 0.67, 95%CI 0.60-0.75) (174). Smoking was found to be protective against both early and late-onset preeclampsia in a US study (80), but a 2000 Norwegian study found no association between smoking and early-onset disease (175). A population-based study from Murmansk, Russia found an inverse dose-response relationship between smoking and preeclampsia (176). An inter-pregnancy change in smoking habits (initiation of smoking between pregnancies) or smoking in two successive pregnancies was associated with a lower risk of preeclampsia in the second of the two pregnancies compared to women who did not smoke in either pregnancy (177).

1.3.3 Obstetric

Infertility and ART

A 2019 systematic review and meta-analysis of 48 studies found a positive association between ART and preeclampsia (pooled RR 1.71, 95%CI 1.11-2.62) (178). A 2020 systematic review and meta-analysis of 72 studies found a 10.8% (95%CI 9.10-12.5%) pooled incidence of preeclampsia among with ART (17). The underlying cause of infertility may affect preeclampsia risk, possibly due to abnormal inflammatory, metabolic and hormonal mechanisms (179). A 2018 systematic review and meta-analysis of 2.87 million deliveries found no association between endometriosis and preeclampsia in women with or without ART (180). However, women with polycystic ovarian syndrome had an increased risk of preeclampsia independent of ART (181). A case-control study of ART due to unexplained infertility compared to matched controls (ART due to male infertility) found no difference in risk of preeclampsia in singleton pregnancies (182).

An increased risk of preeclampsia was seen in pregnancies with hyperestrogenic ovarian hyperstimulation with clomiphene or gonadotropins; non-hyperestrogenic ovarian hyperstimulation with aromatase inhibitors did not increase the risk of preeclampsia compared to spontaneous pregnancies (183). A US retrospective cohort study of over 1 million deliveries found a decreasing trend in the incidence of severe maternal morbidity, including hypertensive disorders of pregnancy, among nulliparous women with ART between 2008 and 2012, although the incidence remained higher than among non-ART women (184).

The association between ART and preeclampsia has also been studied in Norway. A study using birth register data from Norway, Sweden, Denmark and Finland found that preeclampsia risk was higher in twin pregnancies after ART than in spontaneously conceived twins (185). A Scandinavian study found that ART in singleton pregnancies were associated with an increased risk of hypertensive disorders of pregnancy compared to spontaneous conception in women < 35 years old, but there was no difference in risk between the two groups in women ≥ 35 years of age (186). A cohort study using data from the Norwegian Mother and Child Cohort (MoBa) found an increased risk of preeclampsia among women treated for infertility (187). Another population-based Norwegian study found that risk of preeclampsia from ART increases with parity even after adjusting for birth interval and maternal age (188).

Parity

Nulliparity is known risk factor for preeclampsia with a population attributable fraction of approximately 32% (120). The risk of preeclampsia among nulliparous women is two to three times the risk for multiparous women (189). A recent population-based cohort study from France found that increased risk of hypertensive disorders of pregnancy was higher in nulliparous woman, regardless of maternal age (123).

Multifetal pregnancy

Twin pregnancies are associated with an increased risk of hypertensive disorders of pregnancy (190). A recent study using data from the MBRN found that the prevalence of preeclampsia was approximately 3.5 times higher, and the risk of preeclampsia was four times greater in twin compared to singleton pregnancies (aOR 4.07, 95%CI 3.65-4.54), but there was no increased risk of gestational hypertension (83). Growth discordance in dichorionic twin pregnancies was found to be an independent risk factor for preeclampsia (191). The association between twin pregnancies and preeclampsia may be more related to the increased burden of the fetoplacental unit than to a woman's underlying cardiovascular risk factors, as suggested by clinical studies in Norway and Sweden: Preeclampsia recurrence risk was less when preeclampsia was in a prior twin pregnancy compared to a prior singleton pregnancy (192). Additionally, the association between preeclampsia and future cardiovascular disease was seen only in prior singleton pregnancies and not prior multifetal pregnancies (193).

Pregnancy interval

Although multiparity is associated with lower preeclampsia risk, long pregnancy interval may be associated with preeclampsia. A systematic review and meta-analysis of two studies found a 10% increase in preeclampsia risk among women with a pregnancy interval > 4 years, compared to women with a pregnancy interval of 2-4 years (aOR 1.10, 95% 1.02-1.19) (194). A small single-center Australian study found 1.5-2 times increased risk of preeclampsia in pregnancy intervals > 3 years compared to pregnancy interval ≤ 3 years (195). A 2002 Norwegian study found that women with a pregnancy interval ≥ 10 years had preeclampsia risk similar to nulliparous women, even after controlling for maternal age and paternity (196). A small single-center US study found no association between pregnancy interval and risk of preeclampsia (197).

Previous preeclampsia

Hypertensive diseases in pregnancy increase the risk of adverse outcomes, including recurrent preeclampsia in future pregnancies. In a UK study, women with a prior history of preeclampsia had a four-fold increased risk of early-onset preeclampsia and a two-fold increased risk of late-onset preeclampsia compared to nulliparous women (90). A Swedish study found a nearly three-fold increased risk of early-onset preeclampsia in the subsequent pregnancy among women with late-onset preeclampsia and SGA infants, compared to women with late-onset preeclampsia and non-SGA infants (198). A population-based Norwegian study found a 10-fold increased risk of repeat gestational hypertension and term preeclampsia in the next pregnancy, a 27-fold increased risk of repeat late-preterm preeclampsia (33+0 to 36+6 weeks of gestation), and a 97-fold increased risk of repeat early preterm preeclampsia (25+0 to 32+6 weeks of gestation) compared to women without HDP in the first pregnancy (199). Another population-based Norwegian study found a two-fold increased relative risk of preterm birth in a subsequent pregnancy after a term delivery complicated by preeclampsia, compared to uncomplicated deliveries at term (200).

Other previous adverse pregnancy outcomes

Adverse pregnancy outcomes in a previous pregnancy may increase the risk of preeclampsia in a subsequent pregnancy. Previous preterm birth increased the risk of preeclampsia in a subsequent pregnancy in both Danish (201) and Norwegian (200, 202) population-based cohort studies. Compared to women with no prior miscarriage and infertility treatment, women with recurrent miscarriage (≥ 3 pregnancies ending before 22+0 weeks of gestation, including ectopic pregnancies) and a history of infertility treatment had increased risk of preeclampsia, but women with recurrent miscarriage and no prior infertility treatment did not (187). Induced abortion, with or without a prior history of spontaneous abortion, did not increase the risk of preeclampsia (203).

1.3.4 Other

There may be a genetic component to hypertensive disorders of pregnancy, as suggested by studies finding a two to three-fold increased risk of preeclampsia among sisters (90, 204) and/or mothers (90, 205).

Paternity, sperm exposure, and underlying immunological mechanisms may also affect the risk of preeclampsia. A systematic review and meta-analysis of seven studies comprising

over 10 000 women found that pregnancies with donor sperm had a 63% increased risk of preeclampsia compared to pregnancies with a partner's sperm (aOR 1.63, 95%CI 1.36-1.95) (206). Another systematic review and meta-analysis of seven studies including over 7000 women found that nulliparous women with considerable partner sperm exposure or more than one year of co-habitation had lower risk of preeclampsia compared to women with minimal exposure to paternal sperm (207). New paternity in a subsequent pregnancy may increase the risk of preeclampsia compared to same paternity (195), but two Norwegian studies found a lower risk preeclampsia with new paternity after adjusting for pregnancy interval (196, 208). A study from Jordan where there is a high prevalence of first-cousin marriages, found no association between consanguinity and severe preeclampsia (209).

Environmental exposures are also associated with preeclampsia risk. Early pregnancy exposure to organic compounds such as perfluoroalkyl substances has been associated with preeclampsia in a Swedish study (210). A systematic review and meta-analysis of 17 studies found an association between air pollutants and hypertensive disorders in pregnancy (211). A US study found that 1st-trimester exposure to traffic pollution and wood smoke was associated with a dose-response increased risk of early-onset preeclampsia (212). Seasonal variations in preeclampsia prevalence in Norway also suggest possible environmental influences (213).

Severe psychological stress has been associated with preeclampsia, according to a study using population data from Denmark and Sweden, with the greatest association observed between death of a child within six months of conception to the start of the 2nd-trimester of pregnancy and risk of early-onset preeclampsia (aOR 4.03, 95%CI 2.46-6.61) (214). However, neuroticism, as self-reported in the Swedish universities Scales of Personality, was not found to increase the risk of preeclampsia (215).

Emerging data suggests that COVID-19 may be associated with a higher incidence of preeclampsia (216) or a preeclampsia-like syndrome (217). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) binds to angiotensin converting enzyme-2 (ACE-2) receptors which then downregulates the conversion of angiotensin II (vasoconstrictor) to angiotensin-(1-7) (vasodilator and anti-inflammatory) (Figure 6) (218). Reduced angiotensin-(1-7) may promote vasoconstriction, inflammation and thrombosis (218). Placentas from women with COVID-19 have significantly greater evidence of maternal

vascular malperfusion, but no increased findings of acute or chronic inflammation, compared to healthy controls (219). Molecular studies suggest that SARS-CoV-2 is unlikely to infect the placenta since the ACE2 receptor and protease TMPRSS2 used by SARS-CoV-2 to gain entry into the host cell are only minimally expressed by the human placenta throughout pregnancy (220). In addition, vertical transmission is unlikely, as SARS-CoV-2 receptors are not expressed by the chorioamniotic membranes in the third trimester, in contrast to viral receptors utilized by cytomegalovirius and Zika virus that are highly expressed by the human placental tissues (220).

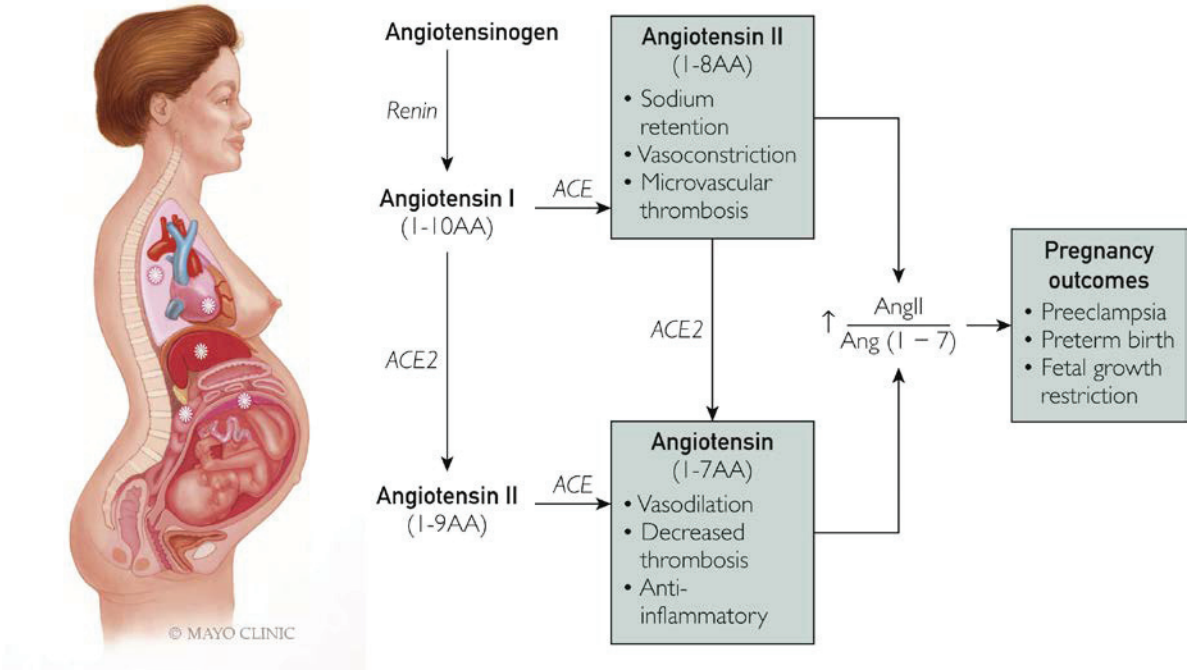


Figure 6. Pregnancy, coronavirus disease 2019 (COVID-19), and mechanisms of vascular damage. Upregulation of angiotensin-converting enzyme 2 (ACE2) receptor in pregnancy may increase the risk of severe acute respiratory syndrome coronavirus 2 infection. Binding of virus to ACE2 causes its downregulation and may increase angiotensin (Ang) II relative to Ang-(1-7), thus favoring vasoconstriction, which can mimic/worsen vascular dysfunction in preeclampsia. Reprinted from *Narang K, Enninga EAL, Gunaratne M, Ibirogba ER, Trad ATA, Elrefaei A, et al. SARS-CoV-2 Infection and COVID-19 During Pregnancy: A Multidisciplinary Review. Mayo Clin Proc. 2020;95(8):1750-65* with permission from Elsevier Science & Technology Journals.

Table 1. Studies published from 2005 to 2021, assessing selected risk factors for preeclampsia. Main risk factors studied are presented in the table, and only significant adjusted Relative Risk (aRR) or adjusted Odds Ratios (aOR) are presented.

Ref #: reference number in reference list. BMI: body mass index. GWG: gestational weight gain. NS: not significant. Ref: reference group in the study. P: parity. yrs: years old. PE: preeclampsia. incr: incremental. GDM: gestational diabetes. +GWG: excessive gestational weight gain. DM: diabetes. DM 1: diabetes type 1. DM 2: diabetes type 2. D/O/H: diabetes/obesity/hypertension. No Hx: no history. +Hx: positive history. HT: hypertension. MENA: Middle East/North Africa. Mat: maternal. Pat: paternal. AA: African American. Aus/NZ-born English: Australian/New Zealand-born English-speakers. US: United States. NHB: non-Hispanic Black. yr: years.

Author (ref #), Year, Country, Study type, Population	**Parity**	**Socioeconomic status**	**Region/ Country of birth/ Ethnicity/ Immigrant**	**Maternal age, in years**	**BMI (kg/m^2)/GWG**	**Diabetes**	**Chronic Hypertension**
Sheen (122) 2020 USA Cross-sectional N = 2 522 091	No data	NS	White Ref Black aRR 1.39 Hispanic aRR 1.08 Asian aRR 1.38 Native American NS Other aRR 1.19	25-29 Ref 15-17 aRR 0.83 18-24 aRR 0.94 30-34 aRR 1.11 35-39 aRR 1.20 40-44 aRR 1.41 45-49 aRR 1.89	No data	No data	No data
Desplances (123) 2019 France Cohort N = 137 791	P ≥ 1 20-24 yrs Ref P = 0 20-24 aOR 1.8 P ≥ 1 25-29 yrs Ref P = 0 25-29 aOR 2.0 P ≥ 1 30.34 yrs Ref P = 0 30-34 aOR 2.3 P ≥ 1 35-39 yrs Ref P = 0 35-39 aOR 1.8 P ≥ 1 40-49 yrs Ref P = 0 40-49 NS	No data	No data	20-24 Ref *P = 0* 25-29 aOR 1.3 30-34 aOR 1.4 35-39 aOR 1.6 40-49 aOR 2.1 *P ≥ 1* 25-29 NS 30-34 NS/ 35-39 aOR 1.6 40-49 aOR 2.2	No data	No data	No data

Table 1 continued

Author (ref #), Year, Country, Study type, Population	Parity	Socioeconomic status	Region/ Country of birth/ Ethnicity/ Immigrant	Maternal age, in years	BMI (kg/m^2)/GWG	Diabetes	Chronic Hypertension
Weiss (127) 2014 USA Cohort N = 16 102	No data	No data	No data	No data	< 30.0 Ref 30.0-34.9 aOR 1.6 ≥ 35.0 aOR 3.3	No data	No data
Biocca (128) 2020 USA Cohort N = 15 818 980	No data	No data	No data	No data	18.5-29.9 Ref Early-onset PE 30.0-34.9 aRR 1.13 35.0-39.9 aRR 1.57 ≥ 40.0 aRR 2.18 Late-onset PE 30.0-34.9 aRR 1.71 35.0-39.9 aRR 2.60 ≥ 40.0 aRR 3.93	No data	No data
Robillard (129) 2019 Reunion Island Cohort N = 96 861	No PE Ref All PE P = 0 aOR 2.43 Early-onset PE P = 0 aOR 2.17 Late-onset PE P = 0 aOR 2.44	No data	No data	No PE Ref All PE 5-yr incr aOR 1.04 Early-onset PE 5-yr incr aOR1.05 Late-onset PE 5-yr incr aOR 1.03	No PE Ref All PE 5kg/m^2 incr aOR 1.05 Early-onset PE 5kg/m^2 incr aOR 1.03 Late-onset PE 5kg/m^2 incr aOR 1.05	No PE ref All PE GDM NS Early-onset PE GDM NS Late-onset PE GDM NS	No PE ref All PE aOR 5.6 Early-onset PE aOR 8.2 Late-onset PE aOR 4.95

Table 1 continued							
Author (ref #), Year, Country, Study type, Population	**Parity**	**Socioeconomic status**	**Region/ Country of birth/ Ethnicity/ Immigrant**	**Maternal age, in years**	**BMI (kg/m^2)/GWG**	**Diabetes**	**Chronic Hypertension**
Wei (18) 2016 China Cohort N = 14 451	No data	No data	No data	No data	18.5-23.9 Ref *GDM* < 18.5 NS 24.0-27.9 OR 1.90 ≥ 28.0 OR 1.89 *No GDM* < 18.5 NS 24.0-27.9 OR 2.20 ≥ 28.0 OR 6.10	No data	No data
Shao (132) 2017 China Cohort N = 9863	No data	No data	No data	No data	18.5-24/GWG Ref <u>Early-onset PE</u> < 18.5/GWG NS < 18.5/+GWG NS 18.5-24/+GWG NS ≥ 24/GWG aOR 4.48 ≥ 24/+GWG aOR NS <u>Late-onset PE</u> < 18.5/GWG NS < 18.5/+GWG aOR 1.81 18.5-24/+GWG aOR 2.27 ≥ 24/GWG aOR NS ≥ 24/+GWG aOR 4.11	No data	No data

Table 1 continued							
Author (ref #), Year, Country, Study type, Population	**Parity**	**Socioeconomic status**	**Region/ Country of birth/ Ethnicity/ Immigrant**	**Maternal age, in years**	**BMI (kg/m^2)/GWG**	**Diabetes**	**Chronic Hypertension**
Eidem (139) 2011 Norway Cohort N = 1 162 399	No data	No data	No data	No data	No data	No DM Ref DM 1 aOR 6.0	No data
Lin (142) 2017 Taiwan Cohort N = 2 350 339	No data	No data	No data	No data	No data	No DM Ref DM 1 aOR 10.27	No data
Persson (143) 2016 Sweden Cohort N = 1 517 443	No data	No data	No data	No data	18.5-24.9 Ref *25.0-29.9* No DM aOR 1.69 DM 1 NS DM 2 NS *≥ 30* No DM aOR 3.22 DM 1 aOR 1.48 DM 2 NS	No DM Ref Preterm PE DM 1 aOR 8.72 DM 2 aOR 3.22 Term PE DM 1 aOR 4.19 DM 2 aOR 1.96	
Berger (144) 2020 Canada Cohort N = 506 483	No data	No data	No data	No data	No D/O/H Ref Preterm PE O aOR 1.91 O/D aOR 7.29 O/H aOR 29.60 O/D/H aOR 67.84	No D/O/H Ref Preterm PE D aOR8.63 D/O aOR 7.29 D/H aOR 65.47 D/O/H aOR 67.84	No D/O/H Ref Preterm PE H aOR 45.42 H/O aOR 29.60 H/D aOR 65.47 D/O/H aOR 67.84

Table 1 continued							
Author (ref #), Year, Country, Study type, Population	**Parity**	**Socioeconomic status**	**Region/ Country of birth/ Ethnicity/ Immigrant**	**Maternal age, in years**	**BMI (kg/m^2)/GWG**	**Diabetes**	**Chronic Hypertension**
Abell (145) 2017 Australia Cohort N = 27 213	No data	No data	No data	No data	No data	No diabetes Ref DM 2 aOR2.75	No data
Bateman (72) 2012 USA Cohort N = 56 494 634	No data	No data	No data	No data	No data	No DM 1,2/HT Ref DM 1,2/HT aOR 13.96 DM 1,2/no HT aOR 3.80	No HT Ref aOR 10.07
Bramham (149) 2014 Meta-analysis 55 studies N = 795 221	No data	No data	No data	No data	No data	No data	No HT Ref pooled RR 7.7
Broekhuijsen (150) 2015 Netherlands Cohort N = 1 033 277	No data	No data	No data	No data	No data	No data	No HT Ref HT aOR 8.0

Table 1 continued							
Author (ref #), Year, Country, Study type, Population	**Parity**	**Socioeconomic status**	**Region/ Country of birth/ Ethnicity/ Immigrant**	**Maternal age, in years**	**BMI (kg/m^2)/GWG**	**Diabetes**	**Chronic Hypertension**
Panaitescu (151) 2017 United Kingdom Cohort N = 109 932	No data	No data	No data	No data	No data	No data	No HT Ref All PE aOR 5.76 Preterm PE aOR 6.23 Term PE aOR 5.41
Urquia (84) 2014 International Cohort N = 9 028 802	No data	No data	Western Europe immigrants Ref Eastern Europe NS Latin America aOR 1.63 South Asia NS East-Southeast Asia NS MENA NS Sub-Saharan Africa aOR 1.72	No data	No data	No data	No data

Table 1 continued							
Author (ref #), Year, Country, Study type, Population	**Parity**	**Socioeconomic status**	**Region/ Country of birth/ Ethnicity/ Immigrant**	**Maternal age, in years**	**BMI (kg/m^2)/GWG**	**Diabetes**	**Chronic Hypertension**
Gong (88) 2012 USA Cohort N = 902 460	No data	No data	USA Ref North Africa NS Sub-Saharan Africa NS East Asia NS Philippines aOR 2.2 South Central Asia NS Non-Hispanic Caribbean NS Hispanic Caribbean NS	No data	No data	No data	No data
Poon (90) 2010 United Kingdom Cohort N = 9149	P = 0 Ref <u>Early-onset PE</u> P ≥ 1/No Hx PE 0.31 P ≥ 1/+Hx PE a OR 4.02 <u>Late-onset PE</u> P ≥ 1/No Hx PE 0.24 P ≥ 1/+Hx PE a OR 2.18	No data	White Ref <u>Early-onset PE</u> Black aOR 3.64 <u>Late-onset PE</u> Black aOR 2.97 Indian/Pakistani aOR 2.66 Mixed aOR 3.31	Late PE NS	Ref not reported BMI aOR 1.10 (Late PE)	NS	No HT Ref HT aOR 8.7
Ray (91) 2016 Canada Cohort N = 881 700	No data	No data	Canada Ref <u>Preterm PE</u> Nigeria aRR 1.79 Philippines aRR 1.54 Colombia aRR 1.68 Jamaica aRR 2.06 Ghana aRR 2.12	No data	No data	No data	No data

Table 1 continued							
Author (ref #), Year, Country, Study type, Population	**Parity**	**Socioeconomic status**	**Region/ Country of birth/ Ethnicity/ Immigrant**	**Maternal age, in years**	**BMI (kg/m^2)/GWG**	**Diabetes**	**Chronic Hypertension**
Urquia (86) 2012 Canada Cohort N = 118 849	No data	No data	Industrial country Ref P ≥ 0 Central/Eastern Europe, MENA, South Asia NS Hispanic America aOR 3.11 Caribbean aOR 3.34 Sub-Saharan Africa aOR 3.14 East Asia/Pacific aOR 1.59 P = 0 Central/Eastern Europe, MENA, East-Asia/Pacific, South Asia NS Hispanic America aOR 2.56 Caribbean aOR 2.27 Sub-Saharan Africa aOR 3.35	No data	No data	No data	No data
Caughey (87) 2005 USA Cohort N = 127 544	No data	No data	White Ref Mat AA aOR 1.49 Mat Hispanic aOR 0.87 Mat Asian aOR NS Pat AA NS Pat Hispanic NS Pat Asian aOR 0.76 Pat ethnic discord aOR 1.13	No data	No data	No data	No data

Table 1 continued							
Author (ref #), Year, Country, Study type, Population	**Parity**	**Socioeconomic status**	**Region/ Country of birth/ Ethnicity/ Immigrant**	**Maternal age, in years**	**BMI (kg/m^2)/GWG**	**Diabetes**	**Chronic Hypertension**
Mogos (93) 2017 Meta-analysis 16 studies N not reported	No data	No data	Native Ref Immigrant pooled aRR 0.74	No data	No data	No data	No data
Siddiqui (108) 2020 France Cohort N = 9579	No data	No data	France/Europe Ref North Africa NS Sub-Saharan Africa aOR 2.53 Other NS	No data	18.5-24.9 Ref Sub-Saharan Africa Obesity-mediated indirect aOR 1.18	No data	No data
Al-Rubaie (109) 2020 Australia Cohort N = 40 824	P ≥ 1 Ref P = 0 aOR NS	*P ≥ 0* NS *P = 0* NS	Aus/NZ-born English Ref *P ≥ 0* MENA aOR 0.55 Southeast Asian NS Northeast Asian aOR 0.33 South Asian aOR 0.73 Others NS *P = 0* MENA aOR 0.34 Southeast Asian NS Northeast Asian aOR 0.32 South Asian NS Others NS	25-29 Ref *P ≥ 0* ≤ 24 NS 30-34 aOR 1.30 ≥ 35 aOR 1.54 *P = 0* ≤ 24 1.40 30-34 aOR 1.69 ≥ 35 aOR 1.84	≤ 24 Ref *P ≥ 0* 25-29 aOR 1.61 30-34 aOR 2.58 ≥ 35 aOR 3.51 *P = 0* 25-29 NS 30-34 aOR 1.92 ≥ 35 aOR 4.26	No DM Ref *P ≥ 0* DM 1,2 aOR 1.65 *P = 0* DM 1,2 aOR NS	No HT Ref *P ≥ 0* HT aOR 4.62 *P = 0* No HT Ref HT aOR 5.83

Table 1 continued							
Author (ref #), Year, Country, Study type, Population	**Parity**	**Socioeconomic status**	**Region/ Country of birth/ Ethnicity/ Immigrant**	**Maternal age, in years**	**BMI (kg/m^2)/GWG**	**Diabetes**	**Chronic Hypertension**
Boakye (110) 2021 USA Cross-sectional N = 2697	No data	No data	US NHB Ref Foreign NHB aOR 0.73 < 10 yr aOR 0.63 ≥ 10 yr NS	No data	No data	No data	No data
Naimy (111) 2015 Norway Cohort N = 1 102 189	P = 0 Ref P = 1 aOR 0.43 P = 2 aOR 0.39 P ≥ 3 aOR 0.38	No data	Norway Ref *P ≥ 0* Somalia aOR 1.25 Migrants total aOR 0.76 *P = 0* Somalia aOR 1.49 Migrants total aOR 0.67	≤ 20 Ref *P ≥ 0* 20-34 NS ≥ 35 aOR 1.38 *P = 0* 20-34 NS ≥ 35 aOR 1.21	No data	No DM Ref *P ≥ 0* DM 1,2,G aOR *P = 0* DM 1,2, G aOR NS	No data
Nilsen (112) 2018 Norway Cohort N = 1 287 270	No data	No data	Norway Ref <u>PE < 37+0 weeks</u> Nordic NS Refugee aOR 1.18 Family aOR 0.88 Labor aOR 0.58 Education NS <u>PE < 34+0 weeks</u> Nordic aOR 0.75 Refugee aOR 1.41 Family NS Labor aOR 0.65 Education NS	No data	No data	No data	No data

Table 1 continued							
Author (ref #), Year, Country, Study type, Population	**Parity**	**Socioeconomic status**	**Region/ Country of birth/ Ethnicity/ Immigrant**	**Maternal age, in years**	**BMI (kg/m^2)/GWG**	**Diabetes**	**Chronic Hypertension**
Vangen (113) 2003 Norway Cohort N = 613 053	No data	No data	No data	No data	No data	No DM 1,2 Ref *Immigrant* DM 1,2 aOR 3.58 *Ethnic Norwegian* DM 1,2 aOR 4.68	No data
Silva (115) 2008 Netherlands Cohort N = 3547	No data	High education Ref Mid-high NS Mid-low aOR 2.61 Low aOR 4.91	No data	No data	No data	No data	No data
Choe (118) 2016 Korea Cohort N = 65 479	No data	Upper income Ref Lower aOR 1.26 Middle aOR NS	No data	25-29 Ref 15-19 NS 20-24 NS 30-34 NS 35-39 aOR 1.43 40-44 aOR 1.90	No data	No DM Re All DM aOR 1.97	No data

1.4 Preeclampsia morbidity and mortality

1.4.1 Maternal

Maternal Morbidity

Adverse maternal outcomes associated with preeclampsia include acute renal failure, cerebrovascular accidents and transient ischemic attack, myocardial infarction, seizure (eclampsia), thrombocytopenia, postpartum hemorrhage, disseminated intravascular coagulation, deep vein thrombosis, pulmonary embolism, pulmonary edema and death (221). Women with severe preeclampsia have higher risk of adverse outcomes than women with mild preeclampsia (221). Severe morbidity from preeclampsia, such as shock, stroke, heart failure, sepsis and blood transfusion, disproportionately affects women at extremes of age; women age 25-34 years old with preeclampsia had the lowest risk of adverse maternal outcome, according to a US study (122). In the same US study, there was a linear association between maternal age and acute renal failure, acute heart failure and stroke due to preeclampsia, but the incidence of eclampsia was highest in the youngest age group (15-17 years old) (122).

Maternal seizures in the setting of preeclampsia is the defining feature of eclampsia (14, 70). Eclampsia can occur antepartum, intrapartum, postpartum (< 48 hours) or, less commonly, late postpartum (< 23 days) (222). Twenty percent of women do not have any premonitory signs or symptoms prior to the first seizure (223). Mean cerebral magnesium levels are lower in women with preeclampsia compared to normotensive pregnant and non-pregnant controls; visual disturbances accompanying preeclampsia also correlates with lower magnesium levels (224).

Eclampsia is often associated with posterior reversible encephalopathy syndrome (PRES), which is characterized by vasogenic cerebral edema, usually in the occipital and parietal lobes, causing headaches, altered mental status and visual symptoms such as visual field deficits and cortical blindness (225-227). A 2020 case-control study of 72 consecutive women with preeclampsia or eclampsia found that hypomagnesemia was more prevalent among those with PRES (24 of 38 cases, 63%) than those without (2 of 34 controls, 6%) (228). Although the exact pathophysiologic mechanism is unknown, it is generally accepted that cerebral dysfunction and injury is due to endothelial dysfunction and disruption of the blood-brain barrier (225, 227). A Swedish cross-sectional case-control study found that glial

cell-derived protein S100B, a cerebral biomarker for blood-brain barrier damage, was significantly increased in women with preeclampsia, and particularly those with visual disturbances, compared to matched controls (229). Elevated cerebral biomarkers are found in women with preeclampsia at least one year postpartum (230).

Stroke associated with hypertensive disorders of pregnancy is primarily due to ischemia or hypertensive intracerebral hemorrhage (225). Women with any hypertensive disorder in pregnancy have a six to nine-fold increased risk of stroke compared to normotensive pregnant women (231). The risk of stroke in preeclampsia is five times greater than in normotensive pregnant women (232). A population-based US study found that hypertensive parturients with either ischemic, hemorrhage or unclassified stroke were more likely to have co-morbidities such as heart disease, peripheral vascular disease, coagulopathies or previous stroke compared to hypertensive women without stroke (233). Another US case-control study found that women with preeclampsia and pregnancy-associated stroke were more likely to have severe preeclampsia, eclampsia, infections on admission, coagulopathies, prothrombotic states or chronic hypertension compared to matched controls, and that stroke was most common in the postpartum period (234).

Hypertensive disorders of pregnancy are associated with an increased risk of peripartum cardiomyopathy, with the risk highest among women with severe preeclampsia (RR 21.1, 95%CI 12.0-37.4), according to a Danish register study (235). Increased anti-angiogenic factor sFlt-1associated with preeclampsia induces maternal cardiac dysfunction (236), and women with preeclampsia who are genetically vulnerable to cardiac disease may be more likely to develop peripartum cardiomyopathy (237).

Preeclampsia is also associated with postpartum depression, especially in the setting of adverse perinatal outcomes (238). Women with severe preeclampsia have a greater risk of postpartum depression compared to women with mild preeclampsia (239). A systematic review and meta-analysis found a positive association between history of preeclampsia and depression, as well as between preeclampsia and a higher severity of depressive symptoms (240).

Maternal mortality

Preeclampsia is the number one cause of maternal mortality in high-income countries (6, 241) and a leading cause (10-17%) of maternal mortality in middle and low-income countries (6, 242). An Australian study found that women with preeclampsia/eclampsia had five times the risk of dying within one year after delivery compared to normotensive women (99). A Danish registry-based retrospective cohort study found an association between hypertensive disorders of pregnancy and early maternal death due to cardiovascular disease (243). Eclampsia is associated with maternal mortality in both high and low-income countries (222, 244, 245). In high income countries, 10-60% of deaths from eclampsia are attributed to intracerebral hemorrhage (246, 247). Eclampsia rates and eclampsia case-fatality declined dramatically in high income countries between 1940 and 1970 due to improvements in prenatal care and improved access to hospitals with obstetric services (248). Routine use of magnesium sulfate for the prevention and treatment of eclampsia has also significantly reduced the incidence of eclampsia and maternal death due to eclampsia (249, 250). Significantly higher rates of maternal mortality from eclampsia in low-income countries are likely due to underlying health inequities in low-resource settings (245).

From 1996 to 2014, the most common cause of maternal death in Norway was hypertensive diseases of pregnancy (16 of 74 deaths), of which 14 (86%) of those deaths were due to substandard obstetric care (251). Of the 13 maternal deaths in Norway from 2012-2018 one death was due to preeclampsia (252).

Long-term maternal complications

Epigenetic changes due to maternal vascular remodeling and systemic inflammation during preeclampsia predispose women with a history of preeclampsia to long-term health complications (30, 253, 254). Preeclampsia is a known risk factor for cardiovascular disease later in life (255, 256) and may be associated with specific vascular-related polymorphisms (257). A population-based Swedish study found that preeclampsia in singleton pregnancies, but not twin pregnancies, increased the risk of future cardiovascular disease [adjusted hazard ratio (aHR) 1.75, 95%CI 1.64-1.86] (193). Preeclampsia is also associated with cardiomyopathy later in life (258).

A history of preeclampsia also increases the risk of future hypertension, end-stage renal disease, diabetes and metabolic disease (256). A Danish registry-based cohort study found

an increased risk of subsequent hypertension and type 2 diabetes in women with previous hypertensive disorders of pregnancy (259). A study using register data in Scotland found that women with a history of hypertensive disorders of pregnancy had an increased risk of developing chronic kidney disease and a shorter time to chronic kidney disease compared to normotensive pregnant women (260). Obesity may be a significant confounder in the association between preeclampsia and subsequent end stage renal disease (261). Women with SLE and hypertensive disorders in pregnancy had a three-fold increased risk of future hypertension and a two-fold increased risk of future cardiovascular disease, according to a 2021 Swedish study (262).

1.4.2 Fetal

Fetal morbidity

Defective deep placentation resulting in thrombosis and atherosis of myometrial spiral arteries in preeclampsia can lead to FGR (263). FGR with ultrasound-derived estimated fetal weight < 10^{th} percentile for gestational age has been associated with peripartum complications such as oligohydramnios, non-reassuring fetal heart tracings, low APGAR scores, umbilical artery pH < 7.00, and stillbirth (56, 264). FGR is also associated with adverse neonatal outcomes such as hematologic disorders, hypothermia, apnea, seizures, sepsis and death (56, 265). Abnormal umbilical artery Doppler indices in the setting of FGR is pathognomonic for uteroplacental insufficiency, and absent or reverse end-diastolic flow is highly predictive of perinatal death (264).

Fetal mortality

Severe preeclampsia is associated with a higher risk of IUFD, with approximately 21 stillbirths per 1000 live births compared to the baseline rate of three stillbirths per 1000 live births after 28+0 weeks of gestation (3). A single-center UK study using data from 1987 to 1997 reported a 16% incidence of stillbirth pregnancies complicated by preeclampsia < 30+0 weeks of gestation (266). A population-based Norwegian study found an overall increased risk of IUFD of 5.2 per 1000 pregnancies compared to the population risk of 3.6 per 1000 pregnancies (267). The risk of stillbirth was dramatically higher in pregnancies complicated by early-onset preeclampsia, namely 11.6 stillbirths per 1000 pregnancies with preeclampsia at 26+0 weeks of gestation compared to 0.1% stillbirths per 1000 pregnancies without preeclampsia at the same gestational age (267). Another Norwegian study using MBRN data from 1967 to 2003 found an inverse relationship between labor induction and

stillbirth over time, suggesting that aggressive management of preeclampsia improved intrauterine fetal survival (4).

1.4.3 Neonatal

Neonatal morbidity

A major neonatal complication of preeclampsia is preterm birth (268). Complications of preterm birth include respiratory distress syndrome, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis, sepsis, neurologic complications such as cerebral palsy, intraventricular hemorrhage, hypoxic ischemic encephalopathy, seizures, periventricular leukomalacia, visual and/or hearing impairment, feeding difficulties and death (101).

BPD is a serious chronic lung disease affecting newborns ≥ 36+0 weeks of gestation who still require supplemental oxygen after mechanical ventilation and treatment with high levels of oxygen due to preterm birth (269). Newborns with BPD have decreased lung angiogenic VEGF, disrupted pulmonary vascular growth and abnormal alveolarization, and the pathophysiology of the disease may start in utero (270, 271). It has been hypothesized that fetal hypoxia due to uteroplacental insufficiency from preeclampsia may adversely affect normal fetal angiogenesis in the lung and predispose the neonate to BPD (3). An observational cohort study found that preeclampsia between 24+0 and 31+6 weeks of gestation was associated with development of BPD in preterm neonates (272). BPD risk was present in preeclampsia pregnancies with FGR, but not without FGR (273).

In early-onset severe preeclampsia, neonatal outcomes including birthweight, APGAR score < 7, NICU admission and length-of-stay, common neonatal morbidities including BPD and birth injury were not worse with induction of labor compared to elective cesarean delivery, however vaginal delivery was rarely successful at < 28+0 weeks of gestation (6.7%) (274). Premature birth at < 28+0 weeks of gestation was associated with more favorable neonatal outcomes in babies born to women with preeclampsia compared to women without preeclampsia, but the trend was reversed in deliveries between 32+0 to 33+6 weeks (275). The authors of this study from a US tertiary care hospital postulated that the higher prevalence of FGR in the preeclampsia cohort may have accounted for the more unfavorable neonatal outcomes at 32+0 to 33+6 weeks of gestation (275).

In general, late preterm delivery (34+0 to 36+6 weeks of gestation) is associated with higher neonatal morbidity (276-278) and mortality (276, 277, 279) compared to term infants. Late preterm birth due to preeclampsia is associated with adverse neonatal outcomes such as respiratory distress syndrome, transient tachypnea of the newborn, persistent pulmonary hypertension, and respiratory failure (3). Nonetheless, planned late preterm delivery for hypertensive disorders of pregnancy is still a common obstetrical practice. A US national database study found that a quarter of women with mild gestational hypertension without any maternal or fetal complications underwent iatrogenic late preterm delivery; these deliveries were associated with a higher prevalence of neonatal complications compared to term infants (280).

Preeclampsia has a direct effect on neonatal outcomes beyond complications due to prematurity alone, and statistical modelling suggests increased risk of perinatal mortality, small-for-gestational age, NICU admission and respiratory distress syndrome in infants delivered at term (37 weeks of gestation) to women with preeclampsia (281). Preeclampsia in a prior pregnancy increased the risk of stillbirth, placental abruption, preterm birth and small-for gestational-age infant in a subsequent pregnancy, according to a Swedish cohort study (282).

Overall, adverse newborn and infant outcomes are related to the severity of hypertension disorder of pregnancy. A study using population-based data from California found that mild preeclampsia did not increase the risk of adverse infant outcomes up to one year of age, whereas severe preeclampsia increased the risk (221). Another US study found no difference in perinatal outcomes in infants born to women with mild gestational hypertension or mild preeclampsia compared to normotensive women; severe gestational hypertension was associated with higher rates of preterm delivery and small-for-gestational age infants compared to women with mild preeclampsia (283). Maternal co-morbidities (chronic hypertension, pre-gestational or gestational diabetes, twin pregnancy) in the setting of early-onset severe preeclampsia did not increase the risk of adverse neonatal outcomes compared to severe preeclampsia alone, with the exception of FGR (284).

Neonatal mortality

The higher prevalence of small-for-gestational age infants born to women with preeclampsia may be a contributing factor to perinatal and infant mortality (285). A Dutch study found

higher perinatal mortality (< 28 days) and infant mortality (< 1 year) in neonates born to women with preeclampsia < 32+0 weeks of gestation compared to age-matched controls (285). Increased use of labor induction in Norway has not affected the two-fold increased risk of neonatal death among babies born to mothers with preeclampsia (4).

Long-term complications in offspring

A population-based Danish study of long-term (up to 27 years after delivery) outcomes of offspring exposed in-utero to preeclampsia found increased risk of hospitalization in every year after delivery due a variety of different diseases, including infection and diseases of metabolic, nutritional, hematologic and endocrine origin, in the exposed group born at term compared to the unexposed group (286). Duration of in-utero exposure to both mild and severe preeclampsia is directly associated with long-term (up to 30 years) morbidity of the offspring (287). In contrast, first-trimester pregnancy-induced hypertension improves long-term morbidity and mortality in the offspring (288). Data from Finland links intrauterine growth restriction with the development of type 2 diabetes, stroke and heart disease later in life (289). The association between FGR and adult-onset disease may be due to epigenetic influences by which different physiologic traits develop due to adverse in-utero conditions (289, 290).

1.5 Preeclampsia prevention

1.5.1 Screening methods

Studies have investigated numerous clinical, sonographic, genetic and biochemical markers in an attempt to predict which women will develop preeclampsia. A 2019 umbrella review of 126 systematic reviews encompassing more than 25 million women, over 90 potential predictors and 52 prediction models found that no single marker had a sensitivity and specificity > 90%, however the use of a select combination of markers increased the sensitivity and specificity to > 80% (291). Screening for early-onset preeclampsia has better overall sensitivity and specificity than for late-onset preeclampsia, but the positive predictive value of screening low-risk women is low (10).

In 2013, a new model for 1st-trimester screening of high-risk women was developed using maternal mean arterial pressure (MAP), mean uterine artery pulsatility index (UtA-PI), serum pregnancy-associated plasma protein-A (PAPP-A) and PlGF at 11+0 to 13+6 weeks of gestation with a 96% sensitivity for preeclampsia requiring delivery before 34+0 weeks

of gestation and a false positive rate 10% (292). A 2017 prospective observational study from the ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial using the aforementioned 1st-trimester screening protocol reported 76.7% sensitivity for preterm preeclampsia and 43.1% sensitivity for term preeclampsia, with a screen-positive rate 10.5% and a false positive rate 9.2% (293).

The Fetal Medicine Foundation (FMF) has developed a risk calculator for preeclampsia screening in all three trimesters, using a combination of maternal characteristics, biophysical markers and biochemical markers (so called "triple test"), with a risk cut-off of 1:100 (Figure 7) (294). Screening with maternal characteristics in all three trimesters include age, BMI, race/ethnicity, smoking during pregnancy, ART, history of preeclampsia, diabetes, chronic hypertension, SLE, antiphospholipid syndrome, parity, gestational age and singleton/twin gestations (294). Biophysical markers in all three trimesters include MAP and mean UtA-PI (294). Trimester-specific biochemical markers include the following:

- 1st-trimester (11+0 to 14+1 weeks of gestation): serum PlGF and/or PAPP-A
- 2nd-trimester (19+0 to 24+6 weeks of gestation): serum PlGF and/or sFlt-1
- 3rd-trimester (30+0 to 37+6 weeks of gestation): serum PlGF and/or sFlt-1 (294)

Using the FMF 1st-trimester combined screening algorithm, the number needed to screen to prevent one case of preeclampsia is 143, 250 and 400 at any gestational age, < 37+0 weeks of gestation and < 34+0 weeks of gestation, respectively (295). A 2014 Norwegian study found that the FMF 1st trimester screening algorithm had a sensitivity of 80% (95%CI 28.4-99.5%) for predicting preterm preeclampsia, but performed poorly when predicting preeclampsia at < 42+0 weeks of gestation (sensitivity 40%, 95%CI 19.1-63.9%) (296).

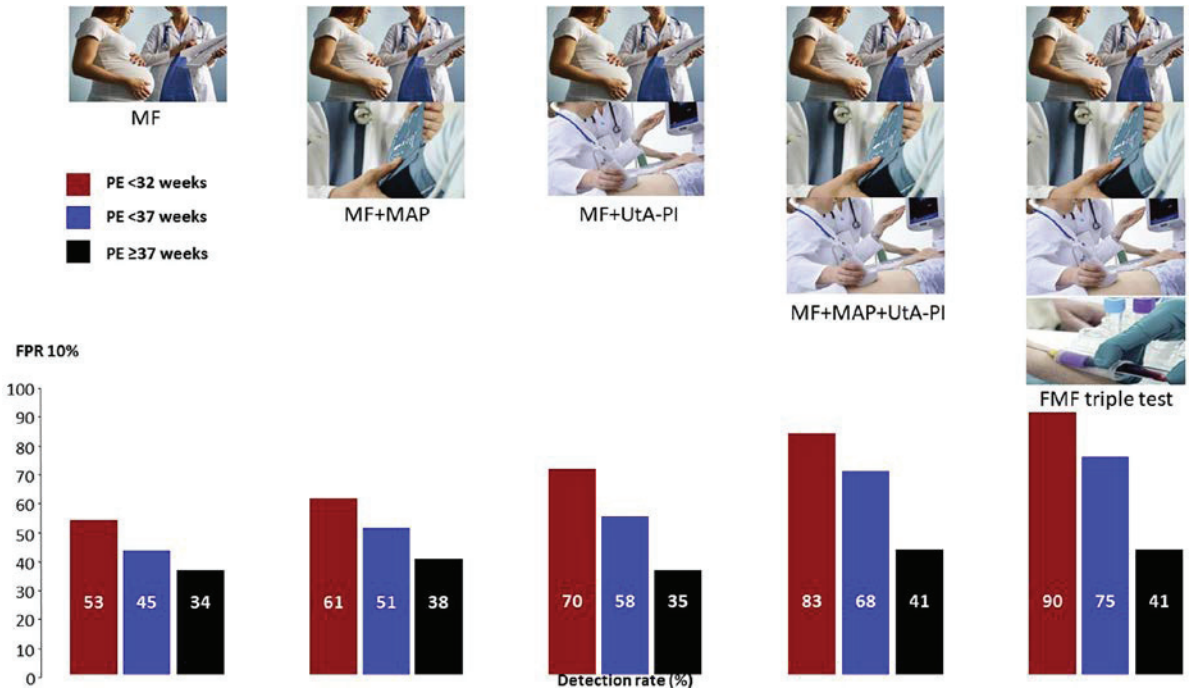


Figure 7. Screening performance of the first trimester FMF prediction model for preeclampsia according to the different combinations at FPR of 10%. Reprinted from *Chaemsaithong P, Sahota DS, Poon LC. First trimester preeclampsia screening and prediction. Am J Obstet Gynecol. 2020 (article in press)* with permission from Elsevier Science & Technology Journals. Screening performance derived from Tan et al.(297).
FMF, Fetal Medicine Foundation; FPR, false-positive rate; MAP, mean arterial pressure; MF, maternal factors; PE, preeclampsia; UtA-PI, uterine artery pulsatility index.

ACOG does not currently endorse routine 1st-trimester screening for preeclampsia using ultrasound and/or biomarkers, citing poor predictive value of these screening modalities (10). Instead, ACOG recommends 1st-trimester screening of women based solely on maternal risk factors for preeclampsia to determine which women should start aspirin for preeclampsia prophylaxis (10). High-risk factors are history of preeclampsia, multifetal gestation, pre-gestational diabetes, chronic hypertension, renal disease and/or autoimmune disease (10). Moderate-risk factors are nulliparity, BMI ≥ 30 kg/m^2, family history of preeclampsia, African-American race, low socioeconomic status, age ≥ 35 years, previous adverse pregnancy outcome including a baby small for gestational age (SGA), and/or inter-pregnancy interval > 10 years (10).

The United States Preventative Services Task Force (USPSTF) recommends 1st-trimester screening for preeclampsia using the same high-risk maternal screening characteristics as ACOG (298), but also recommends screening for preeclampsia using blood pressure measurements throughout pregnancy (299). The UTPSTF does not recommend the use of

predictive models that incorporate serum biomarkers and uterine artery Doppler, as they are considered to have insufficient accuracy for clinical use (298).

In the UK, current National Institute of Health and Care Excellence (NICE) guidelines do not include 1st-trimester screening with ultrasound or biomarkers, but use maternal characteristics, specifically the presence of chronic hypertension, chronic renal disease, pre-gestational diabetes, SLE, antiphospholipid syndrome and/or previous hypertensive disorder in pregnancy (all high-risk factors), maternal age ≥ 40 years, BMI ≥ 35mg/m^2, nulliparity, multifetal pregnancy, pregnancy interval > 10 years and family history of preeclampsia (all moderate-risk factors) to determine eligibility for aspirin intervention (300).

A recent meta-analysis of three randomized controlled studies found that 1st-trimester screening based on NICE or USPSTF guidelines had low sensitivity (8.9-26.4%) and low positive predictive value (14.2-14.6%), but high specificity (91.5-97.2%) and high negative predictive value (95.5-95.8%) for both nulliparous and parous women (301). A 2021 Danish study using observational population-based data to predict preeclampsia using ACOG and NICE 1st-trimester screening criteria reported 61% sensitivity using ACOG criteria and 48% sensitivity using NICE criteria (302). A comparison of screening strategies found superior detection of all preeclampsia and preterm preeclampsia using FMF 1st-trimester combined screening compared to current NICE screening guidelines (303).

FIGO recommends universal 1st-trimester combined screening of all pregnant women, ideally with maternal risk factors, biophysical markers and biochemical markers, but at least with maternal risk factors and MAP (15). Alternatively, but less desirably, contingent screening with UtA-PI and biomarkers can be reserved for at-risk women based on maternal risk factors and blood pressure (15). The ISSHP does not recommend routine screening for preeclampsia with biomarkers PlGF or sFlt-1/PlGF ratio, but does support 1st-trimester combined screening where available for selecting women who may benefit from aspirin prophylaxis 150 mg/day for prevention of preterm preeclampsia (1).

The NGF recognizes the benefit of 1st-trimester combined screening following the FMF's prediction algorithm, but 1st-trimester screening for preterm preeclampsia is not covered by the national insurance scheme for prenatal care (9).

A 2019 randomized trial in the UK found that low PlGF (< 100 pg/ml) in women suspected of having preeclampsia between 20+0 and 36+6 weeks of gestation had a high sensitivity (94.9-96.2%) and high negative predictive value (97.1-98.3%) in diagnosing preeclampsia requiring delivery within 14 days (304). Compared to routine care, PlGF testing significantly reduced the mean time to diagnosis from 4.1 to 1.9 days and significantly reduced severe adverse maternal outcomes by 68% (aOR 0.32, 95%CI 0.11-0.96) with no effect on perinatal adverse outcomes or mean gestational age at delivery (304).

NICE guidelines recommend the use of PlGF or sFlt-1/PlGF ratio from 20+0 to 34+6 weeks of gestation to rule out preeclampsia in women suspected of having the disease (305). In 2020, the Norwegian Institute of Public Health's cost-effectiveness analysis on biomarker testing in the 2nd and 3rd trimester concluded that the estimated 12.4 million kroner annual cost of testing was not justified for use in the national insurance scheme due to insufficient evidence of clinical efficacy and economic benefit (306).

In 2016, a model for 3rd-trimester screening for preeclampsia was developed using a combination of maternal health characteristics, MAP, mean UtA-PI, serum s-Flt-1 and PlGF (so called "triple test") at 35+0 to 36+6 weeks of gestation; the model predicted 84% of preeclampsia compared to 35% using screening by maternal factors alone (307). The same researchers published a prospective observational UK study in 2019 which found that screening for imminent delivery with preeclampsia with the triple test in women 35+0 to 36+6 weeks of gestation had 10% and 20% higher detection rate than using s-Flt-1/PlGF ratio or PlGF alone, respectively (308).

1.5.2 Aspirin prophylaxis

Endothelial prostacyclin production is reduced in preeclampsia, resulting in an imbalance in the normal equilibrium of thromboxane A2 and prostacyclin (309). Thromboxane A2 induces vascular constriction, vascular remodeling, and platelet aggregation and adhesion. Conversely, prostacyclin is a potent vasodilator and inhibitor of vascular remodeling, platelet aggregation and platelet adhesion. Used for the prevention of preeclampsia, aspirin inhibits cyclooxygenase, thus blocking the conversion of arachidonic acid into prostaglandins and causing downstream irreversible decreased synthesis of thromboxane A2 in platelets and the placenta, with little effect on prostacyclin synthesis in endothelial cells (310).

The 2017 landmark randomized controlled ASPRE trial found that prophylactic low-dose aspirin 150 mg/day from 11+0 to 13+6 weeks of gestation until 36+0 weeks of gestation reduced the risk of preterm preeclampsia by 62% in high-risk women based on maternal factors, biophysical findings and biomarkers compared to placebo (OR 0.38, 95%CI 0.20-0.74) (311). A 2018 systematic review and meta-analysis of 16 trials including over 18 000 women found that aspirin reduced the risk of preterm preeclampsia when started ≤ 16+0 weeks of gestation at a dose ≥ 100 mg (312). A 2019 Cochrane review of 77 randomized trials found that aspirin reduced the risk of proteinuric preeclampsia at any gestational age by 18% (RR 0.82, 95%CI 0.77-0.88) with the number needed to treat 61 (95%CI 45-92) (313). Aspirin reduces the risk of small-for-gestational age babies by decreasing the incidence of preeclampsia (313, 314). Aspirin also decreases the risk of premature delivery (313, 315, 316) even in low-risk women without hypertensive disease (317).

Preconception and antenatal low-dose aspirin use is generally safe for women, fetuses and neonates (318), although the Cochrane review found a non-significant increased risk of postpartum hemorrhage (RR 1.06, 95%CI 1.00-1.12) and placental abruption (RR 1.21, 95%CI 0.95-1.54) (313). A 2021 population-based Swedish observational study of over 300 000 women found an increased risk of intrapartum bleeding, postpartum hemorrhage, postpartum hematoma and neonatal intracranial hemorrhage among women with vaginal delivery who self-reported aspirin use at any time during the pregnancy, compared to non-aspirin users (319). Universal aspirin prophylaxis may be a cost-effective alternative to selective intervention, based on a modeling study (320). Aspirin, however, has not been shown to have the same beneficial effect in women with chronic hypertension, although these women are considered high risk using the FMF 1st-trimester combined screening algorithm (321).

Both ACOG (10, 322) and NICE (300) recommend the use of low-dose aspirin for preeclampsia prophylaxis when one or more maternal high-risk factors or two or more maternal moderate-risk factors are present. ACOG recommends the initiation of aspirin 81 mg/day beginning between 12+0 and 28+0 weeks of gestation, and preferably before 16+0 weeks of gestation (10, 322). NICE currently recommends 75-150 mg/day from 12+0 weeks of gestation until delivery (300). Compliance with NICE guidelines was found to be only 23% in a UK study (303). The USPSTF also recommends initiation of aspirin 81

mg/day after 12+0 weeks of gestation in women with at least one high-risk factor (298). The ISSHP recommends initiation of aspirin 75-162 mg/day in high-risk women before 20+0 weeks of gestation, and preferably before 16+0 weeks of gestation (1).

Prenatal low-dose aspirin for preeclampsia prevention in high risk pregnancies, from 12+0 weeks of gestation until delivery (75 mg evening dose) or until 36+0 weeks of gestation (150 mg evening dose), has been a part of standard antenatal care in Norway since 2014 (9, 323). As far back as 1998, aspirin was mentioned in the Norwegian guidelines for preeclampsia prevention in parous women with a previous history of preeclampsia (324). The 2020 Norwegian guidelines are in line with the NICE recommendations (9).

1.5.3 Weight management

High pre-pregnancy BMI, excessive gestational weight gain, and both combined, are associated with a higher risk of hypertensive disorders of pregnancy compared to normal BMI in women with adequate gestational weight gain (137, 325). Findings from a Norwegian study suggest that excessive weight gain seen in preeclampsia may be due to increased total body water and not maternal fat mass or percent body fat (326). Optimal weight gain during pregnancy is inversely proportional to pre-pregnancy BMI, but optimal gestational weight gain is a poor independent predictor of pregnancy outcome (137). Moderately intense physical exercise during pregnancy is associated with a reduced risk of excessive gestational weight gain and may also be inversely related to preeclampsia risk, according to a 2019 umbrella review of 76 systematic reviews and meta-analyses (327). A randomized trial comparing prenatal dietary, exercise and lifestyle advice (intervention) to standard prenatal care (control) in Australia found no difference in adverse maternal or neonatal outcomes, including preeclampsia (328).

A US study found that among women with prior preeclampsia, weight gain > 1 BMI unit between pregnancies increased the risk of recurrent preeclampsia in a dose-response relationship regardless of pre-pregnancy BMI in the first pregnancy (329). Conversely, weight loss > 2 BMI units between pregnancies was associated with a decreased risk of recurrent preeclampsia, but only in women who were overweight or obese in their first pregnancies (329).

1.5.4 Calcium supplements

Low calcium intake is associated with blood pressure elevation due a combination of activation of the renin-angiotensin-aldosterone system, synthesis of calcitriol and stimulation of parathyroid hormone, all which result in increased intracellular calcium concentration in the vascular smooth muscle cell, vasoconstriction and increased peripheral vascular resistance (330). A 2014 systematic review and meta-analysis of observational studies found that low calcium intake was associated with hypertensive diseases of pregnancy (331). In 2017, a systematic review and meta-analysis of 27 randomized controlled trials found that calcium supplementation reduced the risk of preeclampsia by approximately 50% (pooled RR 0.49, 95%CI 0.35-0.69); there was also limited evidence to suggest that vitamin D alone or in combination with calcium may also prevent preeclampsia (332). A 2018 Cochrane review found that calcium supplementation during pregnancy reduces the risk of preeclampsia, especially in populations with low calcium intake and high risk of preeclampsia (333). A 2019 systematic review and meta-analysis of randomized trials found that high (1.2-2.0 g/day), moderate (0.6-1.2 g/day) and low (< 0.6 g/day) dose calcium supplementation was associated with lower preeclampsia risk; high and moderate calcium supplement dosage was also associated with a lower risk of gestational hypertension (334).

The WHO recommends calcium supplementation 1.5-2.0 g/day during pregnancy for all pregnant women for the prevention of preeclampsia in populations with low dietary calcium (70, 335). The 2020 Norwegian guidelines recommend calcium supplementation only for women in Norway with low calcium intake (< 600 mg daily), which is very uncommon (9). A recent randomized control trial performed in South Africa, Zimbabwe and Argentina did not show any effect of calcium supplementation from preconception until 20+0 weeks of gestation in women with previous preeclampsia, which questions the preventive independent effect of calcium supplementation (336).

1.6 Management of preeclampsia and eclampsia

There are no known medical treatments for preeclampsia. Management of preeclampsia is based on maximizing maternal and fetal wellbeing until reaching the optimal time for delivery to reduce the risk of adverse maternal and neonatal outcomes. Blood pressure control and seizure prophylaxis are the main treatment goals (10).

1.6.1 Antihypertensive treatment

Severe hypertension, defined as ≥ 160/110 mmHg, requires treatment to prevent myocardial infarction, congestive heart failure, acute kidney injury and stroke (10). In Norway, blood pressure ≥ 150/100 indicates treatment mainly in order to prevent cerebral hemorrhage (9). Increased use of antihypertensive medications in hospitalized women with preeclampsia has been associated with a decreased incidence of stroke (337). Updated 2021 ISSHP guidelines recommend treatment of severe hypertension with the first-line agents oral nifedipine, oral labetalol, intravenous labetalol, or intravenous hydralazine, with the approach to treatment the same for women with or without co-morbidities associated with hypertension, such as chronic renal disease (338). The recommendations are based on the long clinical tradition of using these antihypertensive agents, and a 2013 Cochrane review found no significant difference between them (339). Oral nifedipine, oral labetotol or oral methyldopa is an inexpensive and effective drug treatment for severe hypertension in low-resource health care settings, although in a randomized control trial in India, oral nifedipine retard had the greatest frequency of blood pressure control compared to the other two medications (340).

Also summarized in the 2021 updated ISSHP guidelines, non-severe hypertension in pregnancy should be treated with the first-line agents oral methyldopa, labetalol, or nifedipine (338). These medications are the most commonly used drugs for blood pressure control, with a treatment goal of ≤ 135/85 mmHg (300), 110-140/80-85 mmHg (1) or < 150/80-100 mmHg (9). In Norway, the treatment goal in women with chronic hypertension is < 140/90 (9). A randomized controlled trial found that non-tight control of diastolic blood pressure (target DBP < 100 mmHg) in women with chronic hypertension did not increase the risk of adverse maternal or neonatal outcomes, but did increase the risk of episodes of severe maternal hypertension compared to women with tight control (target DBP < 85 mmHg), with an aOR 1.80, 95%CI 1.34-2.21 (341). Another study found that women with chronic hypertension randomized to either oral methyldopa or oral nifedipine had similar adverse maternal and neonatal outcomes; these outcomes were significantly lower when compared to women randomized to no antihypertensive medication (342).

1.6.2 Magnesium sulfate

Since 1925, magnesium sulfate (MgSO4) has been used for seizure prophylaxis in the management of preeclampsia (343). In a landmark study published in 1995, intravenous or intramuscular MgSO4 was found to be superior to intravenous phenytoin or intravenous

diazepam for reduction of recurrent seizures in women with eclampsia (249). In addition, there was also a reduced risk of maternal morbidity (mechanical ventilation, pneumonia, ICU admission) and neonatal morbidity (intubation, NICU admission) in pregnancies randomized to MgSO4 compared to phenytoin (249). Seven years later, the Magpie Trial found that MgSO4 reduced the risk of eclampsia (i.e. seizures) by 58% compared to placebo (RR 0.42, 95%CI 0.29-0.60) in women with intrapartum or postpartum preeclampsia (250). A 2010 Cochrane review found that MgSO4 significantly reduced the risk of eclampsia and placental abruption and had a non-significant reduction in maternal mortality, while the risk of Cesarean delivery increased and the risk of stillbirth and neonatal death remained unchanged (344). Dietary magnesium supplementation, however, has not been shown to have any beneficial effect with respect to preeclampsia, perinatal mortality or small-for gestational-age infants (345).

MgSO4 is used for women with gestational hypertension with severe features, preeclampsia with severe features or eclampsia; treatment should be continued during delivery and for 24 hours postpartum (9, 10, 300). Intravenous treatment is preferred over intramuscular treatment when possible due to less pain, fewer side effects and better compliance (250). The optimal dose and plasma concentration of MgSO4 for seizure prophylaxis is not known, but a therapeutic range of 1.8-3.0 mmol/L is considered safe and effective (346). Monitoring of patellar reflexes, urine output, respiratory rate and MgSO4-serum concentration is needed to prevent fatal magnesium toxicity (346).

1.6.3 Antenatal corticosteroids

When the clinical situation necessitates early delivery, antenatal corticosteroids for fetal lung maturity are given when delivery < 34+0 weeks of gestation is indicated or anticipated within one week. Commonly used corticosteroids are betamethasone 12 mg intramuscular injection, 2 doses given 24 hours apart (347, 348) or dexamethasone 6 mg intramuscular injection, 4 doses given 12 hours apart (348). A 2020 Cochrane review found robust evidence for the beneficial use of a single course of antenatal corticosteroids, citing a significant reduction in perinatal death (RR 0.85, 95%CI 0.77-0.93), neonatal death (RR 0.78, 95%CI 0.70-0.87) and respiratory distress syndrome (RR 0.71, 95%CI 0.65-0.78), with no effect on newborn birthweight (349). There was also moderate evidence for reduced risk of neonatal intraventricular hemorrhage and developmental delay (349). Corticosteroids

have probably no significant risk for adverse maternal outcomes such as death, choroamnionitis and endometritis (349).

Corticosteroids have also been used in the treatment of HELLP (69). A 2010 Cochrane review found that although dexamethasone was superior to betamethasone for improving maternal platelet count in HELLP, the use of corticosteroids in the management of HELLP had no clear benefits to maternal or neonatal morbidity or mortality (350). The 2021 ISSHP guidelines are in accordance with this conclusion (338).

1.6.4 Delivery

In the absence of other proven treatments for preeclampsia, delivery is the only option to stop the disease. The Dutch HYPITAT trial published in 2009 found that women with gestational hypertension or mild preeclampsia between 36+0 and 41+0 weeks of gestation randomized to labor induction had a 29% lower risk of a composite adverse maternal outcome (death, eclampsia, HELLP, pulmonary edema, thromboembolism, placental abruption, severe preeclampsia, proteinuria, postpartum hemorrhage) compared to women randomized to expectant management (RR 0.71, 95%CI 0.59-0.86), with no effect on fetal mortality (351).

The 2015 HYPITAT-II trial, which randomized 703 women with non-severe hypertensive disorders of pregnancy between 34+0 and 36+6 weeks of gestation to either immediate delivery (labor induction or cesarean section) or expectant management, found no difference in composite maternal morbidity, but the risk of neonatal respiratory distress syndrome tripled among babies born to mothers in the immediate delivery group (RR 3.3, 95% CI 1.4-8.2) (278). Four years later, the PHOENIX trial found a lower risk of severe maternal hypertension and other adverse maternal outcomes, but a higher risk of NICU admissions (without higher risk of neonatal morbidity) among 901 pregnancies between 34+0 and 36+6 weeks of gestation with preeclampsia or superimposed preeclampsia without persistent severe features randomized to planned delivery compared to expectant management (352). There was a net cost savings for both mother and infant in the planned delivery group (352).

In 2018, a Cochrane review of six trials involving a total of 748 women with severe preeclampsia between 24+0 and 33+6 weeks of gestation found insufficient evidence for comparing risks of adverse maternal outcomes (death, pulmonary edema, HELLP, stroke or

cesarean section) in women randomized to planned delivery versus expectant management (353). However, the Cochrane review found that neonates born to mothers who had planned delivery had higher risks for intraventricular hemorrhage, respiratory distress syndrome, mechanical ventilation, lower gestational age at delivery and longer NICU stays than those born to mothers with expectant management, but they were less likely to have SGA (353). The current recommendation is to offer expectant management of severe preeclampsia < 34+0 weeks of gestation as long as both mother and fetus are clinically stable, with the goal of planned delivery once the pregnancy reaches 34+0 weeks of gestation (1, 9, 10, 300).

Delivery at any gestational age is indicated when there are signs and symptoms of disease progression, such as worsening neurologic symptoms (stroke, eclampsia, persistent headache and/or scotomata), repeated severe hypertensive episodes despite treatment with three antihypertensive medications, pulmonary edema, maternal oxygen saturation < 90%, HELLP, signs of maternal end-organ dysfunction, placental abruption, non-reassuring fetal status (reversed umbilical end-diastolic diastolic flow and/or non-reassuring cardiotocograph) or IUFD (300, 354).

2 AIMS OF THE THESIS

The main aims of this thesis were to assess the prevalence of and the risk factors for hypertensive disorders of pregnancy in Norway over two decades, and to interpret the findings using established models of preeclampsia pathogenesis.

Specifically, the thesis aimed to assess the following:

1. The prevalence of gestational hypertension and preeclampsia among nulliparous and parous women.
2. The association between maternal country of birth and educational level with hypertensive disorders of pregnancy.
3. The prevalence of early, intermediate, and late-onset preeclampsia and gestational hypertension in nulliparous women
4. How maternal diabetes, chronic hypertension and BMI were associated with the risk of early, intermediate, and late-onset preeclampsia and gestational hypertension.
5. How BMI influenced the risk of preeclampsia in pregnancies complicated by maternal diabetes or chronic hypertension.
6. Secular trends of gestational hypertension and preeclampsia over two decades.
7. Changes in clinical practice that may have affected preeclampsia prevalence over time.
8. Interpret the above epidemiologic findings using the revised two-stage model of preeclampsia, the threshold liability model and the competing risk model.

3 MATERIALS AND METHODS

3.1 Data and population

Databases

The data in papers I and II were obtained from the Medical Birth Register of Norway (MBRN) and Statistics Norway (SSB) using a unique identifier such that patient-level data from the two registers were linked. The data in Paper III was obtained from the MBRN. Paper III also used aggregate data from the Norwegian Prescription Database (NorPD).

Medical Birth Register of Norway

Papers I, II and III used data from the MBRN, which has recorded information on all deliveries since 1967. The data is collected by mandatory notification from all hospitals, delivery units as well as home deliveries. MBRN is a massive database that records numerous details of maternal, fetal and obstetric factors related to maternal health before and during pregnancy; intrapartum and postpartum interventions and complications; and neonatal outcomes.

Statistics Norway

Papers I and II obtained data on maternal country of birth and education from SSB. As the national statistical institute of Norway, SSB compiles official socioeconomic, health and population data for the country.

Norwegian Prescription Database

Paper III used aggregate data on aspirin prescriptions from the NorPD. NorPD has collected sex-specific, age-specific, and national, county-level, and regional data on prescription medications since 2004.

Study populations

The study population in Paper I included all singleton pregnancies delivering in Norway between 1999 and 2014 (960 516 deliveries). Multiple gestations, pregnancy outcomes at gestational ages < 23+0 weeks and ≥ 44+0 weeks, and pregnancies with major congenital anomalies were excluded (n = 53 468) resulting in the analysis of 907 048 deliveries.

For Paper II, the study population included all singleton deliveries between 23+0 and 43+6 weeks of gestation by nulliparous women in Norway between 1999 and 2014 (n = 382 618 deliveries). Multiple gestations and pregnancies with major congenital anomalies were excluded.

Paper III studied a population that included all women who delivered a singleton or twin pregnancy between 22+0 and 44+6 week of gestation in Norway between 1999 and 2018 (n = 1 153 227 deliveries).

Table 2: Data source for Papers I-III of the PhD thesis.
MBRN: Medical Birth Register of Norway, SSB: Statistics Norway, NorPD: Norwegian Prescription Database

Main Study Outcome	Population	Source	Design	Study period
Paper I Preeclampsia, Gestational hypertension	960 516 deliveries, nulliparous and parous women	MBRN, SSB	Population-based retrospective cohort	1999-2014
Paper II Preeclampsia, Gestational hypertension	382 618 deliveries, nulliparous women	MBRN, SSB	Population-based retrospective cohort	1999-2014
Paper III Preeclampsia, Gestational hypertension	1 153 227 deliveries	MBRN, NorPD	Population-based retrospective cohort	1999-2018

Independent (exposure) variables and dependent (outcome) variables

Main independent (exposure) variables included

- Maternal socioeconomic characteristics (Paper I)
    - Country of birth
    - Educational level
- Maternal biologic co-morbidities (Paper II)
    - Type 1 diabetes mellitus
    - Type 2 diabetes mellitus
    - Gestational diabetes

- Chronic hypertension
- BMI

- Time period in four-year increments (Paper III)

Secondary exposure variables included

- Consanguinity (Paper I)
- Maternal age (Papers I, II and III)
- Parity (Paper III)
- 1st-trimester smoking (Papers I, II and III)
- Diabetes (Papers I and III)
- Chronic hypertension (Paper III)
- Twin gestation (Paper III)
- ART (Paper III)

Main dependent (outcome) variables in this thesis were

- Preeclampsia (Papers I, II and III)
- Gestational hypertension (Papers I, II and III)

3.2 Definition of variables

Socioeconomic variables

Country of birth

For Papers I and II, maternal country of birth was categorized as one of 11 world regions taking into account political, geographic, economic and cultural characteristics. In all 3 papers, Norway was used as the reference group. European countries other than Norway were grouped into two regions: countries belonging to the European Economic Association plus Switzerland (Europe/EEA), and countries not belonging to the EEA (Europe/non-EEA). Where possible, countries were grouped based on world regions defined by The World Bank, and remaining countries were grouped based on regions defined by SSB. Data on country of birth was obtained from SSB for Papers I and II. For Paper III, data on country of birth was obtained from the MBRN.

The following countries were included in the maternal country of birth variable for Papers I and II:

1. **Norway**
2. **Europe, EEA:** Sweden, Finland, Denmark, Iceland, Cyprus, Bulgaria, Estonia, Croatia, Latvia, Poland, Romania, Lithuania, Slovenia, Hungary, Slovakia, Czech Republic, Belgium, France, Greece, Ireland, Italy, Malta, Netherlands, Liechtenstein, Luxembourg, Portugal, Spain, United Kingdom, Germany, Austria, Switzerland (not actually in the EEA)
3. **Europe, non-EEA**: , Greenland, Faroe Islands, Albania, Belarus, Moldova, Russia, Turkey, Ukraine, Bosnia-Herzegovina, Macedonia, Serbia, Montenegro, Kosovo, Andorra, Gibraltar, Monaco, San Marino, Vatican City State, Guernsey, Jersey, Isle of Man
4. **North America**: Canada, Saint Pierre and Miquelon, United States
5. **Latin American/Caribbean**: United States Virgin Islands, Barbados, Antigua and Barbuda, Belize, Bahamas, Bermuda, British Virgin Islands, Cayman Islands, Costa Rica, Cuba, Dominica, Dominican Republic, Grenada, Guadeloupe, Guatemala, Haiti, Honduras, Jamaica, Martinique, Mexico, Montserrat, Aruba, Sint Maarten, Bonaire, Sint Eustatius and Saba, Anguilla, Curaçao, Nicaragua, Panama, El Salvador, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Trinidad and Tobago, Turks and Caicos Islands, Puerto Rico, Saint Martin, Saint Barthélemy, Argentina, Bolivia, Brazil, Guyana, Chile, Colombia, Ecuador, Falkland Islands, French Guiana, Paraguay, Peru, Suriname, Uruguay, Venezuela
6. **Middle East/North Africa**: Algeria, Egypt, Djibouti, Libya, Morocco, Tunisia, Bahrain, United Arab Emirates, Iraq, Iran, Israel, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Yemen
7. **Sub-Saharan Africa**: Angola, Botswana, Saint Helena, Burundi, Comoros, Benin, Equatorial Guinea, Côte d'Ivoire, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Cameroon, Cape Verde, Kenya, Congo-Brazzaville, Congo, Lesotho, Liberia, Madagascar, Malawi, Mali, Western Sahara, Mauritania, Mauritius, Namibia, Niger, Nigeria, Mozambique, Mayotte, Réunion, Zimbabwe, Rwanda, Sao Tome and Principe, Senegal, Central African Republic, Seychelles, Sierra Leone, Somalia, South Sudan, Sudan, Swaziland, South Africa, Tanzania, Chad, Togo, Uganda, Zambia, Burkina Faso

8. **Transcaucasia/Central Asia**: Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan
9. **South Asia**: British Indian Ocean Territory, Afghanistan, Bangladesh, Bhutan, Sri Lanka, India, Maldives, Nepal, Pakistan
10. **East Asia Pacific**: Brunei, Myanmar, Philippines, Taiwan, Hong Kong, Indonesia, Japan, Cambodia, China, North Korea, South Korea, Laos, Macao, Malaysia, Mongolia, Timor-Leste, Singapore, Thailand, Vietnam, Solomon Islands, Fiji, Vanuatu, Tonga, Kiribati, Tuvalu, Nauru, Federated States of Micronesia, Papua New Guinea, Samoa, Marshall Islands, Palau
11. **Oceania**: American Samoa, Australia, Christmas Island, Cocos (Keeling) Islands, Cook Islands, French Polynesia, Guam, United States Minor Outlying Islands, New Zealand, Niue, Norfolk Island, Pitcairn, Tokelau, Wallis and Futuna Islands, New Caledonia, Northern Mariana Islands

In Paper III, maternal country of birth was dichotomized as Norway or other (all countries except Norway).

Education

Papers I and II included maternal education as an exposure variable. Education was defined as last completed year of school, based on the Norwegian Standard Classification of Education includes Norwegian education codes (nine levels plus one unspecified level) and corresponding codes from the International Standard Classification of Education (ISCED-2011).

For Paper I, education was merged and recoded into four groups: No education to completion of grade 10, which is the end of compulsory education in Norway (none/primary education); completion of grades 11 to 14, which is the end of Norwegian trade school education or university preparatory education (secondary education); completion of grades 15 to 17 corresponding to a lower university degree (higher education – Bachelor); and completion of grades 18 or higher, corresponding to a professional or terminal university degree (highest education – Master/PhD). Secondary education was used as reference group.

For Paper II, education was classified by merging the nine levels of education used in the International Standard Classification of Education (ISCED-2011) into three groups,

according to number of years of completed education. The education variable was categorized as none/primary education (≤ grade 10), secondary education (grades 11 to 14), or higher education ≥ grade 15 (Bachelor, Master or PhD). In Paper II, education was used in the multivariable regression analysis as a possible confounding variable.

Consanguinity

Paper I investigated consanguinity as a possible confounder for risk of hypertensive disorders of pregnancy. Consanguinity was categorized as recorded in the MBRN: None, 1st cousins, distant cousins, other relation and unknown.

Biologic variables

Diabetes

Papers I, II and III included diabetes as an exposure variable. Diabetes was classified into three categories, as provided by MBRN: Type 1 diabetes, type 2 diabetes and gestational diabetes (including diet-controlled and medication-controlled gestational diabetes). No diabetes was used as the reference group. In Norway, information on pre-pregnancy morbidity such as type 1 or 2 diabetes is collected prospectively in the ambulatory prenatal record. Gestational diabetes is recorded both in the prenatal record and in the hospital obstetric database. Mandatory notification to the MBRN occurs immediately after delivery by automatic transfer of midwife and doctor-registered information from the electronic hospital chart.

Norway uses selective screening for gestational diabetes. In Papers I, II and III selective screening for gestational diabetes at 28-30 weeks of gestation was based on risk factors: Family history of type 1 or type 2 diabetes in 1st-degree relative, foreign-born, maternal age > 35 years, BMI > 27 kg/m2. Glycosuria, polyhydramnios, rapid fetal weight gain or random fasting blood glucose between 6.1 mmol/L and 7.0 mmol/L at any time during the pregnancy also prompted screening. Gestational diabetes was defined as a fasting plasma glucose < 7.0 mmol/L and a 2-hour plasma glucose ≥ 7.8 mmol/L and < 11.1 mmol/L after a 75 g oral glucose load.

Chronic hypertension

Papers II and III included chronic hypertension as an exposure variable. Chronic hypertension was defined as a binary variable and excluded hypertension as a complication

of pregnancy, delivery or postpartum. Chronic hypertension was defined as primary or secondary hypertension recorded as a pre-pregnancy diagnosis in the prenatal record.

BMI

Pre-pregnancy BMI in Paper II was categorized using World Health Organization classifications: underweight <18.5 kg/m^2, normal 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, obese ≥30.0 kg/m^2. The MBRN started collecting data on maternal height and weight in 2006. Normal BMI was used as the reference group.

Smoking

1st-trimester smoking is documented in the ambulatory prenatal record and recorded in the MBRN. In Papers I and II, 1st-trimester smoking was coded as no, sometimes and daily, with missing data on smoking status (16% of deliveries) merged into the "no" category. In Paper III, missing data on 1st-trimester smoking was reported as a separate category.

Age

In Papers I and II, maternal age was categorized into four groups: < 20, 20-34, 35-39 and ≥ 40 years. In Paper III, maternal age was categorized into six groups: < 20, 20-24, 25-29, 30-34, 35-39 and ≥ 40 years.

Obstetric variables

Parity

In all three Papers, parity was defined as nulliparous (para 0), primiparous (para 1), parous (para ≥ 1) or multiparous (para ≥ 2). Parity was determined based antenatal history of the affected pregnancy. As such, a woman who delivered her first-born during the study was thus categorized as nulliparous (para 0), whereas a woman delivering her second-born was categorized as primiparous (para 1).

In Paper I, the data were stratified by parity during the affected pregnancy; nulliparous (para 0) and parous (para ≥ 1) women were analyzed separately. Paper II included data on nulliparous women only. Parity was categorized as 0, 1 and ≥ 2 in Paper III.

Assisted reproductive technology

ART was a yes/no variable in Paper III and included, as defined by the MBRN, in-vitro fertilization, intracytoplasmic sperm injection and other technologies.

Twin gestation

Twin gestation was defined as a binary variable in Paper III without regard to chorionicity.

Labor induction

In Paper III, labor induction was studied as a possible explanation for changes in preeclampsia prevalence over time. Induction of labor included amniotomy, oxytocin, prostaglandins or other mechanical methods such as foley catheter used to ripen the cervix and/or start uterine contractions. Labor induction was reported as a binary yes/no variable.

Aspirin

In Paper III, aspirin was studied as a possible explanation for secular changes in preeclampsia prevalence. Population-based data on aspirin use among women aged 15-49 years were taken from NorPD, using the Anatomic Therapeutic Chemical code B01A C06 for acetylsalicylic acid 75 mg, the dose recommended in Norway during the study period for preeclampsia prevention in high-risk women. Only aggregate data was available, reported as use per 1000 women.

Outcome variables

Preeclampsia

In Papers I, II and III, preeclampsia was defined using MBRN's narrow definition of preeclampsia: De novo hypertension after 20+0 weeks of gestation with systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg along with proteinuria ≥ 0.3 g/24 hours or PCr > 0.3 or ≥ 1+ on urine dipstick with a minimum of two measurements (355). Eclampsia is in MBRN defined as generalized seizures occurring antepartum, intrapartum or within the first seven days postpartum with concomitant preeclampsia or gestational hypertension and excluding any other neurologic etiology. Women coded as HELLP and/or eclampsia in the MBRN were merged into the preeclampsia group for the analyses in Papers I, II and III.

Gestational hypertension

Gestational hypertension is in MBRN defined as repeatedly confirmed de novo blood pressure elevation (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) after 20+0 weeks of gestation in the absence of proteinuria, or unspecified maternal hypertension not diagnosed as chronic hypertension, preeclampsia, eclampsia or HELLP syndrome. Papers I and II used MBRN's definition of gestational hypertension.

3.3 Statistics

Continuous data were dichotomized or categorized. Descriptive statistics were performed to identify the prevalence of hypertensive disorders of pregnancy according to maternal characteristics (Papers I, II and III), gestational age at delivery (Papers II and III) and use of labor induction (Paper III). Logistic regression was performed to estimate the crude odds ratios (OR) with 95% confidence intervals (CI) of preeclampsia (Papers I, II and III) and gestational hypertension (Papers I and II). Statistical significance was defined as a p-value of < 0.05.

Paper I applied multivariable regression to assess the independent association of country of birth to preeclampsia and gestational hypertension. Women born in Norway were used as the reference group, and adjustments were made for education, maternal age, consanguinity, diabetes and smoking status. The independent association of education to preeclampsia and gestational hypertension was also explored, using women with a secondary education as the reference group, and adjusting for differences in the above variables. The data were stratified by parity during the affected pregnancy; nulliparous (para 0) and parous (para 1 or more) women were analyzed separately, due to their different associations with hypertensive disorders of pregnancy. IBM SPSS (Statistical Program of Social Sciences) Statistics for Windows version 23.0.0.2 (Chicago, IL) was used for the analyses.

In Paper II, the data were stratified by gestational age at delivery: early (23+0 to 33+6 weeks), intermediate (34+0 to 36+6 weeks) and late (37+0 to 43+6 weeks). Multivariable regression analysis was used to assess the independent association of diabetes to preeclampsia and gestational hypertension, using women without diabetes as the reference group. In model 1, adjustments were made for maternal age, country of birth, education, and smoking status. BMI was added to the analysis in model 2. The independent association of chronic hypertension to preeclampsia was also explored with both models, using women

without chronic hypertension as the reference group and adjusting for possible confounders (model: maternal age, country of birth, education, smoking status, diabetes), model 2: model 1 and BMI). IBM SPSS (Statistical Program of Social Sciences) Statistics for Windows version 23.0.0.2 (Chicago, IL) was used for the analyses.

Multivariable logistic regression was used in Paper III, to assess the independent association of time periods (four-year increments) to preeclampsia, with women delivering in 1999-2002 as the reference group. Adjustments were made for maternal age, parity, twin gestation, ART, country of birth, diabetes, chronic hypertension and 1st-trimester smoking. IBM SPSS (Statistical Program of Social Sciences) Statistics for Windows version 26.0.0.0 (Chicago, IL) was used for the analyses.

3.4 Ethical considerations

This study is part of the larger PURPLE Study, which investigates adverse pregnancy outcomes in Norway from 1967 to 2018 using data from the MBRN and SSB. The study was approved by The Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (#2015/681) and the Institutional Personal Data Officer at Oslo University Hospital. Patient consent was not required for the use of de-identified and anonymized registry data. Aggregate data from NorPD is publically available at www.norpd.no.

4 SUMMARY OF RESULTS

4.1 Paper I

Prevalence of hypertensive disorders of pregnancy

In the study group, 382 618 deliveries were to nulliparous women and 524 430 deliveries were to parous women. Of the 907 048 deliveries, 5.2% of deliveries were affected by hypertensive disorders of pregnancy. The overall prevalence of preeclampsia and gestational hypertension were 3.4% and 1.8%, respectively. Hypertensive disorders of pregnancy were almost two-fold higher among nulliparous than parous women (7.2% vs 3.7%). The prevalence of preeclampsia was 5.0% in nulliparous women and 2.3% in parous women. Gestational hypertension was present in 2.2% of nulliparous deliveries and 1.4% of parous deliveries. The difference in preeclampsia prevalence from nulliparous to parous women was greater than the difference in gestational hypertension prevalence between these parity groups.

Preeclampsia

A significant association between maternal country of birth and education (exposure variables) and preeclampsia (outcome variable) was observed in the crude regression analyses for both nulliparous and parous women. In the multivariable regression analyses, with all the significant variables included, the risk factors and associations remained almost unchanged. Compared to primiparous women (para 1), the adjusted risk for preeclampsia was significantly lower for multiparous women (para ≥2).

Association of country of birth with preeclampsia

Compared to nulliparous women born in Norway, the risk of preeclampsia was significantly lower for nulliparous women born in EEA, non-EEA, Middle East/North Africa, Transcaucasia/Central Asia, South Asia and East Asia Pacific. Nulliparous women born in North America, Caribbean/Latin America, Sub-Sahara Africa, and Oceania had similar risks of preeclampsia compared to nulliparous women born in Norway.

Parous women born in EEA, non-EEA, North America, Middle East/North Africa, South Asia and East Asia Pacific had a significantly lower risk of PE compared to parous women born in Norway. Parous women born in Caribbean/Latin America, Sub-Sahara Africa, Transcaucasia/Central Asia, and Oceania had similar risks for preeclampsia compared to

parous women born in Norway.

After adjusting for education, consanguinity, age, diabetes and 1st-trimester smoking, the risk for preeclampsia remained essentially unchanged among both nulliparous and parous women, except that parous women born in Latin American/Caribbean also had a significantly lower risk of preeclampsia.

Association of education with preeclampsia

Nulliparous women with low education (none/primary) had a lower risk of preeclampsia in the crude analysis (OR 0.91, 95%CI 0.87-0.95), but there was no increased or decreased risk of preeclampsia compared to nulliparous women with secondary education after adjusting for education, consanguinity, age, diabetes and 1st-trimester smoking (aOR 0.97, 95%CI 0.92-1.01). High education (Bachelor or Master/PhD) among nulliparous women significantly reduced the risk for preeclampsia, compared to nulliparous women with secondary education, even after adjusting for possible confounders.

Parous women with low education (none/primary) had no increased risk of preeclampsia compared to parous women with secondary education both in the crude analysis and after adjusting for education, consanguinity, age, diabetes and 1st-trimester smoking (aOR 1.04, 95%CI 0.99-1.10). The risk of preeclampsia was significantly lower among parous women higher education (Bachelor or Master/PhD) compared to parous women with secondary education, and risks remained essentially unchanged after adjusting for possible confounders.

Gestational hypertension

A significant association between maternal country of birth and education (exposure variables) and gestational hypertension (outcome variable) was observed in the crude regression analyses for both nulliparous and parous women.

Association of country of birth with gestational hypertension

Compared to nulliparous women born in Norway, the risk of gestational hypertension was significantly lower for nulliparous women born in EEA, non-EEA, Latin America/Caribbean, Middle East/North Africa, Sub-Saharan Africa, South Asia and East Asia Pacific. Nulliparous women both in North America, Transcaucasia/Central Asia and

Oceania had similar risks of gestational hypertension compared to nulliparous women born in Norway.

Compared to parous women born in Norway, the risk of gestational hypertension was significantly lower for women born in EEA, non-EEA, Latin American/Caribbean, Middle East/North Africa, Sub-Saharan Africa, South Asia and East Asia Pacific. Parous women born in North America, Transcaucasia/Central Asia and Oceania has similar risks of gestational hypertension compared to parous women born in Norway.

The risks did not change significantly even when adjusted for parity, education, consanguinity, age, diabetes and 1st-smoking status, regardless of parity.

Association of education with gestational hypertension

Compared to nulliparous women with a secondary education, nulliparous women with no or only primary education had lower risk for gestational hypertension even after adjusting for education, consanguinity, age, diabetes and 1st-trimester smoking (aOR 0.89, 95%CI 0.82-0.96). However, the risk for gestational hypertension was slightly higher among nulliparous women with a Bachelor (aOR 1.07, 95%CI 1.02-1.13) or Master/PhD (aOR 1.14, 95%CI 1.07-1.22).

Compared to parous women with secondary education, parous women with low education (none/primary) had no increased risk for gestational hypertension after adjusting for education, consanguinity, age, diabetes and 1st-trimester smoking (aOR 0.94, 95%CI 0.87-1.01). Parous women with Bachelor had similar risk (aOR 0.95, 95%CI 0.90-1.00) and women with Master/PhD had decreased risk for gestational hypertension (aOR 0.82, 95%CI 0.75-0.89) compared with parous women with secondary education.

4.2 Paper II

Prevalence and risk indicators of hypertensive disorders of pregnancy

Paper II assessed nulliparous women only, based on gestational age group at delivery. Of the 382 618 singleton deliveries in the study population, 5.0% were affected by preeclampsia and 2.2% were affected by gestational hypertension. Three quarters (76%) of the preeclampsia deliveries were at 37+0 to 43+6 weeks of gestation (late-onset), whereas 14% were at 34+0 to 36+6 weeks (intermediate-onset) and 10% were at 23+0 to 33+6

weeks (early-onset). Although the overall prevalence of early-onset preeclampsia was more than seven times lower than late-onset disease (0.5% vs. 3.8%), the prevalence of preeclampsia among early-onset deliveries was almost seven-fold higher than among deliveries at term; 28.0% vs. 4.1%. Preeclampsia was similarly much more common among deliveries at 34+0 to 36+6 weeks of gestation than among term deliveries; 16.1% vs. 4.1%. Superimposed preeclampsia developed in 23% of women with chronic hypertension. Most of these delivered at term (13.2%), whereas 4.9% delivered at early and intermediate gestational ages, respectively.

The prevalence of gestational hypertension was relatively stable across the three predefined gestational age groups (2.1-2.7%). The majority (93.0%) of the women with gestational hypertension delivered at term.

Approximately 2% of the women in the study had any form of diabetes and 0.5% had chronic hypertension. One third of the women with recorded pre-pregnancy BMI were either overweight (20.0%) or obese (10.5%).

Preeclampsia

Association of diabetes with preeclampsia

Positive significant associations between pre-gestational diabetes and early, intermediate and late-onset preeclampsia were observed in the crude regression analysis, compared to women without diabetes. In model 1 of the multivariable regression analysis, which included adjustment for maternal age, country of birth, education, 1st-trimester smoking and chronic hypertension (model 1), the association between pre-gestational diabetes and preeclampsia remained almost unchanged for all gestational age groups, with the largest magnitude of risk in the type I diabetes group for intermediate preeclampsia (aOR 10.2, 95%CI 8.5-12.3). Adding adjustment for pre-pregnancy BMI (model 2) did not significantly alter the associations. The number of women with reported pre-pregnancy BMI was too small to measure the association between type 2 diabetes and early or intermediate preeclampsia (both $n \leq 5$).

There was no association between gestational diabetes and early-onset preeclampsia in the univariate and both multivariable regression models. Gestational diabetes mellitus was significantly associated with an intermediate and late-onset preeclampsia in the crude

regression analysis with an approximately doubling of risk compared to women without diabetes. The association remained essentially unchanged after adjusting for maternal age, country of birth, education, 1st-trimester smoking and chronic hypertension (model 1). After additional adjustment for pre-pregnancy BMI (model 2) in the multivariable regression, the association between gestational diabetes and late-onset preeclampsia was still present, but significantly reduced (model 1: aOR 1.84, 95%CI 1.65-2.06 vs model 2: aOR 1.24, 95%CI 1.02-1.51).

Association of chronic hypertension with superimposed preeclampsia

Compared to normotensive women, women with chronic hypertension had a 10-fold increased risk of early preeclampsia (OR 10.37, 95%CI 8.37-12.85), eight-fold increased risk of intermediate preeclampsia (OR 7.50, 95%CI 6.06-9.28), and a four-fold increased risk of late preeclampsia (OR 3.85, 95%CI 3.36-4.41). The adjusted risk for preeclampsia in all gestational age groups remained high after adjusting for other possible risk factors (model 1: maternal age, country of birth, education, 1st-trimester smoking, diabetes), including pre-pregnancy BMI (model 2).

Association of BMI with preeclampsia

Compared to normal weight women, women with overweight or obesity had an increased risk of preeclampsia across all gestational age groups. The risks remained essentially unchanged after adjusting for maternal age, diabetes, chronic hypertension, country of birth, education and 1st-trimester smoking. The risk for preeclampsia was highest in early-onset preeclampsia; the risk doubled among women with overweight (aOR 2.22, 95%CI 1.73-2.84) and tripled among women with obesity (aOR 3.20, 95%CI 2.44-4.21).

Gestational hypertension

Association of diabetes with gestational hypertension

A positive significant association between all diabetes types and gestational hypertension (approximately a doubling of risk) was observed in the crude regression analysis, and these associations remained mostly unchanged in model 1 of the multivariable regression analysis after adjustment for maternal age, country of birth, education and 1st-trimester smoking. After additionally adjusting for pre-pregnancy BMI in model 2, there was no longer an increased risk of gestational hypertension among women with type 1 diabetes (model 2: aOR 1.24, 95%CI 0.66-2.34) or type 2 diabetes (model 2: aOR 0.82, 95%CI 0.30-2.24),

whereas gestational diabetes remained a small, but significant, risk factor (model 2: aOR 1.38, 95%CI 1.08-1.77).

Association of BMI with gestational hypertension

Compared to normal weight women, there was an increased risk of gestational hypertension women with overweight (OR 1.89, 95%CI 1.67-2.14) or obesity (OR 4.05, 95%CI 3.58-4.57). The risk remained essentially unchanged after adjusting for maternal age, diabetes, country of birth, education and 1st-trimester smoking.

4.3 Paper III

Prevalence and risk indicators of preeclampsia

Paper III assessed time trends in preeclampsia prevalence. Of the 1 153 227 deliveries in the study population, 3.4% (n = 39 165) were affected by preeclampsia and 1.7% (n = 19 937) were affected by gestational hypertension. Preeclampsia prevalence consistently decreased in all subgroups over time. The prevalence of preeclampsia was highest in the first time period in 1999-2002 (4.3%, 95%CI 4.23-4.44) with decreasing prevalence across successive time periods to 2.7% (95%CI 2.62-2.75) in 2015-2018.

Crude and adjusted odds ratios for preeclampsia in all five time periods showed a decreasing secular trend in preeclampsia risk. After adjustment for risk factors for preeclampsia (maternal age, parity, twin pregnancy, ART, country of birth, diabetes, chronic hypertension and 1st-smoking), a 44% decrease in the risk of preeclampsia (aOR 0.56, 95%CI 0.54-0.58) was observed in 2015-2018 compared to 1999-2002. This adjustment only slightly changed the OR from the univariate analysis (OR 0.61, 95%CI 0.59-0.63), suggesting that the alterations of these risk factors over time did not explain the reduction in preeclampsia prevalence.

Overall, the proportion of women with known risk factors for preeclampsia increased during the study. Giving birth at advanced age (≥ 35 years) increased over the study period from 14.5% in 1999-2002 to 20.4% in 2014-2018. The proportion of nulliparous women increased, and women with higher parity decreased. The prevalence of type 2 and gestational diabetes increased. Use of assisted reproduction increased, while 1st-trimester smoking decreased by 80% between the first and last time periods. Labor induction more than doubled in the study population from 1999-2002 (10.9%) to 2015-2018 (22.2%).

Maternal age

Preeclampsia prevalence reduced in all maternal age groups. Among women ≥ 35 years old, preeclampsia decreased 30% from 4.2% at the start to 2.9% at the end of the study period.

Parity

Preeclampsia prevalence declined 38% in nulliparous women (6.4% in 1999-2002 versus 4.0% in 2015-2018). There was a 43% decrease in preeclampsia among primiparous women (3.0 % in 1999-2002 versus 1.7% in 2015-2018) and a 37% decrease in multiparous women (2.7% in 1999-2002 versus 1.7% in 2015-2018).

Gestational age

Decreased prevalence of preeclampsia in both term and preterm deliveries over time was observed, with the highest prevalence in time period 1999-2002 (gestational age 22+0 to 33+6 weeks: 21.1%, 34+0 to 36+6 weeks: 14.8%, 37+0 to 44+6 weeks: 3.5%) and the lowest prevalence in time period 2015-2018 (gestational age 22+0 to 33+6 weeks: 17.7%, 34+0 to 36+6 weeks: 11.6%, 37+0 to 44+6 weeks: 2.1%).

Multiple gestation and assisted reproduction

The prevalence of preeclampsia decreased by approximately one-third among women with twin gestations (13.6% versus 9.1%) and women with singleton pregnancies (4.1% versus 2.6%) over the study period. There was a similar reduction in preeclampsia prevalence among women with pregnancies resulting from assisted reproduction (7.9% versus 5.2%).

Maternal chronic diseases

Type 2 diabetes remained low and stable during the study period. Type 2 diabetes doubled during the study period from 0.2% to 0.4%. Preeclampsia prevalence among women with type 1 or type 2 diabetes was reduced from the first to the last time period by 35% and 45%, respectively. Gestational diabetes increased five-fold from 0.8% at the study start to 4.9% at the study end, but in these women, the prevalence of preeclampsia was reduced by 52% over time. The prevalence of chronic hypertension was low during all study periods (< 1%), and preeclampsia among women with chronic hypertension decreased 31% throughout the study period, from 21.4% in 1999-2002 to 14.8% in 2015-2018.

Socioeconomic risk factors

The proportion of foreign-born women giving birth in Norway almost doubled during the study period (16.5% in 1999-2002 versus 30.2% in 2015-2018). The prevalence of preeclampsia decreased among both Norwegian-born and immigrant women, by 36% and 39%, respectively. There was a decreasing trend of preeclampsia prevalence among both smokers and non-smokers during the study period, as well as among women with missing data for smoking.

Aspirin

Aggregated data from NorPD showed an increase in aspirin prescriptions among women younger than 40 years old from 2004 to 2018. In 15-19 year-old women, a 146% increase in aspirin prescriptions from 2004 (0.35 per 1000 women) to 2018 (0.86 per 1000 women) was observed. Aspirin prescriptions increased by 65%, 80%, 70% and 29% among women 20-24, 25-29, 30-34, and 35-39 years old, respectively.

Gestational hypertension

Gestational hypertension prevalence had a transient increase from 1.5% (95%CI 1.42-1.52) in 1999-2002 to 2.0% (95%CI 1.90-2.01) in 2007-2010, and then progressively decreased to 1.6% (95%CI 1.55-1.65) in 2015-2018 for a net increase of 6.7% over the study period.

5 DISCUSSION

5.1 Methodology

5.1.1 Study population and design

Study population

The population for this thesis was selected from the MBRN. With few exceptions, the thesis included all women who gave birth in Norway during the study period. All three Papers excluded women with deliveries at the extremes of gestational age with the rationale that extremely early deliveries were mostly incompatible with viability and that extremely late deliveries were most likely due to errors in recording of the correct gestational age at delivery. Papers I and II excluded women with major congenital anomalies and/or multiple gestations in order to eliminate possible confounding effects of the fetus or increased placental mass on the observed association between maternal risk factors and preeclampsia or gestational hypertension. Paper II excluded also parous women, thus focusing the study on nulliparous women delivering at different gestational age groups. Preeclampsia is more prevalent among nulliparous women than parous women, as reported in Paper I. Paper III excluded women with higher order gestations > 2 (i.e. triplets and more), with the thought that these pregnancies are often delivered prematurely and before preeclampsia has time to develop. Exclusion criteria were carefully considered in this thesis in order to select a study population that was most representative of the true population.

Study design

This thesis was an epidemiological study using a population-based retrospective (historical) cohort to achieve the main research aims. Epidemiology is the study of the determinants and patterns of disease and other health-related conditions in a selected population. The goal of epidemiology is to gain a better understanding of diseases or other health conditions in a population and identify interventions can improve health outcomes. A doctor uses her knowledge of anatomy, physiology and pathophysiology to diagnose and treat a disease, but also relies on her understanding of the epidemiology of the disease in order to assess risk, order tests, choose treatment options, predict treatment outcome, tailor patient education and decide the extent and level of follow-up. Public health interventions, health communication, research funding, healthcare policy and clinical guidelines are often based on results and conclusions from epidemiological research.

Epidemiologic research is conducted with either experimental or observational studies. Experimental clinical studies, such as randomized controlled trials, are used to study the effects (outcomes) of an intervention. The study design attempts to reduce the amount of variation between the intervention and control groups to maximize the validity of the study outcome. Experimental studies can be used when an acceptable intervention can be offered to the participant, such as the use (or not) of a medication, a procedure or counseling. Experimental studies must also meet ethical standards for research to minimize the risk of harm to the participant. The major advantage of experimental trials is the ability to infer causation; baseline randomization creates a scenario where, in theory, the only difference between the two groups is the intervention itself (356).

In observational studies, data (exposures and outcomes) in the study population are collected without any intervention on the study participants from the researcher. Observational studies are further subdivided into cohort studies, case-control studies and cross-sectional studies.

Prospective cohort studies start by identifying exposed and un-exposed groups, and then assess for diseases or other health-related outcomes after a period of time. Advantages to prospective cohort studies are minimal recall bias due to exposure data collected at the start of the study, and the ability to estimate the population at risk for disease by comparing exposed and non-exposed groups. These cohort studies usually require data from large populations, take years to conduct, and study results could be biased if many participants are lost to follow-up (357). Examples of large prospective observational studies in Norway are the Trøndelag Health study (HUNT) (358) and the Norwegian Mother, Father and Child Cohort Study (MoBa) (359).

Retrospective (historical) cohort studies, such as used in this thesis, are similar to prospective cohort studies, but the "historic" nature of the study design saves time and money by using already collected individual-level data on exposures and outcomes (360). Retrospective cohort studies often use data from established patient databases or health registers not specifically designed for research. Register-based studies, such as in this thesis, have a number of advantages, namely the use of available data of a complete population independently collected over time (360). Retrospective cohort studies, including register-based studies, have some weaknesses. Missing or inaccurate data, lack of data about

relevant potential confounding exposures, and changes in criteria used to define variables can introduce information bias and affect study outcomes (360, 361).

Case-control studies start by identifying people with the disease ("case") and comparing them to people without the disease ("control"), usually matched by age and sex. Pre-defined exposure history is then assessed in both groups. Case-control studies have a high risk of recall bias and cannot estimate the population at risk for the disease, in terms of incidence or prevalence (362). Cross-sectional studies, often in the form of surveys or questionnaires, describe exposure and outcome prevalence at a single point in time, but cannot assess association between exposure and outcome (363). Since the main focus of the thesis was estimating the association between risk factors (exposures) and preeclampsia or gestational hypertension (outcomes) *and* describing prevalence of both risk factors and the diseases in the study population, a cohort study was used.

A major weakness of observational studies is the general inability of these studies to establish a direct cause-and-effect relationship between the exposure and outcome. Nonetheless, the seminal writings of Sir Austin Bradford Hill (364) on causal association has given researchers a framework by which to infer causation from observational studies when experimental studies cannot be performed. Many commonly known causes of diseases – for example, smoking as a cause of lung cancer, contaminated water as a cause of cholera, thalidomide as a cause of birth defects – were established based on observational studies. Observational studies have led to life-saving public health initiatives and changes in medical management. Not uncommonly in obstetrics, experimental studies are challenging for studying the relationship between an exposure and an outcome, and thus observational studies are often used. In this thesis, the biologic and socioeconomic risk factors (exposures) studied were more amenable to an observational study than an experimental one. The observational design of this thesis allowed for the estimation of association, i.e. "risk", between women's socioeconomic and health status and the development of hypertensive disorders of pregnancy. An understanding of "risk" in the absence of causation is still immensely important, as it can influence clinical management, direct further research and inform healthcare policy.

Statistical methods

In this thesis, "risk" was reported as the odds ratio (OR). Odds ratios are used to compare outcomes in two groups, and they measure the strength of association between the exposure and the outcome (365). Odds ratios are used to report results in case-control studies and observational cohort studies where the outcome is dichotomous and logistic regression is used (366, 367). "Odds" is defined as the probability that an outcome (disease) will occur divided by the probability that the outcome (disease) will not occur. The odds ratio is the odds of an outcome (disease) occurring in the exposed group divided by the odds of an outcome (disease) occurring in the unexposed group.

An example of the OR is described in the 2 x 2 contingency table below, using type 1 diabetes as the exposure/risk factor and preeclampsia as the outcome/disease:

	DISEASE **OUTCOME** Preeclampsia	**NO DISEASE** **NO OUTCOME** No preeclampsia
EXPOSURE **RISK FACTOR** Type 1 diabetes	a	b
NO EXPOSURE **NO RISK FACTOR** No Type 1 diabetes	c	d

Odds of preeclampsia in women with type 1 diabetes = a/b
Odds of preeclampsia in women without type 1 diabetes = c/d

$$\text{Odds ratio (OR)} = \frac{\text{odds of preeclampsia in women with type 1 diabetes}}{\text{odds of preeclampsia in women without type 1 diabetes}}$$

Odds ratio (OR) = (a/b) / (c/d) = ad/bc

Logistic regression was used in this thesis to calculate the OR, and the results were reported along with a 95% confidence interval (CI). The confidence interval gives a range in which there is a high probability (95%) that the "true" OR is found, if multiple, independent random samples were taken from the total (infinite) population and confidence intervals where calculated from each of the samples (368). The use of 95% is actually arbitrary, but it is commonly used for confidence intervals in the medical literature (365, 368). In general,

the larger the sample size, the smaller the confidence interval and the greater the certainty (precision) that the observed OR is close to the true OR. In this thesis, using population-based data with large sample sizes resulted in generally narrow confidence intervals. However, in some analyses where the sample size was smaller, the confidence intervals were larger, resulting in a lower level of precision of the estimated effect. This was seen particularly in model 2 of the univariate and multivariable regressions in Paper II, due to fewer women with available data for BMI.

Logistic regression was used to assess the relationship between exposure(s) and one dichotomous outcome variable, in this thesis either preeclampsia (yes/no) or gestational hypertension (yes/no). Univariate logistic regression investigated how a single risk factor was related to either preeclampsia or gestational hypertension all three Papers. Multivariable logistic regression was used in all three Papers to investigate how multiple risk factors occurring at the same time were related to either preeclampsia or gestational hypertension; this approach allows for the assessment of the independent association of each risk factor to each outcome while adjusting for the other risk factors as possible confounders (369). The multivariable regression was reported as the "adjusted" odds ratio (aOR), which is the OR for each individual risk factor while simultaneously holding all other risk factors constant (367).

5.1.2 Consideration of bias

Bias is a systematic error in the design, conduct or analysis of a study that results in an inaccurate estimate of the association between an exposure (risk factor) and an outcome (disease) that threatens the validity of the study (370). The problem with bias is that it cannot be fixed and the study is flawed. The three major types of bias are selection bias (errors in how participants are selected for a study), information bias (errors in collection of data), and confounding (errors in measurement of association).

Selection bias is a faulty method of participant selection for a study that results in a distortion of the exposure-outcome relationship from that which is actually present in the target population. In population-based studies, participants are sampled from an entire population that shares a common demographic, such as age, gender, geography, profession, or health status. Not all population-based studies include the entire population, however, and these studies are at risk of selection bias when selecting and enrolling participants. A

common selection bias in prospective population-based cohort studies, is the disproportionate enrolment of high-income, well-educated, predominantly healthier participants compared to the general population the study population is supposed to represent (371). Participant drop-out or lost to follow-up can also create selection bias, if those no longer in the study cohort are due to reasons that effect both exposure and outcome (372).

The MBRN database records pregnancy and delivery outcomes from the entire population of Norway, so there really is no significant participant drop-out or loss to follow-up. By studying essentially the entire population of pregnant women in Norway in this thesis, all three Papers were comprised of study populations that adequately represented the "true" population. The Papers had, therefore, very low risk of selection bias. In this thesis, women with deliveries < 23+0 weeks of gestation (Papers I and II) and < 22+0 weeks of gestation (Paper III), were excluded in the study group despite studies showing a positive association between hypertensive disorders of pregnancy and periviable deliveries (373-375). Gestational age at delivery was used to define, or limit, the scope of the study population in Papers I and III; in Paper II, gestational age groups were used to stratify the analysis.

Information bias occurs when data is collected differently, inadequately, or incorrectly in the exposed and unexposed groups, leading to an error in the estimation of association between exposure and outcome (370). There are different subtypes of information bias, such as recall bias, end digit preference bias, apprehension bias, family information bias, expectation bias and reporting bias, but the result is always the same: Information on exposures, outcomes and/or confounders is somehow flawed (370, 376). Information bias can occur because of wrongful reporting of subjective data from a study participant, for example weight or alcohol consumption; incomplete or inaccurate data extracted from medical records, questionnaires or interviews; non-standardized collection of data; erroneous classification of exposure or outcome based on prior knowledge or assumptions; or mistakes in coding variables or categorization of continuous data (376). These errors can be intentional or unintentional on the part of the participant and/or the researcher, and can result in misclassification of the data. Misclassification is the assignment of a participant to the wrong category of exposure or outcome and occurs as either non-differential or differential misclassification.

Non-differential misclassification means that the level of misclassification is the same in the exposed and non-exposed groups; this results in a diluted OR, which is shifted towards 1, and thus an underestimation of the true risk (370, 376). Non-differential misclassification due to underreporting of an exposure with three or more categories, for example BMI, leads to underestimation of the middle categories with a dilution of the OR, but with no effect on the association in highest category (except for wider confidence intervals due to fewer observations); this can lead to an erroneous interpretation of a dose-response relationship where none actually exists (376). Differential misclassification occurs when the level of misclassification differs between the exposed and unexposed groups; this leads to either an increase or decrease in the observed compared to the true association between exposure and outcome (370), in other words, a biased OR. Categorizing continuous variables, whether as an exposure or a confounder, can also lead to biased ORs (377). In addition, non-differential misclassification of continuous variables can lead to differential classification, i.e. biased ORs, when the continuous variable is categorized for analysis (378). Non-differential misclassification of potential confounders can also lead to a biased OR of the main exposure; the greater the error of measurement of the confounder, the larger the bias (376).

In this thesis, data was extracted from the MBRN for all three Papers, and education data from SSB was linked to individual participants in Papers I and II. Since this thesis was a retrospective cohort study using register and population data, there was a risk of information bias. In Papers I and II, 16% of women lacked information on smoking status, and missing data on smoking was categorized as “no smoking”. Paper III reported missing smoking data as a separate category in the analysis. It is possible that missing data for smokers were because smokers were more likely not to divulge their smoking status. Another possible scenario is that information on smoking was less often collected from foreign-born women because of language barriers or underlying assumptions based on national origin, ethnicity or religious affiliation. Assigning “no smoking” to women who were in fact smokers may have led to a differential misclassification of a smoking as a potential confounder. Similarly, if a disproportionate amount of missing smoking data came from foreign-born women, categorizing missing smoking data as “no smoking” would have also created a differential misclassification of smoking exposure among foreign-born women. Either of these possibilities could have resulted in information bias. To check for this, a separate analysis of women with missing smoking data showed that their outcomes were closer to non-smokers

than smokers. Women with missing data on smoking were thus included in the non-smoking group in Papers I and II.

Information on education was lacking in 3.9% of women in Papers I and II, and was assumed to be missing at random. All remaining exposure variables in the thesis were missing in less than 1% of the dataset. Since the study population was large, and the small amount of missing information would not appreciably affect the outcomes, imputation on these variables was not performed. Imputation is a statistical analysis technique by which missing values are given substitute values in an attempt to improve accuracy in the observed estimate and reduce bias (379).

Information bias could have also occurred in this thesis due to errors in data collection and reporting the MBRN, such as variations in how clinicians define disease and record health information in the prenatal record and inpatient hospital chart. There can also be errors in data transfer or input in the MBRN. Reporting of pregnancy, delivery and newborn data to the MBRN takes place within 1 week after discharge of mother and baby from the hospital. The MBRN quality-checks the data against the national population registry, hospitals' own patient databases and autopsy reports, and follows up gaps in case numbers for registered pregnancies that do not result in deliveries. In 2017, the MBRN reported 100% coverage for birth, abortions and newborn admissions, and 80% coverage for ART (380). The MBRN is generally considered to be of good quality and suitable for research (381), and a large number of studies are published based on data from the MBRN. A number of validity studies have been performed citing sufficient validity for MBRN variables for preeclampsia (382, 383), gestational hypertension, gestation age, birthweight, medically indicated delivery (induction of labor or cesarean section before onset of labor) (384), trial of labor after cesarean section (385), unexplained antepartum fetal death (386), ART (387), diabetes, epilepsy (388), rheumatic diseases (389), placental and umbilical cord (390), obstetric sphincter tears (391), Down syndrome (392) and mild hyperemesis gravidarum (393). Conversely, studies have found suboptimal validity for severe hyperemesis gravidarum (393), uterine rupture (394), asthma (388) and medication use in pregnancy (395).

Given that all three Papers used validated MBRN variables for gestational age, induction of labor, diabetes, preeclampsia and gestational hypertension, there is low chance for information bias in the thesis due to these variables, although bias cannot be completely

excluded. Self-reported pre-pregnancy maternal height and weight variables in the MBRN used to calculated BMI have not been validated, so there could be information bias due to the BMI variable used as both an exposure and confounder in Paper II. A 2017 systematic review of self-reported pregnancy weight found that women underreport pre-pregnancy weight leading to a differential misclassification of population prevalence according to pre-pregnancy weight class (both underweight and overweight) and race/ethnicity (396). However, although the authors did report that some studies reporting biased associations between BMI and delivery outcomes, including preeclampsia, the general conclusion was that the bias was low (396).

MBRN still uses the classic definition of preeclampsia as hypertension with proteinuria. Updated definitions of preeclampsia that include signs of preeclampsia-associated organ dysfunction in the absence of proteinuria were not applicable in this thesis, as these data were not available. From an analysis standpoint, it was helpful that the classification of hypertensive disorders of pregnancy did not change over the study period, thus the definition of the outcome variable for preeclampsia remained constant. In reality, approximately 15–25% of women with gestational hypertension will eventually develop proteinuria (397). Women with preeclampsia without proteinuria were registered as gestational hypertension in the MBRN and thus assigned to the gestational hypertension variable in all the analyses in this thesis. This may have resulted in a misclassification of the outcome variables for hypertensive diseases in pregnancy. The misclassification is likely non-differential, as there is no data to support that women with any type of risk factor would be more or less likely to develop preeclampsia without proteinuria. Non-differential misclassification of dichotomous outcome variables tends to bias towards the null and thus, at most, slightly underestimate the observed association between exposure and outcome (398). It is therefore possible that the odds ratios in this thesis are slightly underestimated, but this probably has very little clinical significance.

Confounding is an important consideration in observational studies. Confounding occurs when the observed measured association between the exposure and outcome differs from the true association because of the interference of “something else” not considered, usually another measurable or unmeasurable exposure (370). Three strategies – limiting, stratification and adjustment – were employed to address the problem of confounding in this thesis. In Paper I, the data was stratified by parity (nulliparous, parous), and in Paper II, the

data was first limited to nulliparous women and then stratified by gestational age group at delivery (23+0 to 33+6 weeks, 34+0 to 36+6 weeks, and 37+0 to 43+6 weeks). In all three Papers, multivariable regression was used to adjust for possible confounders (i.e. other possible risk factors that affect both exposure and outcome) to each major risk factor being studied. In Papers I and II, the outcomes for each stratum were reported separately.

5.2 Strengths and limitations

The major strength of the thesis is its large population-based dataset with almost one million deliveries during the study period in Paper I, nearly 400 000 deliveries in Paper II and over one million deliveries in Paper III. Large population-based studies, especially ones that comprise very nearly the entire target population, have high external validity. Data from 1999 was used in the thesis because of major changes in 1998 to the way data were collected and recorded in the MBRN. Most notably, prior to 1999, pregnancy due date was based on the first day of the last menstrual period (LMP). In 1999, routine second trimester ultrasound examination replaced LMP for calculating pregnancy due date. Given the nearly 100% attendance rate for the second trimester ultrasound, the new method fundamentally changed how gestational age at delivery was recorded in the MBRN. It is important to note, however, that second trimester ultrasound is less reliable than first trimester ultrasound measurement of crown-rump length in estimating gestational age and calculating a pregnancy due date (399).

Another strength of the thesis is that new data was added when it became available. Paper III used MBRN data from 2015-2018 in addition to previously available data from 1999-2014. This allowed for comparison of hypertensive disorders of pregnancy over a 20-year time period.

Yet another strength is that all three Papers used multivariable logistic regression, which described the complex covariation of the assessed risk factors. In addition, the precision of the observed associations in all three Papers was very high, as the studies had many participants, i.e. many observations, which yielded predominantly narrow confidence intervals. As discussed in the section about bias, this thesis used previously validated variables from the MBRN (382-384, 387, 388), which reduced the risk of information bias. All foreign-born women delivering in Norway were included in the thesis, not just specific

immigrant groups as in previous studies (111, 113, 192, 400, 401). In addition, all women are entitled to free antenatal care in Norway, and obstetric care is fairly standardized throughout the entire country. The heterogeneity of the study population coupled with the homogeneity of the national health system provided an excellent opportunity to study both socioeconomic and biologic risk factors for preeclampsia in a 16-year period, and then investigate how – and possibly why – preeclampsia prevalence changed over two decades.

The thesis has, of course, some limitations. A limitation of Paper I is the dichotomous categorization of hypertensive disorders of pregnancy into gestational hypertension and preeclampsia. The outcome variable preeclampsia included both early and late-onset preeclampsia, which may have different pathogenic etiologies and clinical outcomes (21, 23, 27). Inclusion of all subtypes of preeclampsia into one outcome variable did not allow for estimation of the association of country of birth and education on early versus late-onset preeclampsia. Paper II, however, specifically assessed maternal risk factors in nulliparous women for early, intermediate and late-onset preeclampsia. Although Paper II focused on maternal biologic risk factors as the main exposures, country of birth and education were included as potential confounders. The univariate and multivariable logistic regression analyses in Paper II confirmed that the associations between country of birth and education found in Paper I were still present even when exposures were stratified by gestational age group at delivery.

Another limitation of Paper I is that women were grouped by country/world region based solely on their country of birth and not on their ethnicity, immigrant status, or length of residence in Norway. Second-generation immigrants [women born in Norway to immigrant parent(s)] were included in the Norwegian-born group. These women may have had biologic and environmental factors that were more similar to foreign-born women from the same country as their parent(s). Similarly, adopted foreign-born women likely grew up with environmental factors similar to Norwegian-born women, and women born abroad to Norwegian parents likely had biologic and possibly environmental factors similar to Norwegian women; nonetheless, these women were grouped as foreign-born. Papers II and III included maternal country of origin as a potential confounder, so the limitations with this exposure variable seen in Paper I were carried over into the other Papers.

Paper I also investigated maternal education as a risk factor for hypertensive disorders of pregnancy. The education levels differed between Norway and the other world regions, and between nulliparous and parous women. In general, women from world regions that had large industrialized countries (for example North America) were more highly educated than those from world regions that had mostly low or middle-income countries (for example Sub-Sahara Africa). There may also be variations in education level between the countries in each world region, but this level of detail is unfortunately lost when assessing maternal education on the level of world region.

The MBRN started collecting data on pre-pregnancy height and weight in 2006. Paper II used pre-pregnancy BMI, calculated from height and weight data, as both a major exposure and a possible confounder. A limitation of Paper II is that 75% of deliveries lacked data for height and weight. This means that although the logistic regression in model 1 (without BMI) included 366 949 nulliparous women, the logistic regression in model 2 (with BMI) had only 88 612 women. A separate sub-analysis of all singleton births to nulliparous women between 2006 and 2014 showed outcomes similar to the larger study population. Nonetheless, since there were fewer women included in model 2, there was less precision in the observed observation (aOR) and much wider 95% confidence intervals than in model 1. It is possible that as more height and weight data becomes available in the MBRN, this could lead to observations not seen in this thesis. For example, in this thesis, the 95% confidence intervals overlapped between model 1 and model 2 in all three gestational age groups for the observed risk of preeclampsia among women with chronic hypertension. In the future, if this study were to be repeated with more women with BMI data, the observed associations (ORs) would be more precise and the 95% confidence intervals would be narrower. If the 95% confidence intervals no longer overlapped, then some of the findings in Paper II might actually be due to a Type 2 error due to a too small sample size. A Type 2 error is when the null hypothesis (H_0) is not rejected when it is false; or in other words, the alternate hypothesis (H_1) is rejected when it is true (368). In Paper II, it is possible that the lack of observed difference in risk of preeclampsia among women with chronic hypertension with or without known BMI could in time prove to be incorrect when more BMI data is available.

The lack of available BMI data was also a limitation in Paper III. Sixty-five percent of deliveries in the dataset lacked BMI, and BMI was not included in the analyses, although it

is a known risk factor for both early and late-onset preeclampsia, as seen in Paper II. The reason for excluding BMI in the analysis in Paper III – despite having more BMI data than in Paper II – was that Paper III focused on secular trends of preeclampsia. It was not feasible to study BMI as risk factor for preeclampsia over time, when BMI data was not available in the first two time periods (1999-2002 and 2003-2006) and was missing among the majority of women in the first half of the time period 2007-2010.

Another limitation of Paper III was the lack of individual data for aspirin use in pregnancy. Although the MBRN collects data on medication use in pregnancy, individual-level data on aspirin use was not used because the variable has poor validity. This is likely due to the use of an open text box on the notification form instead of a pre-coded field as used for maternal diseases (395). Population-level data for aspirin was used instead, but specific indications for aspirin use were not available. Although there was an observed increased in prescriptions for low-dose aspirin to women < 40 years old from 2004 to 2018 which coincided with a reduction in preeclampsia prevalence, it was not possible to estimate an association between low-dose aspirin and preeclampsia based on the available data in this thesis.

5.3 Interpretation of results

Risk factors for hypertensive disorders of pregnancy

There is growing evidence that preeclampsia is due to malplacentation and declining placental function with synctiotrophoblast stress and an imbalance of antiangiogenic and angiogenic factors that cause the clinical syndrome of maternal hypertension, multi-organ dysfunction and FGR. Papers I and II investigated maternal "exposures" as risk factors for developing preeclampsia and gestational hypertension. By screening for risk factors, prenatal healthcare providers can identify women most at risk of developing preeclampsia so that these high-risk women can be offered low-dose aspirin aimed at preventing the syndrome and reducing adverse perinatal outcomes. Hopefully, a greater understanding of the shared underlying pathophysiology that links diverse maternal risk factors to the preeclampsia syndrome will ultimately lead to affordable and effective targeted or universal primary preventive strategies that virtually eliminate preeclampsia, improve maternal and neonatal health, and prevent long-term health problems in both mother and child.

Given the biologic model for preeclampsia pathogenesis, it is difficult to see how maternal country of origin or education, the two exposures investigated in Paper I, could be risk factors for the disorder. However, poverty, pollution, poor hygiene, inadequate sanitation, dangerous living conditions, overcrowding, malnutrition, unemployment, low education, domestic violence, substance abuse, sedentary lifestyle and lack of access to health care can create health inequalities or health inequities that increase the risk of many diseases, including diabetes, obesity and cardiovascular disease – all risk factors for preeclampsia. It is therefore important to consider socioeconomic risk factors for hypertensive diseases in pregnancy even though the diseases do not have a direct environmental etiology.

Paper I showed that foreign-born women had the same or lower risk of preeclampsia and gestational hypertension as Norwegian-born women, regardless of parity. In addition, low education did not increase the risk of preeclampsia compared to secondary education, also regardless of parity. These findings were adjusted for age, consanguinity, 1st-trimester smoking and diabetes, but they may have been affected by variations in underlying social and biologic factors, including BMI, not accounted for in the study.

Paper I was the first study to explore the association between education level and hypertensive diseases in Norway. Education is a good proxy for measuring socioeconomic inequality as it is less likely to be influenced by adult-onset diseases than other measures such as income and occupation (402). Despite documented educational inequalities in health in Norway (403), low education was not a risk factor for preeclampsia in this thesis. This finding is in contrast to other studies estimating an inverse association between socioeconomic status and hypertensive disorders of pregnancy in other high-income countries (118, 404, 405). The reason for this is unknown, but it may be due to fairly standardized and easily accessible antenatal care offered free to all pregnant women in Norway.

Maternal country of birth was also used as an objective socioeconomic variable. Although race or ethnicity is often used as a socioeconomic variable in observational studies, they were not considered in this thesis. Neither SSB nor the MBRN collect data on race or ethnicity; in fact, these variables are not allowed to be registered in any public document. Classifications of race or ethnicity simply do not exist in Norway. Race is not considered a biologic measure, and there is no agreement about the definition of race as a social

construct. This is in contrast to other countries, such as the US, where self-defined race is considered an important asset for research and is indeed seen as a mandatory variable to explore in research settings.

Studies outside Norway show that immigrant women have delayed antenatal care and fewer antenatal visits compared to host country women (406-408), possibly due to poor language proficiency, fewer economic resources, and lower maternal education (409). Differential antepartum care practices between immigrant and native women may also lead to delays in preeclampsia and gestational hypertension diagnoses among immigrants (410). In Oslo where the greatest percentage of foreigners live, female immigrants utilize more health care services than Norwegians (411). Although immigrants nationwide tend to utilize primary care services less often than Norwegians, for those that do, they do so at a higher frequency (412). Healthcare providers most certainly face challenges when caring for pregnant women of foreign birth, possibly due to barriers in communication, poor health literacy, cultural misunderstandings, variations in utilization of health care services, and higher prevalence of co-morbidities. The same or lower risk of hypertensive diseases in pregnancy in women with foreign birth is less likely due to under-diagnosis or underreporting of disease, underutilization of healthcare services, or differential treatment. The findings in Paper I are more likely a reflection of a well-functioning national health system in Norway that offers uniform and free prenatal care and obstetric services to all women, regardless of national origin.

Immigrants to Europe tend to be healthier than their native hosts due to strict national immigration policies (413) and self-selection bias, where the healthiest and most resourceful are likely to immigrate successfully. The “healthy immigrant effect” is more pronounced in adult immigrants and those with the shortest length of stay in the host country (414). Since the findings in Paper I are based on foreign-born women of relatively young age who have arrived in Norway sometime during their lifetime, the healthy immigrant effect could be a major contributing factor to the observed risk estimate. On the other hand, specific immigrant groups have a poorer health profile than Norwegians (411), so the healthy immigrant effect may have less influence in the thesis.

Although maternal country of origin was used as a socioeconomic variable in this thesis, it is worth considering this variable as a potential proxy for genetic risk factors for

hypertensive disorders of pregnancy. A recent secondary analysis of two US randomized control trials investigating the use of aspirin for preeclampsia prevention in low and high-risk women, found that low-dose aspirin 60 mg had no effect on preeclampsia prevention in certain ethnic and racial minorities, suggesting that there may be genetic polymorphisms related to aspirin intolerance in certain populations (415). These finding may not necessarily be relevant to Norway where there is a huge mix of Caucasian origin among women, people of color come from many different parts of the world, and children are born to parents with different genetic origins. Nonetheless, there may be high-risk foreign-born women in Norway with a genetic intolerance to aspirin who will not benefit from aspirin prophylaxis at current recommended doses. Further studies are needed to identify who these women are and how best to treat them.

Whereas Paper I focused on socioeconomic risk factors for hypertensive diseases in pregnancy in nulliparous and parous women, Paper II focused on three known biologic risk factors in nulliparous women only, namely diabetes, chronic hypertension and pre-pregnancy BMI. Paper II found that these maternal exposures were independent risk factors for early, intermediate and late-onset preeclampsia and gestational hypertension. One exception was the lack of association between gestational diabetes and early-onset preeclampsia, but this was probably due to these women having less time to develop gestational diabetes before the pregnancy ended in preterm delivery. Pre-pregnancy BMI did not significantly modify the risk of preeclampsia in women with pre-gestational diabetes or chronic hypertension, indicating the independent effects of obesity/overweight, pre-pregnancy diabetes or chronic hypertension. Pre-pregnancy BMI partially confounded the risk of late-onset preeclampsia in women with gestational diabetes; the risk was still present, but the magnitude of the risk was significantly decreased. The association between pre-gestational diabetes and gestational hypertension was fully confounded by pre-pregnancy BMI.

Diabetes is associated with impaired endothelial-dependent vasodilation and arterial stiffness, likely due to a combination of hyperglycemia, insulin resistance, oxidative stress and vascular inflammation (416-418). The interplay between type 2 diabetes and vascular inflammation is a bidirectional process, as diabetes leads to vascular inflammation with the overproduction of pro-inflammatory cytokines, and vascular inflammation promotes the development of diabetes (416). Insulin resistance is also present in type 1 diabetes, often in

conjunction with obesity, but also possibly due to the administration of high doses of exogenous insulin (419).

In general, the prevalence of diabetes in Norway is low compared to some other western countries. The Norwegian Institute of Public Health's national report on diabetes estimates a 4.7% prevalence of the disease in the entire population, of which approximately 88% is type 2 diabetes; the incidence of type 1 diabetes is approximately 300 children per year (420). In the general population, the prevalence of type 2 diabetes has increased steadily over the past few decades, and this trend was confirmed among pregnant women in Paper III. Nonetheless, the prevalence of type 2 diabetes in Norway is much lower among women, especially younger women, compared to men. In fact, unlike in the general Norwegian population, type 1 diabetes was three times more prevalent than type 2 diabetes in pregnancy, as shown in Paper II. Whereas the proportion of pregnant women with type 1 diabetes remained constant over 20 years at 0.4%, Paper III showed that the prevalence of type 2 diabetes in pregnancy doubled from 1999-2002 to 2015-2018, although the absolute increase was still very low.

Any type of diabetes tripled from study start to end, as reported in Paper III. This finding was driven mostly by a quintupling of gestational diabetes prevalence. Gestational diabetes prevalence is very much dependent on screening criteria and blood glucose cutoff values. Stricter screening criteria and higher blood glucose cutoff values will decrease the reported prevalence of the disease due to under-diagnosis (fewer false positives, more false negatives). Conversely, more liberal screening criteria, such as universal screening, and lower blood glucose cutoff values will increase the reported prevalence of gestational diabetes, but will also include women who may not have clinically significant disease (fewer false negatives, more false positives). Gestational diabetes prevalence is expected to increase to approximately 10% of the pregnant population in Norway, partly based on lifestyle choices and genetic factors, but more likely because of newer more liberal screening guidelines and lower blood-glucose cutoff values (421).

Since women with gestational diabetes are at risk for preeclampsia, they may benefit from prevention. Aspirin prophylaxis, the only known preventive medication, is generally not applicable in this group as it is started in early second trimester based on first-trimester risk assessment; gestational diabetes is not diagnosed until the third trimester. The findings in Paper II show that BMI attributes partially to the increased risk of preeclampsia at term in

women with gestation diabetes. If the first stage of late-onset preeclampsia starts with placental functional decline due to the combination of increased placental mass coupled with limited uterine capacity, women with gestational diabetes, especially those with high BMI, could possibly lower their risk of preeclampsia by a preventive strategy other than aspirin. Unfortunately, current interventions such as nutrition education, diet, exercise, self-glucose monitoring, and even insulin treatment, have not been found to decrease the risk of hypertensive diseases in pregnancy in women with gestational diabetes compared to healthy controls (422, 423). Metformin, an oral insulin sensitizer used to treat type 2 diabetes, reduces antiangiogenic factors such as s-Flt-1 and improves endothelial dysfunction (424). In an in-vitro study, the effect on s-Flt-1 was more pronounced when metformin was combined with sulfasalazine, a synthetic salicylic acid derivative with anti-inflammatory properties (425). A 2018 systematic review and meta-analysis found that among women with gestational diabetes, metformin significantly reduced the risk of gestational hypertension but had no effect on the risk of preeclampsia, although the quality of evidence was low (426).

One-third of the nulliparous women in Paper II had overweight or obesity, and these women had an increased risk of preeclampsia across all three gestational age groups, as well as an increased risk of gestational hypertension, even after adjustment for possible confounders. Obesity is a state of chronic low-grade inflammation, as metabolic adipocyte dysfunction promotes the release of pro-inflammatory cytokines and induces oxidative stress (427). In addition, perivascular adipose tissue becomes dysfunctional and decreases production of vaso-protective adipocyte-derived relaxing factors while also increasing the production of pro-inflammatory cytokines and inducing oxidative stress, thus contributing to vascular inflammation and endothelial cell dysfunction (428). The observed higher magnitude of risk of late-onset preeclampsia with rising pre-pregnancy BMI may be secondary to intervillous malperfusion and hypoxia due to mechanical restrictions as the growing placenta reaches its size limit, coupled with underlying excessive vascular inflammation (23, 28-30). This conceptual mechanism is summarized in the revised two-stage model of preeclampsia (27).

The prevalence of obesity in the Norwegian general population has increased over the past 60 years, even in those least genetically predisposed to obesity, suggesting a combination of biologic and environmental etiologies to the obesity epidemic (429). Because of considerable missing pre-pregnancy height and weight data in the study period, Paper III

could not investigate any secular trends of BMI in this thesis. Most likely, however, average pre-pregnancy BMI has increased among pregnant women, reflecting national and international trends in high-income countries. An observational studying using all available MBRN height and weight data from 2006-2014 found an inverse relationship between pre-pregnancy BMI and population density (430). Geographic differences in pre-pregnancy BMI suggest a considerable environmental component to obesity in pregnancy, although the possible confounding genetic influence of assortative pairing and sibling effect cannot be excluded.

BMI most likely represents both a socioeconomic and biologic risk factor for hypertensive diseases in pregnancy, and most concerning is that the prevalence of maternal overweight/obesity is likely to increase over time. Pregnant women with overweight or obesity have decreased insulin sensitivity and are at increased risk of developing metabolic syndrome later in life (431). Additionally, preeclampsia itself is a risk factor for early development of metabolic syndrome (432). Aspirin has a beneficial effect in the prevention of preterm preeclampsia in women with elevated BMI (321), but an effective preventive intervention for term preeclampsia among overweight or obese women has yet to be found. A 2021 systematic review and meta-analysis found no effect of either exercise or metformin on hypertensive disorders of pregnancy among overweight pregnant women, but the authors cited low-quality evidence in the studies (433). Future studies are needed to investigate whether interventions such as metformin, with or without aspirin (or another anti-inflammatory), has a beneficial role in term preeclampsia prevention among women with gestational diabetes, obesity, or both. Finding effective preeclampsia prevention strategies in this sub-group is particularly important to improve pregnancy outcomes, prevent future cardiovascular and metabolic diseases, and reduce the overall burden of disease in the general population.

Chronic hypertension increased the risk of preeclampsia in nulliparous women in all gestational age groups in Paper II; the magnitude of risk was highest for early-onset preeclampsia and lowest for late-onset preeclampsia. Chronic hypertension is associated with oxidative stress and vascular inflammation, and the interplay of these two pathophysiologic processes lead to endothelial dysfunction (434). Women with chronic hypertension may need additional surveillance, counseling and treatment in early third-trimester when the risk of preeclampsia is highest. This is particularly important since

aspirin prophylaxis in women with chronic hypertension may not have the same protective effect against preeclampsia as it does in women with other high-risk factors (321). Considering the two-stage biologic model of preeclampsia, maternal inflammatory or metabolic stress from chronic hypertension may have such a negative effect on spiral artery remodeling and placentation that aspirin prophylaxis may need to be started even earlier than 12+0 weeks of gestation – perhaps even pre-conceptually – in order to achieve its protective effect. Low-dose aspirin initiated < 11+0 weeks of gestation, however, does not appear to prevent any type of hypertensive disorder of pregnancy in high-risk women, according to a recent meta-analysis, although non-significant reductions were found for both preeclampsia and gestational hypertension (435). Further studies are needed to find if there is an optimal time, if any, or optimal dosage, for aspirin initiation in the sub-group of women with chronic hypertension.

Secular trends in hypertensive disorders of pregnancy

After studying socioeconomic and biologic risk factors for hypertensive disorders of pregnancy, attention was turned toward investigating secular trends in preeclampsia and gestational hypertension prevalence over two decades. The novel finding in Paper III was that despite the increased proportion of high-risk women over time, there was a reduction in preeclampsia prevalence in all subgroups of women with known risk factors studied. The decreasing trend was also seen in all gestational age groups at delivery. Overall preeclampsia prevalence decreased by 37% between the first and last four-year time increments. This trend was observed despite an increasing proportion of high-risk parturients with advanced maternal age, type 2 diabetes, gestational diabetes and ART – all risk factors for preeclampsia. First-trimester smoking, which is inversely associated with preeclampsia, decreased. The prevalence of other known risk factors, such as nulliparity, twin gestations, type 1 diabetes and chronic hypertension remained fairly stable, whereas the proportion of foreign-born women nearly doubled over the study period. Observed population changes could not fully explain the 44% decreased risk of preeclampsia over the study period.

The transient increase in gestational hypertension concurrent with reduced preeclampsia prevalence observed in the early years of the study, could be interpreted as merely a shift from the more severe form (preeclampsia) of hypertensive disorders of pregnancy to the clinically less severe form (gestational hypertension). This may indeed have been the case in

the beginning of the study period. However, gestational hypertension prevalence at the end of the study was roughly similar to the study start (net increase of 6.7%), whereas preeclampsia prevalence continued to fall. This suggested a more profound effect across the hypertensive disorder group, where less women were affected, and with a less severe phenotype.

The findings in Paper III may reflect an increasingly healthier population in Norway. Pregnant women, despite having a higher prevalence of risk factors for preeclampsia, may have better baseline health status now compared to women two decades ago. Although hypertension prevalence in the general Norwegian population has increased with age, BMI, and genetic risk factors during the study period (436), both mean systolic and diastolic blood pressures have decreased among women in Norway in all age groups over the past several decades (437, 438). This trend has occurred despite a greater prevalence of overweight/obesity (429) and diabetes (420) in the population. The cause of this paradox is unknown, but may be due to dietary changes including reduced salt intake, or increased use of antihypertensive medications for non-hypertensive diseases (438). There may also be a number of overweight or obese women who are actually normotensive and metabolically healthy, with minimal inflammatory activity and preserved insulin sensitivity (439).

An association between health, wellbeing, and socioeconomic status in Norway has been reported (440). General improvement in health behavior with more focus on diet, physical activity and smoking cessation may also have had an overall positive effect on maternal health during the study period. Coinciding with the substantial decrease in smoking rates in Norway over the past 20 years, the use of snuff (oral smokeless tobacco) has dramatically increased and is now the most common form of tobacco product among 16-44 year olds (441, 442). The MBRN does not collect data on snuff use, and the association between snuff and preeclampsia is unclear, with studies observing no risk (443) or an increased risk (444) of the disease. Changes in dietary, lifestyle and substance use resulting in fewer hypertensive complications in pregnancy may represent an unmeasurable confounder in Paper III.

Since the observed risk factors could not explain the decreased incidence of preeclampsia, changes in clinical management were considered as possible explanations for decreased preeclampsia incidence. In recent years, expectant management of preterm preeclampsia in the absence of maternal or fetal indications for delivery (278), has become standard clinical

practice in Norway (9). Labor induction at ≥ 37+0 weeks of gestation is now the standard treatment of preeclampsia, in order to reduce the risk of severe complications such as HELLP and cerebral hemorrhage, and it is considered a safe alternative to cesarean delivery, when possible (274, 351). Induction of labor for all pregnancies > 41+0 weeks of gestation has also become standard care in the past decade (445-447), as it reduces the risk of adverse perinatal outcomes (448, 449), including late-onset preeclampsia. Norway has not implemented elective labor induction at 39 weeks in low-risk nulliparous women, despite some studies showing decreased risk of cesarean delivery (450), maternal morbidity and perinatal mortality (451) compared to expectant management. In Paper III, labor induction increased overall and specifically in women with preeclampsia or gestational hypertension. The MBRN does not record indications for labor induction, so the temporal increase in labor induction juxtaposed with a temporal decreased prevalence of preeclampsia is purely observational with no claims of causal inference. Nonetheless, increased labor induction regardless of indication could partially explain the reduction of preeclampsia in late gestation, but not in earlier gestations where induction of labor is rarely indicated.

Prenatal low-dose aspirin for preeclampsia prevention in high risk pregnancies, from 12+0 weeks of gestation until delivery (75 mg evening dose) or until 36+0 weeks of gestation (150 mg evening dose), has been a part of standard antenatal care in Norway since 2014 (9, 323). However, as far back as 1998, aspirin was mentioned in the Norwegian guidelines for preeclampsia prevention in parous women with a previous history of preeclampsia (324). Aspirin 75 mg, which is only available by prescription, increased among women < 40 years old in Norway from 2004-2018, although data on aspirin prescriptions used specifically for preeclampsia prevention was not available. Low-dose aspirin is used for prevention of cardiovascular diseases in high-risk populations (452), but women taking aspirin for this indication are mainly not of reproductive age (453). Aspirin used for pain, fever and rheumatologic illnesses are usually prescribed at much higher doses.

Although the specific reasons for increased aspirin use among younger women is unknown, it is likely that the increased use of low-dose aspirin in reproductive age women was due increased rate of attempted preeclampsia prevention. Norwegian recommendations for aspirin prophylaxis have targeted mainly parous women with previous obstetric complications, and therefore cannot fully explain the 38% reduction of preeclampsia prevalence among the nulliparous women in Paper III. Nonetheless, the observed decreased

preeclampsia risk in Paper III coincided with increased aspirin use in women of reproductive age, regardless of indication. Although the specific pathophysiologic effects of aspirin in preventing especially early-onset preeclampsia remain unknown, a recent paper suggests that efficient aspirin prophylaxis delays the metabolic clock of gestation in high-risk women (454).

Models of preeclampsia pathogenesis

This thesis investigated socioeconomic and biologic risk factors for hypertensive disorders of pregnancy, and how these exposures influenced the prevalence of preeclampsia over time. The findings of the thesis are consistent with the revised two-stage biologic model of preeclampsia pathogenesis (21, 23, 27-30), supporting a multifactorial pathway to early, intermediate and late-onset disease. Chronic maternal diseases increased the risk of preeclampsia in all gestational age groups. The chronic baseline vascular inflammatory state promoting endothelial dysfunction in women with diabetes, chronic hypertension and overweight/obesity may lead to early malplacentation and placental malperfusion associated with early-onset preeclampsia. Alternatively, chronic maternal diseases may contribute to declining placental functional at later gestations due to chorionic villous crowding, increased placental cellular senescence and placental oxidative stress in previously normal placental (27). More importantly, the findings in this thesis support the theory that chronic maternal diseases contribute to both pathophysiologic processes. Lastly, chronic maternal diseases may also contribute to synctiotrophoblast stress and the production of antiangiogenic factors such as sFlt-1 and sENG. These findings are particularly relevant in nulliparous women who have an elevated risk of preeclampsia as compared to parous women, likely due to immunological and anatomical factors related to uteroplacental artery remodeling and other placentation processes (27).

It is worth considering, however, why some women who have one or more risk factors develop preeclampsia, while others do not. Using the threshold liability model (192, 455), all women are at risk of preeclampsia, but that due to underlying genetic polymorphisms or epigenetic reprogramming, some women are more susceptible to the additional "risk" of the socioeconomic and biologic exposures investigated in this thesis. These more genetically vulnerable women are thus pushed over a certain disease threshold and develop preeclampsia, whereas less genetically or biologically vulnerable women do not, despite having the same measurable risk factors. This model is supported by studies showing

increased risk of preeclampsia in families (90, 204, 205) and increased risk of recurrent preeclampsia in subsequent pregnancies (199, 200). This model could also partially explain why despite increasing prevalence of known risk factors in this thesis, there was a decrease in preeclampsia prevalence and risk over two decades, perhaps due to general improvements in baseline health. The threshold liability model can also explain why some high-risk women respond to aspirin prophylaxis, while others do not.

Lastly, the findings of this thesis should be considered using the competing risk model (27, 29, 292, 307, 456-458), which assumes that all women will develop preeclampsia if their pregnancies had an infinite gestational length. The clinical syndrome of preeclampsia is dependent on whether a woman is delivered before or after her personal threshold for the disease. A woman's individual threshold for disease, meaning the gestational age which preeclampsia develops, is lower in the presence of any number of "risks", such as maternal socioeconomic and biologic exposures as well as other measurable biophysical and biochemical markers. Conversely, in a woman with no risk factors or protective risk factors for preeclampsia, the gestational age at which preeclampsia develops is so high, that she will complete her pregnancy well before she reaches her threshold. The findings in this thesis support the competing risk model. The overall increased use of labor induction in Norway may have reduced preeclampsia prevalence simply by delivering some women before they reached their predestined gestational age threshold for preeclampsia. In addition, improvements in baseline maternal health, despite an increased prevalence of preeclampsia risk factors, may have increased the gestational age threshold for preeclampsia. Lastly, increased aspirin use among reproductive-aged women may have shifted the gestational age threshold for preeclampsia for some of these women beyond 41 weeks, the gestational age where all women are offered induction.

Generalizability of the results

The main findings of this thesis are generalizable to populations similar to Scandinavia and Northern Europe, with well-organized and accessible national health systems, increasing maternal age, and prevalence of chronic diseases typically seen in high-income countries.

6 CONCLUSIONS

This thesis was an epidemiological study using a population-based retrospective (historical) observational cohort to achieve the main research aims. The risk and prevalence of hypertensive disorders was explored using available data from the MBRN, SSB and NorPD. The risk of systematic bias was considered low.

Foreign-born women, who comprised 20% of deliveries in Papers I and II and 30% of deliveries in Paper III, had predominantly the same or lower risk of hypertensive diseases in pregnancy compared to women born in Norway, regardless of parity. Poorly educated women, also regardless of parity, had no increased risk of hypertensive diseases in pregnancy compared to women with a secondary education. These findings may partly be due to the healthy immigrant effect, but can also be explained by a well-functioning national health system in Norway that offers free prenatal care to all women, regardless of national origin or socioeconomic status.

Nulliparous women with diabetes, chronic hypertension or obesity had increased risk of early (23+0 to 33+6 weeks of gestation), intermediate (34+0 to 36+6 weeks of gestation) and late (37+0 to 43+6 weeks of gestation)-onset preeclampsia. Pre-pregnancy BMI did not significantly further modify the risk of preeclampsia in women with pre-gestational diabetes or chronic hypertension where BMI data was available. However, pre-pregnancy BMI partially modified the risk of late-onset preeclampsia in women with gestational diabetes. The above findings support the concept of multifactorial pathways to the heterogeneous group of hypertensive disorders of pregnancy.

Preeclampsia prevalence decreased by 37% whereas the prevalence of gestational hypertension increased by 6.7% over the two decades. Despite decreasing preeclampsia prevalence, the proportion of women with risk factors for preeclampsia increased. However, concurrent with decreasing preeclampsia prevalence, labor inductions and low-dose aspirin use among young women in the general population increased.

This thesis explored socioeconomic and biologic risk factors for hypertensive disorders of pregnancy based on parity and gestational age group at delivery, and found that despite an increasing prevalence of high-risk women, the prevalence and risk of preeclampsia decreased over time. Possible explanations for these findings are a small shift to the lesser

severe phenotype of gestational hypertension, the increased use of labor induction, the increased use of low-dose aspirin among reproductive-aged women, and possibly improved general health in the Norwegian population. These findings support the revised two-stage model of preeclampsia, as well as the threshold liability model and competing risk model.

As with many observational studies, causal inferences cannot be made. Nonetheless, this thesis raises a number of questions for future research.

7 FURTHER STUDIES

This doctoral thesis has generated ideas for future research projects, such as:

- **Temporal trends in preeclampsia prevalence**
  Observational study using individual level data on pre-conceptual and prenatal aspirin use and indications for labor induction to investigate secular trends in preeclampsia prevalence and risk.

- **Fetal growth restriction and neonatal outcomes**
  Observational study using neonatal birthweight and birth weight/placenta weight ratios (as a proxy for FGR) to investigate the association between maternal risk factors and hypertensive disorders of pregnancy, with and without SGA.

  Observational study using neonatal birthweight and birth weight/placenta weight ratios (as a proxy for FGR) to investigate the association between hypertensive disorders of pregnancy and adverse neonatal outcomes.

- **Obesity and gestational diabetes**
  Observational study to investigate the association between gestational diabetes and hypertensive disorders of pregnancy using more liberal screening criteria and lower blood-glucose cutoff values than used in this thesis.

  Clinical trial to investigate whether metformin, with or without aspirin, prevents preeclampsia among women with gestational diabetes, overweight/obesity or both.

- **Chronic hypertension**
  Clinical trial investigating whether pre-conceptual aspirin at various doses decreases the risk of preeclampsia in women with chronic hypertension

- **Preeclampsia screening and aspirin prophylaxis**
  Clinical trial comparing FMF's proposed model (295) for screening, prediction and management of preeclampsia to current standard of care in Norway. Primary outcomes are preterm and term preeclampsia. Secondary outcomes are short and long-term composite adverse maternal and offspring outcomes.

Cost-effectiveness analysis of four aspirin prophylaxis strategies before 16+0 weeks of gestation: no aspirin use, aspirin prophylaxis based on FMF combined 1st-trimester screening, current NGF aspirin prophylaxis recommendations, or universal aspirin.

Cost-effectiveness analysis of 2nd and 3rd-trimester screening for preeclampsia (after 20+0 weeks of gestation) including prevention of long-term cardiovascular and metabolic disease sequelae in the analysis.

- **Genetic polymorphisms and epigenetic reprogramming**
  Basic science studies to identify genetic polymorphisms and epigenetic associations with preeclampsia. Translational research is needed to investigate how genetic and epigenetic findings can be used in screening, prevention and treatment of preeclampsia.

8 ERRATUM

9 REFERENCE LIST

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10 PAPERS I-III

I

Received: 28 February 2018 | Accepted: 4 June 2018

DOI: 10.1111/aogs.13393

ORIGINAL RESEARCH ARTICLE

AOGS Acta Obstetricia et Gynecologica Scandinavica

The association of maternal country of birth and education with hypertensive disorders of pregnancy: A population-based study of 960 516 deliveries in Norway

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Funding information
This work was supported by the Norwegian SIDS and Stillbirth Society, grant number 554.04/14.

Abstract

Introduction: Previous studies estimating the association of maternal country of birth and education with hypertensive disorders of pregnancy (HDP) have shown conflicting results. The aim of the study was to assess the prevalence of HDP and estimate the association of maternal country of birth and education level with preeclampsia/eclampsia and gestational hypertension in Norway.

Material and methods: We performed a population-based observational cohort study linking two population datasets: The Medical Birth Registry of Norway and Statistics Norway (SSB). Singleton deliveries in Norway between 1999 and 2014 (907 048 deliveries) were stratified by parity. Multiple regression analysis was performed.

Results: In 20% of the deliveries the woman was born outside of Norway. Foreign-born women had lower risk of preeclampsia/eclampsia and gestational hypertension compared with Norwegian-born women. High education reduced the risk for preeclampsia/eclampsia by 34% (adjusted odds ratio 0.66, 95% CI 0.62-0.69), compared with women with secondary education among nulliparous women, and by 39% (adjusted odds ratio 0.61, 95% CI 0.57-0.65) among parous women. Poorly educated women had no increased risk of HDP compared with women with secondary education. Among highly educated nulliparous women the risk of preeclampsia/eclampsia was lower but the risk of gestational hypertension higher compared with women of similar parity with secondary education. Adjustment for confounding variables had minimal effect on these estimates.

Conclusions: Maternal country of birth and education were associated with HDP. Women with higher education had the lowest risk of HDP, and Norwegian-born women had the highest risk of HDP, regardless of parity and other confounding factors.

KEYWORDS

country of birth, eclampsia, education, foreign-born, hypertension, immigrant, preeclampsia, pregnancy

Abbreviations: aOR, adjusted odds ratio; BP, blood pressure; CI, confidence interval; EEA, European Economic Association; GH, gestational hypertension; HDP, hypertensive disorders of pregnancy; MBRN, Medical Birth Registry of Norway; OR, odds ratio; PE, preeclampsia/eclampsia.

1 | INTRODUCTION

Norway has experienced an influx of immigrants since the millennium. The immigrant population (defined as being born outside Norway) increased from approximately 5% in 1999 to 13% by the end of 2014, with the largest immigrant groups arriving from Poland, Sweden, Lithuania, Somalia, Germany and Iraq.[1] Previous studies have investigated the association between immigrants and hypertensive disorders of pregnancy (HDP) with conflicting results. Single-country and multinational observational studies report an increased risk of preeclampsia among specific immigrant groups delivering in industrialized countries.[2-6] A recent systematic review and meta-analysis of epidemiologic studies, however, found a lower risk of HDP among immigrant populations to industrialized countries.[7] In low- and middle-income countries, low maternal educational level is associated with poor pregnancy outcome.[8] Few previous studies have assessed the association between education and HDP in industrialized countries. Small studies from Australia to Korea indicate that economically disadvantaged women have a higher risk of preeclampsia and eclampsia.[9,10]

Due to this knowledge gap, we wanted to explore the relation between the mother's country of birth, educational level and HDP, assessing the subgroups preeclampsia/eclampsia (PE) and gestational hypertension (GH), in addition to the known risk factors such as nulliparity, advanced maternal age and diabetes (type 1 and type 2, and gestational). The main aim of this population-based observational cohort study was to estimate the association between country of birth and educational level with HDP among women delivering in Norway, stratified by parity.

Key Message

Foreign-born women had a predominantly lower risk of hypertensive disorders of pregnancy compared with Norwegian-born women. Poorly educated women had no increased risk of hypertensive disorders of pregnancy compared with women with secondary education. These findings were consistent among nulliparous and parous women.

2 | MATERIAL AND METHODS

2.1 | Study design and population

We performed a population-based observational cohort study linking two population datasets: The Medical Birth Registry of Norway (MBRN) and Statistics Norway. The MBRN is a complete population-based registry of all deliveries in Norway since 1967, including home deliveries. Data pertaining to maternal health, pregnancy characteristics, obstetric outcomes and neonatal outcomes are reported by the deliverer (usually the midwife) immediately following every delivery. Other data such as occupation, lifestyle habits and assisted reproduction information are collected only with patient consent. Statistics Norway, the national statistical institute of Norway, compiles official socioeconomic and population data for the country, including data on immigration, country of birth and education.

The study population included all singleton pregnancies delivering in Norway between 1999 and 2014 (960 516 deliveries). Multiple gestations, pregnancy outcomes at gestational ages less than 23 weeks and equal to or over 44 weeks, and pregnancies with major congenital anomalies were excluded (n = 53 468), resulting in the analysis of 907 048 deliveries. Gestational age at birth was calculated by ultrasound fetal biometry. Nearly all women in Norway receive an ultrasound examination between approximately 17 and 20 weeks of gestational age as part of routine prenatal care in the national health system. Where ultrasound-dating of gestational age was not available, the gestational age at delivery in the MBRN was based on the first day of the last menstrual period.

2.2 | Variables

We assessed both previously well-established HDP risk factors (parity, maternal age, diabetes) and previously under-studied factors such as maternal country of birth, educational level and consanguinity.

Mother's country of birth was grouped into one of 11 world regions, taking into account political, geographic, economic and cultural characteristics (Table 1). European countries were grouped into three regions: Norway, countries belonging to the European Economic Association plus Switzerland (Europe/EEA) and countries not belonging to the European Economic Association (Europe/non-EEA). Canada and USA were grouped together (North America). Other countries were grouped based on world regions defined by The World Bank, and remaining countries were grouped based on regions defined by Norway Statistics.

Education was used as a proxy measure of socioeconomic status. The Norwegian Standard Classification of Education includes Norwegian education codes and corresponding codes from the International Standard Classification of Education (ISECD-2011). The eight levels used in ISECD-2011 were merged into four levels in this study, according to numbers of years of highest completed education: No education to completion of grade 10, which is the end of compulsory education in Norway (primary education); completion of grades 11 to 14+, which is the end of Norwegian trade school education or university preparatory education (secondary education); higher education (Bachelor level) and highest education (Master/PhD). Secondary education was used as the reference group.

Information on maternal age, consanguinity, diabetes and smoking at onset of pregnancy was obtained from MBRN. Maternal age was categorized as <20, 20-34, 35-39 and ≥40 years. Consanguinity was categorized as recorded in the MBRN as "none", "1st cousins", "distant cousins", "other relation" and "unknown". Maternal diabetes

TABLE 1 Selected demographics and clinical characteristics. Singleton deliveries ≥23 wk and <44 wk of gestational age, 1999-2014. Exclusions: major fetal anomalies. n = 907 048

	Nulliparous (para 0)						Parous (≥para 1)					
	Total deliveries		PE		GH		Total deliveries		PE		GH	
	%	n	%	n	%	n	%	n	%	n	%	n
Deliveries	100.0	382 618	5.0	18 957	2.2	8562	100.0	524 430	2.3	11 929	1.4	7314
Parity												
0	42.2	382 618	5.0	18 957	2.2	8652						
1							36.2	328 745	2.3	7669	1.4	4536
2							15.7	142 610	2.2	3117	1.4	997
3							4.0	36 708	2.2	812	1.5	560
4							1.1	10 115	2.3	234	1.3	132
5 or more							0.7	6252	2.5	157	1.4	89
Birthplace, by region												
Norway	79.8	305 189	5.3	16 141	2.4	7374	79.9	418 913	2.4	10 006	1.5	6285
Europe/EEA[a]	7.0	26 931	3.5	951	2.0	540	5.3	27 928	1.6	449	1.2	333
Europe/non-EEA[b]	2.4	9093	3.1	282	1.3	119	2.4	12 440	1.9	233	0.9	109
North America[c]	0.4	1619	4.1	66	1.7	28	0.5	2364	1.1	27	1.2	28
Latin America/Caribbean[d]	1.0	3770	4.6	174	1.2	46	0.8	4077	2.0	83	1.0	40
Middle East/North Africa[e]	1.9	7214	2.7	196	1.1	76	2.4	12 338	1.5	191	0.8	98
Sub-Saharan Africa[f]	2.0	7605	5.7	432	1.1	86	3.1	16 424	2.5	416	0.8	130
Transcaucasia/Central Asia[g]	0.1	360	1.7	6	1.4	5	0.1	446	1.6	7	0.7	3
South Asia[h]	1.8	6957	3.4	234	1.6	111	2.4	12 431	2.1	255	1.1	136
East Asia Pacific[i]	3.0	11 662	3.5	403	1.2	141	2.6	13 795	1.8	255	0.9	121
Oceania[j]	0.1	257	3.1	8	2.7	7	0.1	278	2.2	6	1.1	3
Education												
None/primary education	15.4	58 935	5.1	3002	1.6	938	17.1	89 608	2.5	2222	1.2	1052
Secondary education	28.6	109 366	5.6	6163	2.2	2375	31.0	162 713	2.6	4233	1.5	2397
Bachelor's	38.7	148 197	5.0	7369	2.5	3672	37.1	194 586	2.2	4220	1.5	2918
Master's/PhD	13.2	50 451	3.8	1927	2.7	1349	11.0	57 561	1.7	991	1.3	773
Consanguinity												
None	95.8	366 457	5.0	18 149	2.3	8267	95.8	502 546	2.3	11 497	1.4	7081
1st cousins	0.3	1326	2.6	34	1.5	20	0.5	2517	2.1	52	1.0	25
Distant cousins	0.1	438	4.8	21	1.1	5	0.1	721	1.9	14	0.7	5
Other relation	0.5	1925	4.4	84	1.6	30	0.5	2681	1.8	47	0.8	22
Unknown	3.2	12 433	5.4	669	1.9	240	3.0	15 913	2.4	379	1.1	181

(Continues)

TABLE 1 (Continued)

	Nulliparous (para 0)						Parous (≥para 1)					
	Total deliveries		PE		GH		Total deliveries		PE		GH	
	%	n	%	n	%	n	%	n	%	n	%	n
Age, in years												
<20	4.9	18 632	5.2	977	1.1	199	0.2	1161	1.8	21	0.3	3
20-34	86.5	330 824	4.9	16 121	2.2	7227	75.8	397 365	2.1	8446	1.2	4943
35-39	7.4	28 326	5.4	1528	3.3	937	20.3	106 285	2.7	2849	1.8	1904
>40	1.3	4808	6.9	331	4.1	197	3.7	19 578	3.4	672	2.4	463
Diabetes												
None	97.9	374 764	4.8	18 035	2.2	8272	97.6	511 430	2.2	11 180	1.4	6953
Type 1	0.5	1855	20.2	374	3.8	70	0.5	2432	9.8	238	3.4	82
Type 2	0.2	646	12.4	80	4.6	30	0.2	1296	8.3	107	3.0	39
Gestational	1.4	5353	8.7	468	3.5	190	1.7	8847	5.2	464	2.7	240
Smoking, 1st trimester[k]												
No/missing	85.9	328 772	5.0	16 537	2.3	7694	87.4	458 587	2.3	10 718	1.5	6657
Sometimes	1.9	7197	4.3	310	2.2	158	1.4	7298	2.0	143	1.1	82
Daily	12.2	46 649	4.5	2110	1.5	710	11.2	58 545	1.9	1128	1.0	575

GH, gestational hypertension; PE, preeclampsia/eclampsia.

[a]Europe/EEA: Sweden, Finland, Denmark, Iceland, Cyprus, Bulgaria, Estonia, Croatia, Latvia, Poland, Romania, Lithuania, Slovenia, Hungary, Slovakia, Czech Republic, Belgium, France, Greece, Ireland, Italy, Malta, Netherlands, Liechtenstein, Luxembourg, Portugal, Spain, UK, Switzerland (not actually in the EEA), Germany, Austria.

[b]Europe/non-EEA: Greenland, Faroe Islands, Albania, Belarus, Moldova, Russia, Turkey, Ukraine, Bosnia-Herzegovina, Macedonia, Serbia, Montenegro, Kosovo, Andorra, Gibraltar, Monaco, San Marino, Vatican City State, Guernsey, Jersey, Isle of Man.

[c]North America: Canada, Saint Pierre and Miquelon, USA.

[d]Latin America/Caribbean: United States Virgin Islands, Barbados, Antigua and Barbuda, Belize, Bahamas, Bermuda, British Virgin Islands, Cayman Islands, Costa Rica, Cuba, Dominica, Dominican Republic, Grenada, Guadeloupe, Guatemala, Haiti, Honduras, Jamaica, Martinique, Mexico, Montserrat, Aruba, Saint Maarten, Bonaire, Saint Eustatius and Saba, Anguilla, Curaçao, Nicaragua, Panama, El Salvador, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Trinidad and Tobago, Turks and Caicos Islands, Puerto Rico, Saint Martin, Saint Barthélemy, Argentina, Bolivia, Brazil, Guyana, Chile, Colombia, Ecuador, Falkland Islands, French Guiana, Paraguay, Peru, Suriname, Uruguay, Venezuela.

[e]Middle East/North Africa: Algeria, Egypt, Djibouti, Libya, Morocco, Tunisia, Bahrain, United Arab Emirates, Iraq, Iran, Israel, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Yemen.

[f]Sub-Saharan Africa: Angola, Botswana, Saint Helena, Burundi, Comoros, Benin, Equatorial Guinea, Côte d'Ivoire, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Cameroon, Cape Verde, Kenya, Congo-Brazzaville, Congo, Lesotho, Liberia, Madagascar, Malawi, Mali, Western Sahara, Mauritania, Mauritius, Namibia, Niger, Nigeria, Mozambique, Mayotte, Réunion, Zimbabwe, Rwanda, Sao Tome and Principe, Senegal, Central African Republic, Seychelles, Sierra Leone, Somalia, South Sudan, Sudan, Swaziland, South Africa, Tanzania, Chad, Togo, Uganda, Zambia, Burkina Faso.

[g]Transcaucasia/Central Asia: Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan.

[h]South Asia: British Indian Ocean Territory, Afghanistan, Bangladesh, Bhutan, Sri Lanka, India, Maldives, Nepal, Pakistan.

[i]East Asia Pacific: Brunei, Myanmar, Philippines, Taiwan, Hong Kong, Indonesia, Japan, Cambodia, China, North Korea, South Korea, Laos, Macao, Malaysia, Mongolia, Timor-Leste, Singapore, Thailand, Vietnam, Solomon Islands, Fiji, Vanuatu, Tonga, Kiribati, Tuvalu, Nauru, Federated States of Micronesia, Papua New Guinea, Samoa, Marshall Islands, Palau.

[j]Oceania: American Samoa, Australia, Christmas Island, Cocos (Keeling) Islands, Cook Islands, French Polynesia, Guam, United States Minor Outlying Islands, New Zealand, Niue, Norfolk Island, Pitcairn, Tokelau, Wallis and Futuna Islands, New Caledonia, Northern Mariana Islands.

[k]1st trimester smoking: missing data coded as "No".

was coded as "none", "Type 1", "Type 2" and "gestational diabetes". Smoking status was coded as "no", "sometimes" and "daily", with missing data on smoking status coded as "no".

The two main outcomes studied were PE and GH. In MBRN, preeclampsia is defined as sustained de novo blood pressure elevation (systolic blood pressure (BP) ≥140 mm Hg and/or diastolic BP ≥90 mm Hg) after 20 weeks of gestation along with proteinuria (≥0.3 g/24 hours or total protein/creatinine ratio >0.3 or ≥1+ on urine dipstick with a minimum of two measurements). In MBRN, eclampsia is defined as generalized seizures occurring antepartum, intrapartum or within the first 7 days postpartum with concomitant preeclampsia or GH and excluding any other neurologic etiology. In MBRN, GH is defined as sustained de novo blood pressure elevation (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg) after 20 weeks of gestation in the absence of proteinuria, or unspecified maternal hypertension not diagnosed as chronic hypertension, preeclampsia, eclampsia or HELLP syndrome.

2.3 | Statistical analyses

Continuous data were categorized. Descriptive statistics were performed to identify the prevalence of hypertensive disorders of pregnancy according to maternal characteristics. The risks of GH and PE were estimated as crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) by applying logistic regression analysis. A *P*-value of <.05 was used to define statistical significance. Chi-square test was used in the bivariate analysis. Multivariate regression analysis was used to assess the independent association of country of birth to HDP. Women born in Norway were used as the reference group and adjustments were made for differences in education, age, consanguinity, diabetes and smoking status. The independent association of education to HDP was also explored, using women with a secondary education as the reference group and adjusting for differences in the above variables. The data were stratified by parity during the affected pregnancy; nulliparous (para 0) and parous (para 1 or more) women were analyzed separately, due to their different associations with HDP. IBM SPSS Statistics for Windows version 23.0.0.2 (IBM Corp., Armonk, NY, USA) was used for the analyses.

2.4 | Ethical approval

This study is part of The PURPLE Study that was approved by the Regional Ethical Committee South East Norway (#2015/681) as well as by the Institutional Personal Data Officer at Oslo University Hospital. No individual patient consent is required for this registry.

3 | RESULTS

Of the 907 048 deliveries in the study group, 5.2% of deliveries were affected by HDP. The overall prevalence of the PE and GH were 3.4% and 1.8%, respectively (Table 1). HDP was almost 2-fold higher among nulliparous than parous women (7.2 vs 3.7%). The reduction in PE prevalence from nulliparous to parous women was greater than the reduction in GH prevalence.

3.1 | Nulliparous deliveries

In the study group, 382 618 deliveries were to nulliparous women (Table 1). A positive significant association between maternal country of birth, educational level, age, diabetes, consanguinity (1st cousins) and PE was observed in the crude regression analyses (Table 2). First-trimester smoking was negatively associated with PE. In the multivariate regression analyses, with all the significant variables included, the risk factors and associations remained almost unchanged (Table 2). Compared with women born in Norway, the risk of PE was significantly lower for nulliparous women born in EEA, non-EEA, Middle East/North Africa, Transcaucasia/Central Asia, South Asia and East Asia Pacific. High education reduced the risk for PE by 34% (adjusted OR [aOR] 0.66, 95% CI 0.62-0.69) compared with women with secondary education. Type 1 diabetes was the most important risk factor for PE and increased the risk almost 5-fold (aOR 4.80, 95% CI 4.28-5.39), type 2 diabetes tripled the risk (aOR 2.67, 95% CI 2.09-3.40) and gestational diabetes doubled the risk (aOR 1.94, 95% CI 1.76-2.14). Advanced maternal age (≥40 years) increased the risk for PE by 41% (aOR 1.41, 95% CI 1.26-1.59) (Table 2).

Similar trends regarding GH risk among nulliparous deliveries were found as for PE. Compared with women born in Norway, the risk of GH was significantly lower for nulliparous women born in EEA, non-EEA, Latin America/Caribbean, Middle East/North Africa, Sub-Saharan Africa, South Asia and East Asia Pacific. The risk of GH based on country of birth remained significant even when adjusted for education, consanguinity, age, diabetes and smoking status (Table 2). Compared with women with a secondary education, women with no or only primary education had a significantly lower risk for GH (aOR 0.89, 95% CI 0.82-0.96), whereas the risk for GH was significantly higher among women with a Bachelor's (aOR 1.07, 95% CI; 1.02-1.13) or Master's/PhD (aOR 1.14, 95% CI 1.07-1.22). The most important risk factors for GH were type 2 diabetes (aOR 2.18, 95% CI 1.50-3.17), type 1 diabetes (aOR 1.65, 95% CI 1.30-2.11), gestational diabetes (aOR 1.68, 95% CI 1.45-1.95) and advanced maternal age (≥40 years) (aOR 1.82, 95% CI 1.57-2.11) (Table 2).

3.2 | Parous deliveries

In the study group, 524 430 deliveries were to parous women (Table 1). Compared with primiparous women (para 1), the adjusted risk for PE was significantly lower for multiparous women with a parity of 2 or more (Table 3). Women born in EEA, non-EEA, North America, Middle East/North Africa, South Asia and East Asia Pacific had a significantly lower risk of PE compared with parous women born in Norway. After adjusting for education, consanguinity, age, diabetes and smoking status, the risk for PE remained almost unchanged, except that women born in Latin America/Caribbean also

TABLE 2 Nulliparous women: Association of sociodemographic and biological risk factors with hypertensive disorders of pregnancy. Singleton pregnancies delivered ≥23 wk and <44 wk of gestational age, 1999-2014. Crude (OR) and adjusted odds ratios (aOR)

	Nulliparous (para 0) n = 382 618											
	Preeclampsia/Eclampsia (PE)						Gestational hypertension (GH)					
	Crude			Adjusted			Crude			Adjusted		
	OR	95% CI	*P*-value	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value
Birthplace, by region												
Norway	REF			REF			REF			REF		
Europe/EEA	0.66	0.61-0.70	<0.001	0.71	0.66-0.77	<0.001	0.83	0.76-0.90	<0.001	0.78	0.70-0.86	<0.001
Europe/non-EEA	0.57	0.51-0.65	<0.001	0.59	0.52-0.67	<0.001	0.54	0.45-0.64	<0.001	0.57	0.47-0.69	<0.001
North America	0.76	0.60-0.97	0.03	0.84	0.65-1.09	0.19	0.71	0.49-1.03	0.07	0.64	0.43-0.95	0.03
Latin America/Caribbean	0.87	0.74-1.01	0.07	0.86	0.73-1.02	0.08	0.50	0.37-0.67	<0.001	0.45	0.33-0.62	<0.001
Middle East/North Africa	0.50	0.43-0.58	<0.001	0.49	0.41-0.57	<0.001	0.43	0.34-0.54	<0.001	0.48	0.38-0.62	<0.001
Sub-Saharan Africa	1.08	0.98-1.19	0.13	1.00	0.90-1.12	0.96	0.46	0.37-0.57	<0.001	0.50	0.39-0.63	<0.001
Transcaucasia/Central Asia	0.30	0.14-0.68	<0.01	0.26	0.10-0.69	<0.01	0.57	0.24-1.38	0.21	0.50	0.19-1.34	0.17
South Asia	0.62	0.55-0.71	<0.001	0.63	0.54-0.73	<0.001	0.66	0.54-0.79	<0.001	0.60	0.48-0.75	<0.001
East Asia Pacific	0.64	0.58-0.71	<0.001	0.61	0.55-0.68	<0.001	0.49	0.42-0.59	<0.001	0.49	0.41-0.58	<0.001
Oceania	0.58	0.29-1.16	0.12	0.66	0.31-1.41	0.29	1.13	0.53-2.40	0.75	1.29	0.60-2.74	0.52
Education												
Secondary education	REF			REF			REF			REF		
None/primary education	0.91	0.87-0.95	<0.001	0.97	0.92-1.01	0.17	0.73	0.68-0.79	<0.001	0.89	0.82-0.96	<0.01
Bachelor's	0.88	0.85-0.91	<0.001	0.85	0.82-0.88	<0.001	1.15	1.09-1.21	<0.001	1.07	1.02-1.13	0.01
Master's/PhD	0.67	0.63-0.70	<0.001	0.66	0.62-0.69	<0.001	1.24	1.16-1.32	<0.001	1.14	1.07-1.22	<0.001
Consanguinity												
None	REF			REF			REF			REF		
1st cousins	0.51	0.36-0.71	<0.001	0.62	0.42-0.91	0.02	0.66	0.43-1.03	0.07	0.81	0.47-1.42	0.57
Distant cousins	0.97	0.62-1.50	0.88	0.90	0.54-1.48	0.67	0.50	0.21-1.21	0.12	0.43	0.14-1.33	0.14
Other relation	0.88	0.70-1.09	0.24	0.94	0.75-1.18	0.59	0.67	0.48-0.98	0.04	0.81	0.56-1.18	0.28
Unknown	1.09	1.01-1.18	0.31	1.11	1.03-1.21	0.01	0.85	0.75-0.97	0.02	0.88	0.77-1.00	0.05
Age, in years												
20-34	REF			REF			REF			REF		
<20	1.08	1.01-1.15	0.02	1.05	0.97-1.12	0.22	0.48	0.42-0.56	<0.001	0.58	0.50-0.67	<0.001
35-39	1.11	1.06-1.18	<0.001	1.13	1.07-1.19	<0.001	1.53	1.43-1.64	<0.001	1.50	1.40-1.61	<0.001

(Continues)

TABLE 2 (Continued)

	Nulliparous (para 0) n = 382 618										
	Preeclampsia/Eclampsia (PE)						Gestational hypertension (GH)				
	Crude			Adjusted			Crude			Adjusted		
	OR	95% CI	*P*-value	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value
≥40	1.44	1.29-1.61	<0.001	1.41	1.26-1.59	<0.001	1.91	1.66-2.21	<0.001	1.82	1.57-2.11	<0.001
Diabetes												
None	REF			REF			REF			REF		
Type 1	5.00	4.46-5.60	<0.001	4.80	4.28-5.39	<0.001	1.74	1.37-2.21	<0.001	1.65	1.30-2.11	<0.001
Type 2	2.80	2.21-3.54	<0.001	2.67	2.09-3.40	<0.001	2.16	1.50-3.12	<0.001	2.18	1.50-3.17	<0.001
Gestational	1.90	1.72-2.09	<0.001	1.94	1.76-2.14	<0.001	1.63	1.41-1.89	<0.001	1.68	1.45-1.95	<0.001
Smoking, 1st trimester												
No/missing data	REF			REF			REF			REF		
Sometimes	0.85	0.76-0.95	0.01	0.78	0.69-0.88	<0.001	0.94	0.80-1.10	0.42	0.97	0.82-1.13	0.67
Daily	0.89	0.85-0.94	<0.001	0.79	0.75-0.83	<0.001	0.65	0.60-0.70	<0.001	0.68	0.63-0.74	<0.001

had a significantly lower risk of PE (Table 3). The risk of PE was significantly lower among parous women with a Bachelor's (aOR 0.79, 95% CI 0.76-0.82) or a Master's/PhD (aOR 0.61, 95% CI 0.57-0.65) than among women with secondary education. Among parous women, type 1 diabetes was also the most important risk factor for PE and increased the risk 5-fold, whereas type 2 diabetes increased the risk 4-fold and gestational diabetes more than doubled the risk for PE. Advanced maternal age (≥40 years) increased the risk for PE by 73% (aOR 1.73, 95% CI 1.59-1.88).

Compared with parous women born in Norway, the risk of GH was significantly lower for women born in EEA, non-EEA, Latin America/Caribbean, Middle East/North Africa, Sub-Saharan Africa, South Asia and East Asia Pacific. The risk did not change significantly even when adjusted for parity, education, consanguinity, age, diabetes and smoking status. Women with a Master's/PhD had a decreased risk for GH (aOR 0.82, 95% CI 0.75-0.89) compared with the reference group (women with secondary education). All types of diabetes more than doubled the risk of GH among parous women (Table 3).

4 | DISCUSSION

To the best of our knowledge, this is the first study estimating the association of maternal country of birth and education with HDP among all women delivering in Norway between 1999 and 2014. Foreign-born women had a predominantly lower risk of HDP compared with Norwegian-born women. Poorly educated women had no increased risk of HDP compared with women with secondary education. These findings were consistent among nulliparous and parous women. Our large population-based study confirmed nulliparity as a major risk for HDP in Norway. Also in accordance with previous large population-based studies, both pregestational and gestational diabetes were significant risk factors for HDP across all parities. Advanced maternal age was also a moderate independent risk factor for HDP across parities.

Our results are in line with similar findings in Swedish studies that women born outside of Nordic countries had at least a similar or lower risk of HDP than women born in Nordic countries.[11,12] An earlier study from Norway assessing deliveries in a time period with a lower number of immigrants in Norway than in our study (1986-2005) compared specific immigrant groups with Norwegian women and found similar or lower prevalence and risk of preeclampsia among immigrants, with the exception of Somalis.[13] In our study, the prevalence of PE was highest among women born in sub-Saharan Africa, but after adjustment with other covariates these women had a similar risk of PE compared with Norwegian-born women. Whereas other studies have found an increased risk of preeclampsia among sub-Saharan African,[2,3] South Asian,[4-6] and Latin American/Caribbean[2,3] women as compared with women without an immigrant background in industrialized countries, our study found either no difference or a significantly lower risk of PE and GH among foreign-born women in Norway.

TABLE 3 Parous women: Association of sociodemographic and biological risk factors with hypertensive disorders of pregnancy (HDP). Singleton pregnancies delivered ≥23 wk and <44 wk of gestational age, 1999-2014. Crude (OR) and adjusted odds ratios (aOR)

	Parous (≥para 1) n = 524 430											
	Preeclampsia/Eclampsia (PE)						Gestational hypertension (GH)					
	Crude			Adjusted			Crude			Adjusted		
	OR	95% CI	*P*-value	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value
Parity												
1	REF			REF			REF			REF		
2	0.94	0.90-0.98	<0.01	0.88	0.84-0.92	<0.001	1.02	0.96-1.07	0.58	0.95	0.90-1.01	0.08
3	0.95	0.88-1.02	0.15	0.82	0.76-0.88	<0.001	1.11	1.01-1.21	0.02	1.01	0.92-1.11	0.78
4	0.99	0.87-1.13	0.90	0.82	0.72-0.94	<0.01	0.95	0.79-1.13	0.53	0.90	0.75-1.08	0.26
5 or more	1.08	0.92-1.27	0.36	0.81	0.68-0.96	0.02	1.03	0.84-1.28	0.77	1.00	0.80-1.26	0.99
Birthplace, by region												
Norway	REF			REF			REF			REF		
Europe/EEA	0.67	0.61-0.74	<0.001	0.68	0.62-0.76	<0.001	0.79	0.71-0.89	<0.001	0.77	0.68-0.86	<0.001
Europe/non-EEA	0.78	0.68-0.89	<0.001	0.78	0.68-0.89	<0.001	0.58	0.48-0.70	<0.001	0.57	0.47-0.71	<0.001
North America	0.47	0.32-0.69	<0.001	0.44	0.29-0.67	<0.001	0.79	0.54-1.14	0.21	0.75	0.51-1.11	0.15
Latin America/Caribbean	0.85	0.68-1.06	0.14	0.78	0.61-0.98	0.03	0.65	0.48-0.89	0.01	0.67	0.48-0.92	0.01
Middle East/North Africa	0.64	0.56-0.74	<0.001	0.56	0.48-0.66	<0.001	0.53	0.43-0.64	<0.001	0.51	0.41-0.64	<0.001
Sub-Saharan Africa	1.06	0.96-1.17	0.24	0.95	0.85-1.07	0.38	0.52	0.44-0.62	<0.001	0.48	0.39-0.59	<0.001
Transcaucasia/Central Asia	0.65	0.31-1.38	0.26	0.73	0.35-1.54	0.41	0.45	0.14-1.38	0.16	0.48	0.15-1.50	0.21
South Asia	0.86	0.76-0.97	0.02	0.75	0.65-0.86	<0.001	0.73	0.61-0.86	<0.001	0.72	0.60-0.87	0.001
East Asia Pacific	0.77	0.68-0.87	<0.001	0.71	0.62-0.81	<0.001	0.58	0.49-0.70	<0.001	0.57	0.47-0.69	<0.001
Oceania	0.90	0.40-2.03	0.80	0.88	0.36-2.13	0.78	0.72	0.23-2.24	0.57	0.79	0.25-2.48	0.69
Education												
Secondary education	REF			REF			REF			REF		
None/primary education	0.95	0.90-1.00	0.06	1.04	0.99-1.10	0.13	0.80	0.74-0.86	<0.001	0.94	0.87-1.01	0.10
Bachelor's	0.83	0.80-0.87	<0.001	0.79	0.76-0.82	<0.001	1.02	0.96-1.08	0.52	0.95	0.90-1.00	0.06
Master's/PhD	0.66	0.61-0.70	<0.001	0.61	0.57-0.65	<0.001	0.91	0.84-0.99	0.02	0.82	0.75-0.89	<0.001
Consanguinity												
No consanguinity	REF			REF			REF			REF		
1st cousins	0.90	0.68-1.19	0.46	1.04	0.77-1.41	0.81	0.70	0.47-1.04	0.08	0.96	0.62-1.49	0.86
Distant cousins	0.85	0.50-1.44	0.54	0.98	0.58-1.67	0.95	0.49	0.20-1.18	0.11	0.64	0.27-1.55	0.33

(Continues)

TABLE 3 (Continued)

	Parous (≥para 1) n = 524 430											
	Preeclampsia/Eclampsia (PE)						Gestational hypertension (GH)					
	Crude			Adjusted			Crude			Adjusted		
	OR	95% CI	*P*-value	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value
Other relation	0.76	0.57-1.02	0.07	0.73	0.54-1.00	0.05	0.58	0.38-0.88	0.01	0.60	0.38-0.94	0.03
Unknown	1.04	0.94-1.16	0.44	1.07	0.96-1.19	0.23	0.81	0.69-0.93	<0.01	0.85	0.73-0.98	0.03
Age, in years												
20-34	REF			REF			REF			REF		
<20	0.85	0.55-1.31	0.46	0.84	0.54-1.31	0.43	0.21	0.07-0.64	0.01	0.18	0.04-0.70	0.01
35-39	1.27	1.22-1.32	<0.001	1.35	1.29-1.41	<0.001	1.45	1.37-1.53	<0.001	1.44	1.36-1.52	<0.001
≥40	1.64	1.51-1.77	<0.001	1.73	1.59-1.88	<0.001	1.92	1.75-2.12	<0.001	1.88	1.70-2.08	<0.001
Diabetes												
None	REF			REF			REF			REF		
Type 1	4.86	4.24-5.56	<0.001	4.74	4.14-5.43	<0.001	2.53	2.03-3.16	<0.001	2.51	2.01-3.13	<0.001
Type 2	4.03	3.30-4.92	<0.001	3.90	3.17-4.79	<0.001	2.25	1.64-3.10	<0.001	2.26	1.62-3.15	<0.001
Gestational	2.48	2.25-2.73	<0.001	2.40	2.18-2.65	<0.001	2.03	1.78-2.31	<0.001	2.03	1.77-2.31	<0.001
Smoking, 1st trimester												
No/missing data	REF			REF			REF			REF		
Sometimes	0.84	0.71-0.99	0.03	0.77	0.65-0.91	<0.01	0.77	0.62-0.96	0.02	0.75	0.60-0.93	0.01
Daily	0.82	0.77-0.87	<0.001	0.72	0.67-0.77	<0.001	0.67	0.62-0.73	<0.001	0.64	0.59-0.70	<0.001

The strength of this study is its large population-based dataset of almost 1 million deliveries during the study period, with a previously published validation study showing high validity of the preeclampsia diagnosis in the MBRN.[14] All foreign-born women delivering in Norway were included in this study, not merely specific immigrant groups as in previous studies.[13,15-18] We performed multivariate regression analyses, which describe the complex covariation of the assessed risk factors.

Another strength is that all women receive equal and free-of-charge antenatal care in Norway. Quality of care and definitions are standardized in the entire country, giving us an opportunity to compare women with different backgrounds/countries of birth within a fairly homogeneous national health system. Such comparison is difficult when comparing women giving birth in different countries due to the different data collection methods and local variations in delivery of care.[2]

A weakness of this study is that 16% of deliveries lacked data on maternal smoking status. A separate analysis of these women showed that their outcomes were closer to non-smokers than smokers (results not shown). We therefore included women with missing data on smoking in the non-smoking group, similarly to a previously published preeclampsia study using MBRN data.[19] The amount of missing data in the other variables was in general low and not greater than 3.9% (eg the education variable). Although registry data will always include some errors and missing data, the MBRN data are considered of high quality and suitable for research.[20]

The significantly lower risk of HDP among all groups of foreign-born women as compared with women born in Norway may be influenced by underlying social and biological factors. Immigrants to European countries tend to be healthier than their native-born hosts, partly due to strict national immigration policies[21] or self-selection bias, where the healthiest foreigners are more likely to succeed in emigrating and immigrating. In Norway, however, specific immigrant groups have a poorer health profile than Norwegians,[22] so the healthy immigrant effect may not be present in our study. In Oslo, female immigrants and immigrants with low education tend to utilize more healthcare services than Norwegians.[22] Nationwide, immigrants tend to utilize primary care services less often than Norwegians, but those that do access primary care do so at a higher rate than Norwegians.[23] Because of variations in utilization of primary care services, language competency and baseline health among immigrant women in Norway, prenatal care providers may face diagnostic challenges. The lower risk of HDP is less likely due to an underdiagnosis of HDP among foreign-born women, as the diagnoses are finalized at the delivering hospitals, which offer the same surveillance and care to all women.

To date there are no other studies exploring the relation between education level and HDP in Norway. Education is a good proxy for socioeconomic status as it is less likely to be influenced by adult-onset diseases than are other measures such as income and occupation.[24] Our study found that, regardless of place of birth or parity, women with the lowest education level did not have an increased risk of HDP. Among highly educated nulliparous women the risk of PE was lower but the risk of GH higher compared with women of similar parity with secondary education. Our findings are in contrast to other studies estimating an inverse association between socioeconomic status and HDP in high-income countries.[9,10,25]

The classic diagnosis of PE that MBRN used during the study data collection time period included development of new-onset proteinuria in addition to new-onset hypertension after gestational week 20. Approximately 20% of all pregnant women first developing GH will also develop proteinuria before delivery.[26] Such women will thereby be diagnosed with PE in the MBRN as the maternal outcome diagnosis for this pregnancy. The variation in risk of PE and GH associated with education level may be due to a difference in utilization of healthcare services. We cannot confirm this, as the MBRN does not collect data on number of prenatal visits, duration of HDP, diagnosis on admission or indication for delivery.

In our study population, only 0.5% of nulliparous women and 0.6% of parous women were registered with chronic hypertension. We performed a sensitivity analysis with chronic hypertension as a risk factor in the multiple regression analysis and found that it did not change our conclusions for any of the exposures in this study (data not shown).

Diabetes and advanced maternal age were, in addition to nulliparity, the strongest risk factors for HDP. This is in line with a previous study from Norway which found a significantly increased risk of preeclampsia in both immigrant and Norwegian women with diabetes.[18]

Consanguinity and the risk of HDP have not been previously studied in Norway. Although this was not the primary aim of our study, we found a negative association between consanguinity (1st cousins) and PE among nulliparous women. Studies from other countries show conflicting results.[27,28] Consanguinity among certain immigrant groups in Norway has been linked to perinatal death and birth defects,[16,29] with the risks persisting in second-generation immigrants and in subsequent pregnancies.[15,30,31] An association between consanguinity and HDP is possible, but given the very low number of women in the consanguinity group in our study, this may be a spurious finding. Further studies should be performed in cohorts with detailed pedigrees.

5 | CONCLUSION

Our study found that maternal country of birth and education were associated with HDP. Women with higher education had the lowest risk of HDP and Norwegian-born women had the highest risk, regardless of parity and other confounding factors. Further investigation of other possible risk factors and healthcare utilization patterns might help explain the relative differences in the HDP subgroups among women of different education levels and countries of birth.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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How to cite this article: Sole KB, Staff AC, Laine K. The association of maternal country of birth and education with hypertensive disorders of pregnancy: A population-based study of 960 516 deliveries in Norway. *Acta Obstet Gynecol Scand*. 2018;97:1237–1247. https://doi.org/10.1111/aogs.13393

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Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 25 (2021) 25–33

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Maternal diseases and risk of hypertensive disorders of pregnancy across gestational age groups

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ARTICLE INFO

Keywords:
Body Mass Index (BMI)
Diabetes
Gestational age
Hypertension
Preeclampsia
Pregnancy

ABSTRACT

Objectives: To estimate the risk of hypertensive disorders of pregnancy in nulliparous women with diabetes, chronic hypertension or obesity in three gestational age groups.
Study design: Population-based observational cohort study of 382 618 nulliparous women (94 280 with known BMI) using Medical Birth Registry of Norway and Statistics Norway. Main exposure variables were diabetes, chronic hypertension, Body Mass Index (BMI). Multiple regression analysis was performed without (model 1) and with (model 2) BMI.
Main outcome measures: Preeclampsia stratified by gestational age group at delivery: early (23^0-33^6 weeks), intermediate (34^0-36^6 weeks) and late (37^0-43^6 weeks), and gestational hypertension.
Results: In model 1, Type 1 diabetes was associated with early (aOR = 5.0, 95%CI 3.8, 6.7), intermediate (aOR = 10.2, 95%CI 8.5, 12.3) and late preeclampsia (aOR = 2.7, 95%CI 2.4, 3.2), compared to no diabetes. Compared to normotensive women, women with chronic hypertension had an increased risk of preeclampsia in all groups: early (aOR = 8.68, 95%CI 6.94, 10.85), intermediate (aOR = 5.59, 95%CI 4.46, 7.02), late (aOR = 3.45, 95%CI 3.00, 3.96). The same trends persisted after adjusting for BMI (model 2). Obesity remained an independent risk factor for hypertensive disorders of pregnancy.
Conclusions: Maternal diabetes, chronic hypertension and obesity were associated with an increased risk of hypertensive disorders of pregnancy across all gestational age groups in nulliparous women. Adjusting for BMI did not further modify the risk in these women, although 75% of the women in the study lacked BMI data.

1. Introduction

Hypertensive disorders of pregnancy represent major causes of maternal and fetal mortality and morbidity world-wide, also affecting long-term health in the survivors [1]. As the time of onset is most often less reliably recorded than time of delivery, preeclampsia "onset" is for simplicity often dichotomized according to preterm and term delivery (delivery prior to or from gestational week 37) or into a very preterm delivery (delivery prior to gestational week 34) or not [2–4]. Early-onset preeclampsia is generally defined as occurring before 34 weeks gestational age [5].

Previous models of preeclampsia have suggested that early-onset preeclampsia may arise predominantly from placental dysfunction, whereas late-onset preeclampsia may be due to exaggerated maternal response to inflammatory or metabolic stress from underlying disorders such as diabetes, chronic hypertension and obesity with or without poor placentation [6–8]. An alternative model suggests that both early and late-onset preeclampsia results from placental malperfusion and syncytiotrophoblast stress [9], but that the causes and timing of placental malperfusion differ [3,4,10]. This model fits better with the clinical heterogeneity of preeclampsia as well as gestational hypertension.

Nulliparous women have an increased risk of preeclampsia compared to parous women [11], likely due to immunological and anatomical factors related to uteroplacental artery remodeling and other placentation processes [10]. Known risk factors for preeclampsia include increasing maternal age, pre-gestational diabetes mellitus,

Abbreviations: aOR, adjusted odds ratio; BMI, Body Mass Index; CHTN, chronic hypertension; CI, confidence interval; GH, gestational hypertension; ISCED, International Standard Classification of Education; MBRN, Medical Birth Registry of Norway; OR, odds ratio; PE, preeclampsia/eclampsia; SSB, Statistics Norway.

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https://doi.org/10.1016/j.preghy.2021.05.004
Received 2 November 2020; Received in revised form 27 December 2020; Accepted 8 May 2021
Available online 14 May 2021

chronic hypertension, antiphospholipid syndrome, assisted reproduction, multiple pregnancy and obesity, but there is decreased risk with smoking [1,12]. Maternal country of birth and education are also associated with preeclampsia and gestational hypertension [11,13,14]. Population-based studies estimating the association between common chronic maternal diseases and any subtype of hypertensive disorders of pregnancy across specific gestational age groups are lacking.

Pregnancies affected by a hypertensive disorder might necessitate iatrogenic delivery for maternal and/or fetal indications [15–17]. Late preterm delivery (34^0–36^6 weeks) is not without risk to the offspring [18,19]. The aim of this study was therefore to determine the prevalence of early, intermediate, and late-onset hypertensive disorders of pregnancy among nulliparous women, and to estimate the association of maternal comorbidity, namely diabetes, chronic hypertension and obesity with preeclampsia and gestational hypertension. We also wanted to investigate how pre-pregnancy Body Mass Index (BMI), as a proxy for obesity, influenced the risk of hypertensive disorders of pregnancy complicated by maternal diabetes or chronic hypertension. Our hypothesis was that nulliparous women with any of these chronic diseases had an increased risk of any form of hypertensive disorders of pregnancy, and that the magnitude of risk was highest in the early gestational age groups.

2. Material and methods

This study is part of the larger PURPLE Study, which investigates adverse pregnancy outcomes in Norway from 1967 to 2014 using linked data from the Medical Birth Registry of Norway (MBRN) and Statistics Norway (SSB).[11,20–22] The Regional committee for Medical and Health Research Ethics in South-Eastern Norway (#2015/681) and the Institutional Personal Data Officer at Oslo University Hospital approved this study. Individual patient consent was not required for the use of anonymous registry data.

Our study population included all singleton deliveries by nulliparous women in Norway between 1999 and 2014 at gestational age $\geq$ 23 and $<$ 44 weeks (382 618 deliveries). Pregnancies with major congenital anomalies were excluded. Gestational age at birth was calculated by fetal biometry performed during mid-trimester ultrasound examination (17–20 weeks gestation), or was based on the last menstrual period in the rare instances when ultrasound-dating was not available.

The main exposure variables in our study were maternal diabetes, chronic hypertension and BMI. These exposures along with other maternal morbidity are routinely recorded in the standardized ambulatory prenatal record used throughout Norway. Mandatory notification to the MBRN occurs immediately after delivery by automatic transfer of midwife and doctor-registered information from the electronic hospital chart.

Diabetes was classified into three categories: Type 1 diabetes, type 2 diabetes and gestational diabetes. Selective screening for gestational diabetes at 28–30 weeks gestational age is in Norway based on risk factors: family history of type 1 or type 2 diabetes in 1st-degree relative, foreign-born, maternal age $>$ 35 years, BMI $>$ 27 kg/m^2. Glycosuria, polyhydramnios, rapid fetal weight gain or random fasting blood glucose between 6.1 mmol/L and 7.0 mmol/L at any time during the pregnancy also prompts screening. Gestational diabetes was in the study period defined as a fasting plasma glucose $<$ 7.0 mmol/L and a 2-hour plasma glucose $\geq$ 7.8 mmol/L and $<$ 11.1 mmol/L after a 75 g oral glucose load.

Chronic hypertension is defined in the MBRN as a binary YES/NO variable and includes the following diagnoses: chronic hypertension, essential (primary) hypertension, hypertensive heart disease, hypertensive kidney disease, hypertensive heart and kidney disease and secondary hypertension. Chronic hypertension excludes hypertension as a complication of pregnancy, delivery or postpartum.

Pre-pregnancy BMI, calculated by recorded maternal height and pre-pregnancy weight, was categorized using World Health Organization classifications: underweight $<$ 18.5 kg/m^2, normal 18.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2, obese $\geq$ 30.0 kg/m^2. The MBRN started collecting data on maternal height and weight in 2006.

Other risk factors for hypertensive disorders of pregnancy were assessed as possible confounders to the main exposure variables. These included maternal age, country of birth, education, and first-trimester smoking. Maternal age was categorized into 4 groups ($<$20, 20–34, 35–39 and $\geq$ 40 years). Country of birth was categorized into 11 world regions defined by The World Bank and Statistics Norway [11]. Education was classified by merging the 8 levels of education used in the International Standard Classification of Education (ISCED-2011) into 4 levels, according to number of years of completed education. First-trimester smoking was categorized into 3 groups (no, sometimes, daily), with missing data coded as "no".

The two main outcome variables studied were preeclampsia (including eclampsia) and gestational hypertension. Preeclampsia, during the study period, was defined as sustained de novo blood pressure elevation $\geq$ 140/90 mmHg after 20 weeks gestational age accompanied by proteinuria. Proteinuria is traditionally diagnosed in Norway by $\geq 1^+$ on urine dipstick with a minimum of two measurements, or by urine protein $\geq$ 0.3 g/24 h or $>$ 0.3 total protein/creatinine ratio. Eclampsia was defined as peripartum generalized seizures occurring up to 7 days postpartum associated with preeclampsia or gestational hypertension, and merged with the preeclampsia group in the analyses. Gestational hypertension was defined with the same blood pressure criteria as preeclampsia, but without concomitant proteinuria. Gestational hypertension excluded chronic hypertension, preeclampsia, eclampsia and HELLP syndrome.

Preeclampsia onset was categorized into three groups according to gestational age at delivery: early (23^0–33^6 weeks), intermediate (34^0–36^6 weeks) and late (37^0–43^6 weeks). Gestational hypertension was used a single outcome encompassing all gestations between 23^0 and 43^6 weeks.

IBM SPSS Statistics for Windows version 23.0.0.2 was used for the analysis. We used descriptive statistics to determine the prevalence of preeclampsia (grouped by gestational age at delivery) and gestational hypertension, according to maternal characteristics. Logistic regression was performed to estimate the crude odds ratios (OR) with 95% confidence intervals (CI) of preeclampsia and gestational hypertension. Statistical significance was defined as a p-value of $<$ 0.05. Using multivariate regression analysis, we assessed the independent association of diabetes to hypertensive disorders of pregnancy, using women without diabetes as the reference group. In model 1, adjustments were made for maternal age, country of birth, education, and smoking status. BMI was added to the analysis in model 2. We also explored the independent association of chronic hypertension to preeclampsia with both models, using women without chronic hypertension as the reference group and adjusting for differences in the above variables.

3. Results

Of the 382 618 singleton deliveries in the study population, 5.0% were affected by preeclampsia and 2.2% were affected by gestational hypertension (Table 1). Three quarters (76%) of the preeclampsia deliveries were at $\geq 37^0$ weeks gestational age, whereas 14% were at 34^0-36^6 weeks and 10% were at 23^0-33^6 weeks. Although the overall prevalence of early preeclampsia was >7 times lower than late-onset disease (0.5% vs. 3.8%), the prevalence of preeclampsia among all early deliveries 23^0-33^6 weeks was almost 7-fold higher than among all deliveries at term (37^0-43^6 weeks); 28.0% vs. 4.1%. Preeclampsia was similarly much more common among all deliveries 34^0-36^6 weeks than among all term deliveries; 16.1% vs. 4.1%. Superimposed preeclampsia developed in 23% of women with chronic hypertension. Most of these delivered at term (13.2%), whereas 4.9% delivered at early and intermediate gestational ages, respectively.

The prevalence of gestational hypertension was relatively stable

Table 1
Selected demographics and clinical characteristics by pregnancy outcome group: Nulliparous women with singleton deliveries.

Maternal Characteristics	Total Deliveries n	Early PE[a] 23^0–33^6 % (n)	Intermediate PE 34^0–36^6 % (n)	Late PE 37^0–43^6 % (n)	GH[b] 3^0–43^6 % (n)
Deliveries	382 618	0.5 (1980)	0.7 (2697)	3.8 (14 708)	2.2 (8562)
Gestational age, in weeks[days]					
23^0-33^6	7072	28.0 (1980)			2.1 (1 4 9)
34^0-36^6	16 715		16.1 (2697)		2.7 (4 5 4)
37^0-43^6	358 831			4.1 (14 708)	2.2 (7959)
Maternal age, in years					
<20	18 632	0.5 (98)	0.8 (1 4 5)	4.0 (7 4 6)	1.1 (1 9 9)
20–34	330 824	0.5 (1634)	0.7 (2267)	3.8 (12 596)	2.2 (7227)
35–39	28 326	0.7 (2 0 1)	0.8 (2 3 0)	4.0 (1131)	3.3 (9 3 7)
>40	4808	1.0 (47)	1.1 (55)	4.9 (2 3 5)	4.1 (1 9 7)
Birthplace, by region					
Norway	305 189	0.5 (1634)	0.7 (2264)	4.1 (12 635)	2.4 (7374)
Europe, EEA	26 931	0.3 (91)	0.5 (1 2 2)	2.8 (7 5 8)	2.0 (5 4 0)
Europe, non-EEA	9093	0.3 (30)	0.6 (52)	2.2 (2 0 3)	1.3 (1 1 9)
North America	1619	0.7 (11)	0.8 (13)	2.7 (44)	1.7 (28)
Latin America/ Caribbean	3770	0.6 (21)	0.7 (26)	3.4 (1 2 9)	1.2 (46)
Middle East/ North Africa	7214	0.5 (37)	0.4 (31)	1.8 (1 2 8)	1.1 (76)
Sub-Saharan Africa	7605	1.0 (74)	0.7 (57)	4.0 (3 0 3)	1.1 (86)
Transcaucasia/ Central Asia	360	0.0 (0)	0.6 (2)	1.1 (4)	1.4 (5)
South Asia	6957	0.5 (34)	0.5 (38)	2.4 (1 6 5)	1.6 (1 1 1)
East Asia Pacific	11 662	0.3 (39)	0.6 (72)	2.5 (2 9 3)	1.2 (1 4 1)
Oceania	257	n ≤ 5	n ≤ 5	2.3 (6)	2.7 (7)
Educational level					
None/primary education	58 935	0.5 (3 1 8)	0.7 (4 1 6)	3.9 (2324)	1.6 (9 3 8)
Secondary education	109 366	0.5 (9 4 7)	0.7 (1301)	4.3 (4734)	2.2 (2375)
Higher education	198 648	0.5 (7 4 2)	0.7 (1040)	3.7 (7309)	2.5 (5021)
Diabetes					
No	374 764	0.5 (1882)	0.7 (2461)	3.8 (14 107)	2.2 (8272)
Type 1	1855	3.0 (55)	7.1 (1 3 1)	10.5 (1 9 4)	3.8 (70)
Type 2	646	1.9 (12)	2.8 (18)	7.7 (50)	4.6 (30)
Gestational	5353	0.6 (31)	1.6 (87)	6.7 (3 5 7)	3.5 (1 9 0)
Smoking, 1st-trimester[c]					
No/missing	328 772	0.5 (1731)	0.7 (2377)	3.9 (12 816)	2.3 (7694)
Sometimes	7197	0.4 (29)	0.5 (38)	3.5 (2 5 5)	2.2 (1 5 8)
Daily	46 649	0.5 (2 2 0)	0.6 (2 8 2)	3.5 (1637)	1.5 (7 1 0)
Chronic Hypertension					
No	380 746	0.5 (1888)	0.7 (2605)	3.8 (14 461)	2.2 (8562)
Yes	1872	4.9 (92)	4.9 (92)	13.2 (2 4 7)	NA
BMI[d], pre-pregnancy					
Underweight	4815	0.3 (13)	0.5 (24)	2.0 (96)	0.6 (28)
Normal	60 643	0.3 (1 6 2)	0.5 (2 9 1)	2.7 (1637)	1.1 (6 8 4)
Overweight	18 891	0.6 (1 1 7)	0.7 (1 2 7)	4.3 (8 0 9)	2.1 (3 9 8)
Obese	9931	0.9 (93)	0.9 (86)	7.3 (7 2 0)	4.4 (4 3 8)

[a] PE: Preeclampsia/eclampsia.
[b] GH: Gestational hypertension.
[c] Smoking, 1st-trimester: missing data coded as "No".
[d] BMI: Body Mass Index, underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese (≥30.0 kg/m^2).

across our 3 predefined gestational age groups (2.1–2.7%, Table 1). The majority (93.0%) of the women with gestational hypertension delivered at term.

Overall, approximately 2% of the women had any form of diabetes and 0.5% had chronic hypertension. One third of the women with recorded BMI were either overweight (20.0%) or obese (10.5%) (Table 1).

3.1. Association of diabetes with preeclampsia and gestational hypertension

Positive significant associations between pregestational diabetes and early, intermediate and late preeclampsia were observed in the crude regression analysis (Figs. 1–3). Similarly, gestational diabetes mellitus was significantly associated with intermediate and late preeclampsia (Figs. 2 and 3). In model 1 of the multivariate regression analysis, which included adjustment for all risk factors except BMI, the association between pregestational and gestational diabetes and preeclampsia remained almost unchanged for all gestational age groups (Figs. 1–3), with the largest magnitude of risk in the type I diabetes group for intermediate preeclampsia (aOR = 10.2, 95%CI 8.5, 12.3; Fig. 2). Adding adjustment for BMI (model 2) did not significantly alter the associations (Figs. 1–3). The number of women with reported BMI was too small to measure the association between type 2 diabetes and early or intermediate preeclampsia (both n ≤ 5).

A positive significant association between all diabetes types and gestational hypertension (approximately a doubling of risk) was observed in the crude regression analysis, and these associations remained mostly unchanged in model 1 of the multivariate regression analysis (Fig. 4). After adjusting for BMI there was no longer an increased risk of gestational hypertension among women with type 1 or type 2 diabetes, whereas gestational diabetes remained a small, but significant, risk factor (model 2: aOR = 1.4, 95%CI 1.1, 1.8; Fig. 4).

3.2. Association of chronic hypertension with superimposed preeclampsia

Compared to normotensive women, women with chronic hypertension had a 10-fold increased risk of early preeclampsia (OR = 10.37, 95%CI 8.37, 12.85; Fig. 1), 8-fold increased risk of intermediate

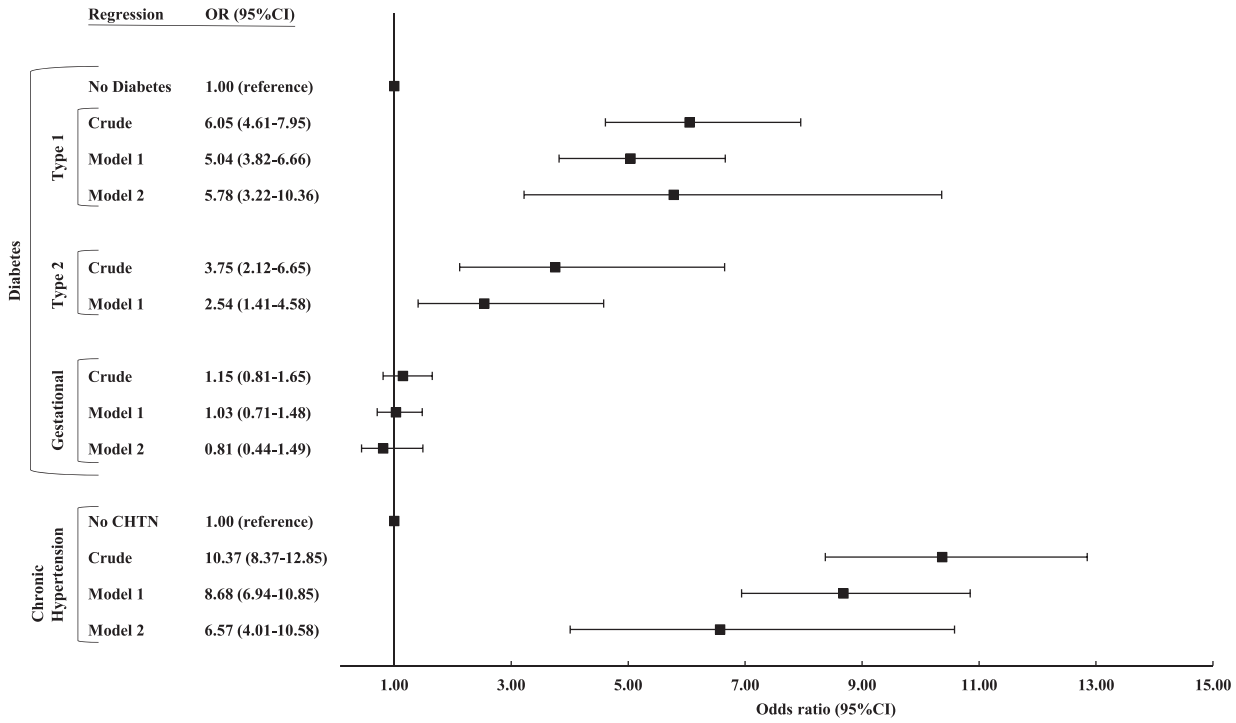

Fig. 1. Association of diabetes and chronic hypertension in nulliparous women with early-onset preeclampsia. Crude and adjusted odds ratio (OR) with 95% confidence interval (95%CI) at delivery between 23^0 and 33^6 weeks gestation. Model 1: n = 366 949 deliveries, 1919 with early-onset preeclampsia. Adjusted for maternal age, country of birth, education and 1st-trimester smoking. Model 2: n = 88 612 deliveries, 367 with early-onset preeclampsia. Adjusted for maternal age, country of birth, education, 1st-trimester smoking and Body Mass Index (BMI). CHTN: chronic hypertension.

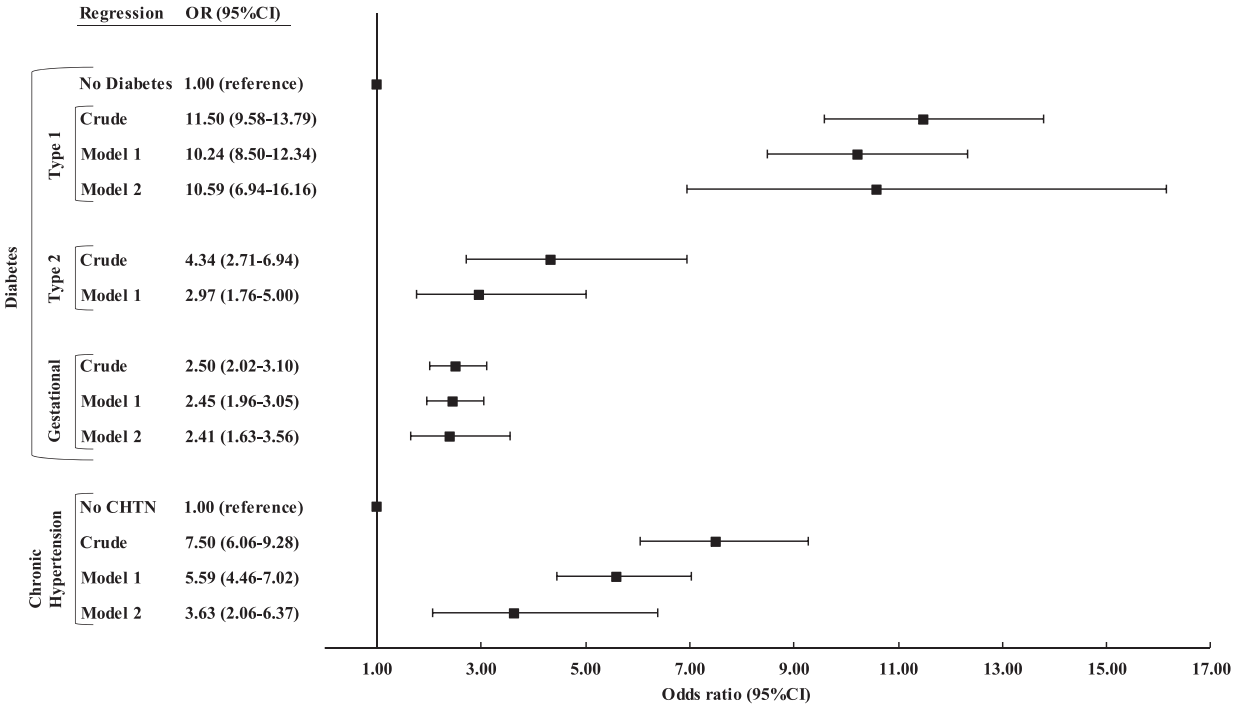

Fig. 2. Association of diabetes and chronic hypertension in nulliparous women with intermediate-onset preeclampsia. Crude and adjusted odds ratio (OR) with 95% confidence interval (95%CI) at delivery between 34^0 and 36^6 weeks gestation. Model 1: n = 366 949 deliveries, 2614 with intermediate-onset preeclampsia. Adjusted for maternal age, country of birth, education and 1st-trimester smoking. Model 2: n = 88 612 deliveries, 502 with intermediate-onset preeclampsia. Adjusted for maternal age, country of birth, education, 1st-trimester smoking and Body Mass Index (BMI). CHTN: chronic hypertension.

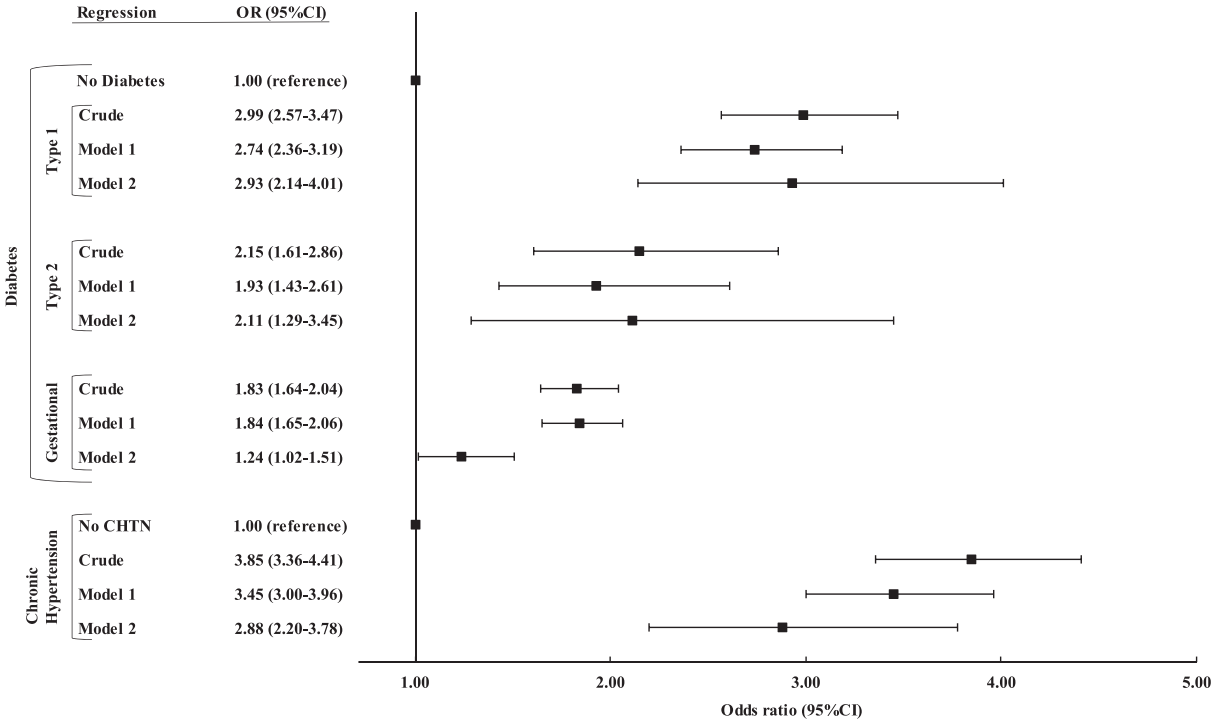

Fig. 3. Association of diabetes and chronic hypertension in nulliparous women with late-onset preeclampsia. Crude and adjusted odds ratio (OR) with 95% confidence interval (95%CI) at delivery between 37^0 and 43^6 weeks gestation. Model 1: n = 366 949 deliveries, 14 367 with late-onset preeclampsia. Adjusted for maternal age, country of birth, education and 1st-trimester smoking. Model 2: n = 88 612 deliveries, 3141 with late-onset preeclampsia. Adjusted for maternal age, country of birth, education, 1st-trimester smoking and Body Mass Index (BMI). CHTN: chronic hypertension.

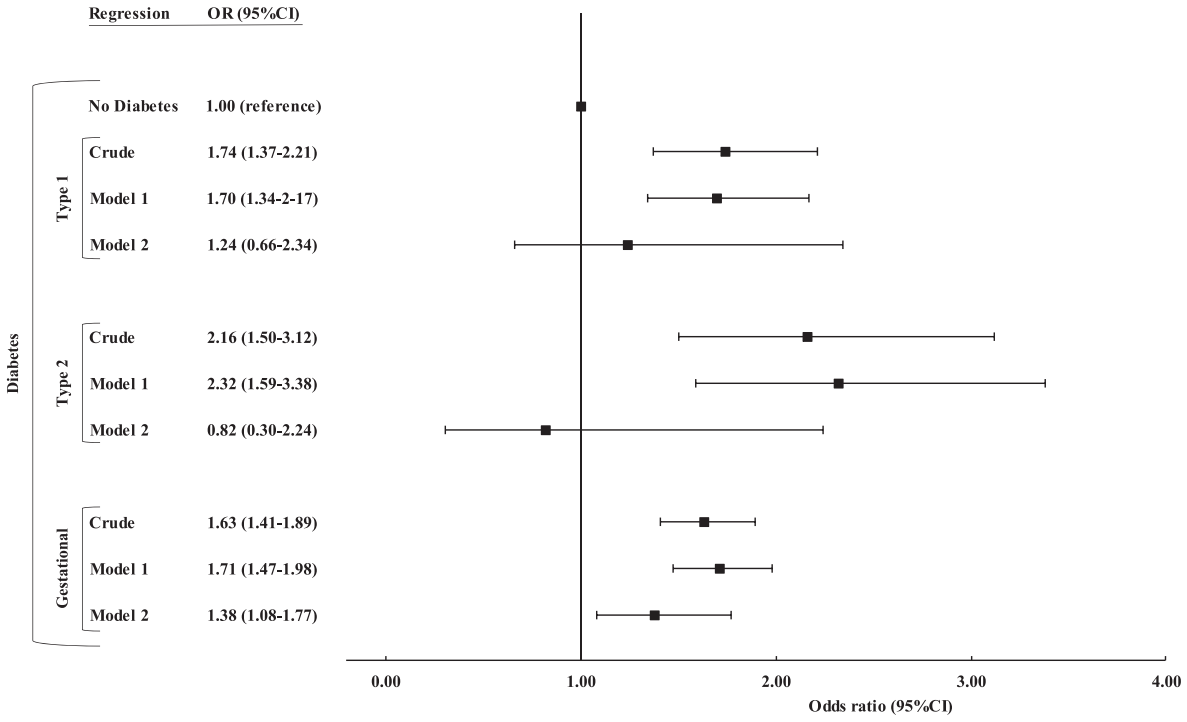

Fig. 4. Association of diabetes in nulliparous women with gestational hypertension. Crude and adjusted odds ratio (OR) with 95% confidence interval (95%CI) at delivery between 23^0 and 43^6 weeks gestation. Model 1: n = 366 949 deliveries, 8334 with gestational hypertension. Adjusted for maternal age, country of birth, education and 1st-trimester smoking. Model 2: n = 88 612 deliveries, 1494 with gestational hypertension. Adjusted for maternal age, country of birth, education, 1st-trimester smoking and Body Mass Index (BMI).

preeclampsia (OR = 7.50, 95%CI 6.06, 9.28; Fig. 2), and a 4-fold increased risk of late preeclampsia (OR = 3.85, 95%CI 3.36, 4.41; Fig. 3). The risk for preeclampsia in all gestational age groups remained high after adjusting for other possible risk factors (model 1), including BMI (model 2) (Figs. 1–3).

3.3. Association of BMI with preeclampsia and gestational hypertension

Compared to normal weight women, women with overweight or obesity had an increased risk of preeclampsia across all gestational age groups and increased risk of gestational hypertension (Fig. 5). The risk remained essentially unchanged after adjusting for the main exposures; maternal diabetes and chronic hypertension (Fig. 5).

4. Discussion

4.1. Principal findings

This study estimated the association of diabetes, chronic hypertension and obesity with early, intermediate, and late preeclampsia as well as gestational hypertension among nulliparous women with singleton pregnancies. Our study had several principal findings: Firstly, type 1 diabetes was an independent risk factor for early, intermediate and late-onset preeclampsia. Secondly, gestational diabetes was an independent, but weak, risk factor for gestational hypertension. Thirdly, chronic hypertension was positively associated with preeclampsia across all gestational age groups, and the risk was higher in early compared to late-onset disease. Lastly, overweight/obesity was an independent risk factor for hypertensive disorders of pregnancy. BMI, however, did not significantly additionally alter the risk of hypertensive diseases in pregnancy among nulliparous women with either diabetes or chronic hypertension across all gestational age groups.

To the best of our knowledge, this is the first study specifically estimating the association between pre-existing diabetes and hypertensive diseases of pregnancy among nulliparous women in the intermediate gestational age of 34^0–36^6 weeks. A small Finnish study with 903 nulliparous and parous women found a positive association between type 1 diabetes and early and intermediate-onset preeclampsia, but no association at term [7]. A Swedish study of both nulliparous and parous women with pregestational diabetes showed an increased risk of both preterm (<37 weeks) and term (≥37 weeks) preeclampsia [23]. We found that nulliparous women with type 1 diabetes had increased risk of preeclampsia across all 3 gestational age groups. Most notably, the risk of preeclampsia in the intermediate gestational age group (34^0 – 36^6 weeks) was of at least similar magnitude as in the early gestational age group.

Previous studies have investigated the association between gestational diabetes and gestational hypertension with conflicting results. A small Swedish cohort study did not find an association between the two [24], whereas a US case-control study found a positive association [25]. Our large population-based cohort study showed a moderately increased risk of gestational hypertension among women with gestational diabetes, even after controlling for other risks, including BMI. Similar to other studies, we found no independent association between type 1 or type 2 diabetes and gestational hypertension, after adjustment analyses [26]. The lack of association between gestational diabetes and early-onset preeclampsia is compatible with the group having less time to develop gestational diabetes before delivery, since selective screening for diabetes occurred mostly between 28 and 30 weeks gestation, based on national guidelines [27].

Similar to other published estimates [12], 23% of women with chronic hypertension in our study developed superimposed preeclampsia. Previous studies have found a positive association between chronic hypertension and superimposed preeclampsia [28–32], but have not studied preeclampsia outcomes by gestational age group. We found that the magnitude of risk of preeclampsia in women with chronic

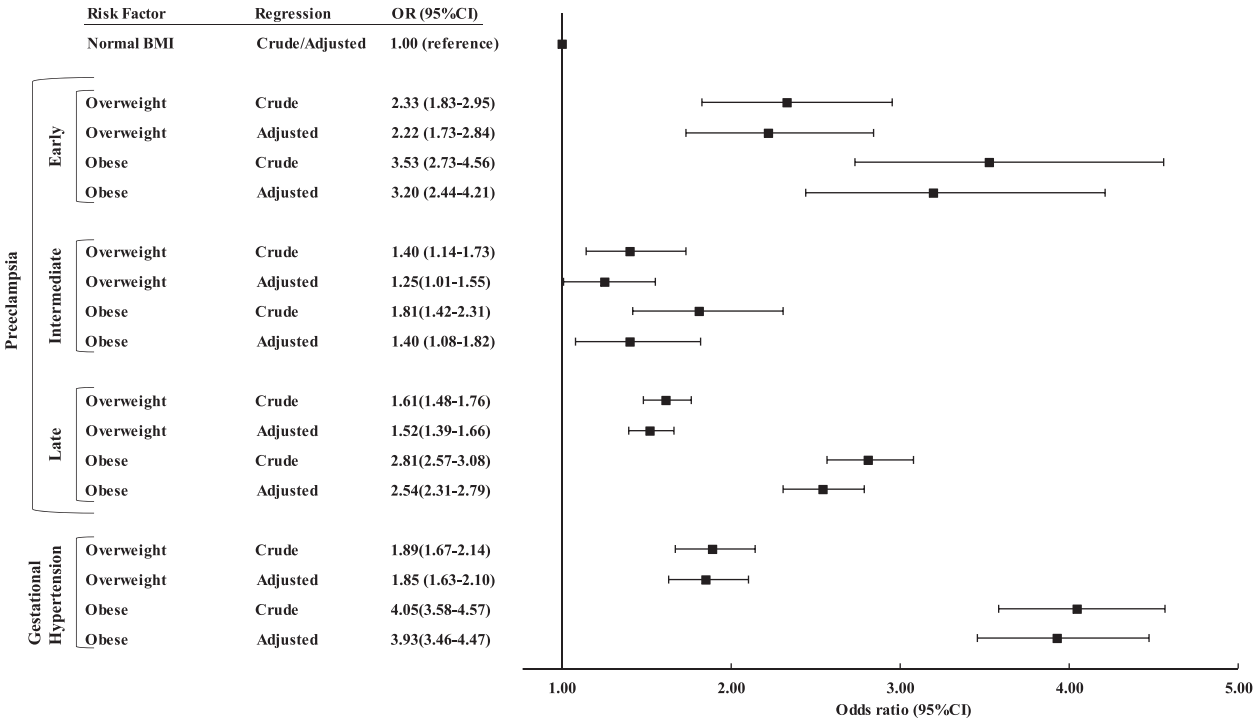

Fig. 5. Association of Body Mass Index in nulliparous women with preeclampsia and gestational hypertension. Crude and adjusted odds ratio (OR) with 95% confidence interval (95%CI). Adjusted for maternal age, country of birth, education, 1st-trimester smoking, diabetes and chronic hypertension. n = 88 612 deliveries. Preeclampsia: early (23^0-33^6 weeks gestational age) n = 367 deliveries, intermediate (34^0-36^6 weeks gestational age) n = 502 deliveries, late (37^0-43^6 weeks gestational age) n = 3141 deliveries. Gestational hypertension: 23^0-43^6 weeks gestational age. BMI: Body Mass Index, normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese (≥30.0 kg/m^2).

hypertension was inversely proportional to the gestational age group at delivery.

Our results also showed that women with pre-pregnancy BMI classified as overweight or obese had an increased risk of preeclampsia across all three gestational age groups and gestational hypertension, even after adjustment for possible confounders. Our findings are in contrast to other studies showing no increased risk of early [7,33] or intermediate-onset preeclampsia [7] among overweight and obese women. A recent large US study [34] also found a positive association between obesity and hypertensive disorders of pregnancy, but the study classified overweight women with normal weight women, and excluded women with chronic hypertension. Robillard et al. showed a positive association between pre-pregnancy BMI and early and late-onset preeclampsia, with a linear correlation between 5 kg/m^2 increments in BMI and preeclampsia present only in late-onset disease [35]. Our study found that women with obesity had a higher risk for late-onset preeclampsia (aOR = 2.54, 95%CI 2.31, 2.79; Fig. 5) than women who were overweight (aOR = 1.52, 95%CI 1.39, 1.66; Fig. 5), but there was no notable difference in the magnitude of risk between overweight and obesity in either early or intermediate-onset preeclampsia. Women with overweight or obesity have baseline excessive vascular inflammation, and the observed higher risk of late-onset preeclampsia with rising BMI may be secondary to intraplacental (intervillous) malperfusion and hypoxia due to mechanical restrictions as the growing placenta reaches its size limit [3,4,10]. The discrepancies between our study results may be due to the much higher rate of obesity and overweight in Robillard's study (over 80%) as compared to ours (30.5%). Obesity leads to larger placentas and thereby most likely increases risk of late-onset preeclampsia development [10].

We also found that although obesity and overweight are independent risk factors for preeclampsia, adjustment for BMI does not appreciably affect the preeclampsia risk in women with any type of diabetes across all gestational age groups, indicating independent effects of both obesity/overweight and diabetes. Our results are in line with a study of twin pregnancies showing no significant change in risk of preeclampsia among women with pregestational or gestational diabetes after adjusting for BMI [21]. Our findings in nulliparous women differ, however, from a recent Canadian study suggesting a lower risk of preterm preeclampsia among women with chronic hypertension and obesity compared to women with chronic hypertension alone, although the study did not address nulliparity specifically [31].

4.2. Strengths and limitations

The strength of this study is its large population-based dataset of 382 618 first deliveries using previously validated MBRN variables for diabetes [36] and hypertensive disorders of pregnancy [37]. In general, MBRN data are of high quality and suitable for research [38]. For the multivariate regression analyses, we included socio-economic exposure variables associated with hypertensive disorders of pregnancy previously studied in the same population [11]. Norway's national health system provides free prenatal and obstetric care based on national guidelines to all pregnant women. As such, the risk of information bias is low.

In our study, approximately 2% of the women had any type of diabetes, reflecting the overall low prevalence (4.7%) of diabetes in Norway [39]. As in many other western countries, the incidence of type 2 diabetes has increased steadily over the past few decades. The incidence of type 1 diabetes is approximately 300 children per year [39]. Gestational diabetes prevalence in our study was 1.4%, which is likely due to the national selective screening criteria and chosen blood glucose cutoff values during the study period.

Since the MBRN started collecting data on pre-pregnancy height and weight only in 2006, a weakness of this study is that 75% of deliveries lacked data for BMI. A separate sub-analysis of all singleton births to nulliparous women between 2006 and 2014 showed outcomes similar to our study (results not shown). Previous studies using BMI data from the MBRN in the same time period have been published [21,22]. Data on maternal smoking status was missing in 16% of the deliveries. These women were included in the non-smoking group, similar to other previously published preeclampsia studies using MBRN data [11,20,21,40]. Information on education was missing among 3.9% of the women, similar to previous studies [11,20–22]. Remaining exposure variables had <1% missing data.

MBRN's classic definition of preeclampsia during the study period included new-onset proteinuria and hypertension after 20 weeks gestational age. Updated definitions of preeclampsia that include signs of preeclampsia-associated organ dysfunction with or without proteinuria [12,41] are not applicable in this study, as these data are not available from the MBRN. Approximately 15–25% of women with gestational hypertension will eventually develop proteinuria [42]. Accordingly, such pregnancies were in our study registered as complicated by preeclampsia in the MBRN and in our study. The MBRN does not collect data on duration of hypertensive diseases of pregnancy or indication for delivery.

Robillard et al. [43] found that optimal weight gain during pregnancy has a protective effect against the development of late-onset preeclampsia among women with overweight or obesity. A small Norwegian study suggested that the association between excessive gestational weight gain and preeclampsia might be due to addition total body water and not increased fat mass [44]. Increased weight, especially immediately prior to delivery, could reflect increasing edema in women with severe preeclampsia features due to excessive vascular inflammation and extravasation of fluid and albumin. This type of weight gain is due the pathophysiologic effects of preeclampsia and does not likely represent an independent risk factor for the disease. Our study did not include gestational weight gain during pregnancy. We could not therefore estimate the effect of gestational weight gain on preeclampsia over the 3 gestational age groups. Nonetheless, a recent *meta*-analysis, of which 37.9% of the study participants were from Norway, suggested that pre-pregnancy BMI, more so than gestational weight gain, is associated with adverse maternal outcomes, including preeclampsia [45].

4.3. Clinical implications

The results of our study from Norway are generalizable to other populations with similar demographics and health service. Although our study found a positive association between elevated pre-pregnancy BMI and preeclampsia, in line with previous studies, we found that BMI does not further modify the risk of preeclampsia in nulliparous women with diabetes or chronic hypertension. Women with these chronic diseases should be offered careful follow-up, including low-dose aspirin prophylaxis, regardless of BMI. Women with gestational diabetes should also be offered intensified antenatal follow-up, but aspirin prophylaxis is generally not applicable in this group, as it should be started in early second trimester [46].

Risk assessment of hypertensive disorders of pregnancy among women with diabetes or chronic hypertension can help inform shared clinical decision-making regarding timing of delivery, particularly in the intermediate gestational age of 34^0-36^6 weeks where higher neonatal morbidity [17,47,48] and mortality [17,47,49] are seen compared to term infants. This is especially relevant for women with type 1 diabetes mellitus, as our study found the risk of preeclampsia to be as least as high in the gestational age of 34^0-36^6 weeks as in earlier gestational age groups.

We found that the magnitude of risk of preeclampsia among women with chronic hypertension was inversely proportional to the gestational age at delivery. Women with chronic hypertension may need additional surveillance, counseling and treatment between 23^0-33^6 weeks when the risk of preeclampsia is the highest.

5. Conclusion

We found that maternal diabetes or chronic hypertension was associated with an increased risk of hypertensive disorders of pregnancy in nulliparous women across all gestational age groups of early (23^0-33^6 weeks), intermediate (34^0-36^6 weeks) late (37^0-43^6 weeks) gestational age, and BMI did not appreciably modify the risk. We also found that BMI, as an independent risk factor, increased the risk of hypertensive disorders of pregnancy in all gestational age groups in nulliparous women. Our study supports the concepts of multifactorial pathways to the heterogeneous group of hypertensive disorders of pregnancy [10]. This model also seems valid for nulliparous women who have an elevated risk of preeclampsia as compared to parous women, likely due to immunological and anatomical factors related to uteroplacental artery remodeling and other placentation processes [10].

Low-dose aspirin is used for the prevention of preterm preeclampsia [50], although aspirin does not have the same beneficial effect in women with chronic hypertension, at least for those screened as high risk with circulating PlGF, uterine artery blood flow and maternal risk factors [51]. Previous studies have shown increasing prevalence and risk of preeclampsia when more than one risk factor is present [21,31,52]. Further studies are needed to delineate how biologic, socioeconomic and lifestyle determinants of diabetes, hypertension and obesity affect maternal and fetal outcomes in pregnancies complicated by gestational hypertension or preeclampsia, including which subgroups have the largest effect of aspirin prophylaxis on premature delivery.

Author contribution

Kristina Baker Sole declares that she participated in the conception and design of the research, data collection, data analysis and interpretation, drafting of the article and critical revision of the article, and that she has seen and approved the final version.

Anne Cathrine Staff declares that she participated in the conception and design of the research, data collection, data analysis and interpretation, drafting of the article and critical revision of the article, and that she has seen and approved the final version.

Katariina Laine declares that she participated in the conception and design of the research, data collection, data analysis and interpretation, drafting of the article and critical revision of the article, and that she has seen and approved the final version.

Source of funding

This research was funded, in part, by a grant by the Norwegian SIDS and Stillbirth Society, grant number 554.04/14 (K.L.). The Norwegian SIDS and Stillbirth Society had no involvement in the study design; data collection, analysis or interpretation; writing of the manuscript, or decision to submit the article for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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III

Substantial decrease in preeclampsia prevalence and risk over two decades: A population-based study of 1 153 227 deliveries in Norway

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Abstract

Objectives: Analyze secular trends of preeclampsia in Norway based on risk factors.

Study design: Population-based cohort study of 1 153 227 women using data from Medical Birth Registry of Norway from 1999 to 2018. Aggregated data from Norwegian Prescription Database from 2004 to 2018 were used. Main exposure variable was time period. Descriptive statistics identified the prevalence of preeclampsia, labor induction and aspirin use. Multiple logistic regression analysis was performed to estimate the risk of preeclampsia during the time periods.

Main outcome measures: Preeclampsia

Results: Overall preeclampsia prevalence decreased from 4.3% in 1999-2002 to 2.7% in 2015-2018. A reduction was observed in all subgroups of women with known risk factors (age, nulliparity, diabetes, chronic hypertension, assisted reproduction, twin pregnancy). Adjusted risk of preeclampsia was reduced by 44% from 1999-2002 to 2015-2018 (aOR = 0.56, 95%CI 0.54, 0.58), while the net prevalence of gestational hypertension remained stable over the study period. Labor induction increased 104%. Aspirin prescriptions increased among fertile women in the general Norwegian population.

Conclusions: Preeclampsia prevalence and risk were reduced regardless of risk factors and despite an increased proportion of high-risk parturients (advanced age, lower parity, use of assisted reproduction). A corresponding increase in aspirin prescriptions among fertile women and an overall increase in labor inductions were also observed, suggesting that clinical interventions may partly explain the observed reduction in preeclampsia prevalence. Lower average blood pressure and improved health in the population may also explain some of the reduction.

Key words: aspirin, labor induction, hypertension, preeclampsia, pregnancy, secular trends

Abbreviations: aOR: adjusted odds ratio, ART: assisted reproductive technology, ATC: Anatomic Therapeutic Chemical, BMI: Body Mass Index, CHTN: chronic hypertension, CI: confidence interval, GH: gestational hypertension, MBRN: Medical Birth Registry of Norway, OR: odds ratio, PE: preeclampsia/eclampsia

Source of Funding: This research was funded, in part, by a grant by the Norwegian SIDS and Stillbirth Society, grant number 554.04/14 (K.L.). The Norwegian SIDS and Stillbirth Society had no involvement in the study design; data collection, analysis or interpretation; writing of the manuscript, or decision to submit the article for publication.

Introduction

Preeclampsia is a complex medical syndrome affecting 3-5% of pregnancies worldwide [1]. The etiology of preeclampsia is likely due to spiral artery pathology, placenta malperfusion and syncytiotrophoblast stress of other causes [2-5]. A two-stage paradigm describes how placenta syncytiotrophoblast stress and underlying maternal factors increase susceptibility to the generalized maternal vascular inflammatory response that causes endothelial dysfunction and clinical disease. [4]. Perinatal adverse effects of preeclampsia can cause long-term health consequences for both mother and child [6-8].

Previous studies have reported associations between several biologic risk factors and preeclampsia, such as extremes of maternal age, nulliparity, pre-gestational and gestational diabetes mellitus, chronic hypertension [9], prior history of preeclampsia [10], autoimmune disease [11], assisted reproductive technology (ART) [12], multiple gestation [13] and obesity [14]. We also have evidence for the association between socioeconomic factors and preeclampsia, such as maternal country of birth and education [15], while smoking has shown to be protective [16].

Interventions to reduce the risk of preeclampsia have also been studied. Prophylactic low-dose aspirin reduces the risk of pre-term preeclampsia (before 37 weeks gestation) in high-risk women based on maternal factors, biophysical findings, and placental and maternal biomarkers [17].

Although many studies have focused on preeclampsia risk factors, studies on temporal trends [18] of hypertensive disorders of pregnancy are scarce. The demographics of delivering women has changed, and updated reports of preeclampsia prevalence are needed. The aim of this study was to analyze secular trends of preeclampsia in Norway from 1999 to 2018 based on risk factors, and reflect on how the increasing trend of clinical interventions, such as labor induction and aspirin use may have altered the prevalence of the disease over time.

Methods

This study is part of the larger PURPLE Study, which investigates adverse pregnancy outcomes in Norway from 1967 to 2018 using data from the Medical Birth Registry of Norway (MBRN). The study was approved by The Regional committee for Medical and Health Research Ethics in South-Eastern Norway (#2015/681) and the Institutional Personal Data Officer at Oslo University Hospital. Patient consent was not required for the use of de-identified and anonymized registry data.

Our study population included all women who delivered a singleton or twin pregnancy in Norway between 1999 and 2018 at gestational age ≥ 22 and < 45 weeks (n = 1 153 227 women). The main exposure variable was time period of delivery, using 4-year increments.

Obstetric history, past medical history and other current maternal morbidity are routinely recorded in the standardized ambulatory prenatal record used throughout Norway. Mandatory notification to the MBRN occurs immediately after delivery by automatic transfer of information from the electronic hospital charts of both mother and baby. Gestational age at birth was based on fetal biometry performed at 17-20 weeks of gestation (98% of the study population), or on the first day of the last menstrual period in the rare instances when ultrasound-dating was not available (2%).

The main outcome variable was preeclampsia. Women with eclampsia were merged into the preeclampsia group for the analysis. Preeclampsia was defined as repeatedly confirmed de novo blood pressure elevation ≥ 140/90 mmHg after 20 weeks gestational age accompanied by proteinuria. Proteinuria was defined as ≥ 1^{+} on urine dipstick with a minimum of two measurements, or by urine protein ≥ 0.3 g/24 hours or total protein/creatinine ratio > 0.3. Eclampsia was defined as peripartum generalized seizures occurring up to 7 days postpartum associated with preeclampsia or gestational hypertension.

Risk factors for hypertensive disorders of pregnancy were assessed as possible confounders to the main exposure variable. Maternal age at delivery was categorized into 6 groups (< 20, 20-24, 25-29, 30-34, 35-39 and ≥ 40 years). Parity was categorized as 0, 1 and ≥ 2. Maternal country of birth was assigned as Norway or other. First-trimester smoking was categorized into four groups (no smoking, sometimes, daily, missing information). Maternal diabetes was classified into three categories: Type 1, type 2 and gestational diabetes based on national screening criteria in use at the time of the pregnancy. Chronic hypertension was defined as a binary variable and excluded hypertension as a complication of pregnancy, delivery or postpartum. Pre-pregnancy Body Mass Index (BMI) was categorized using World Health Organization classifications. Twin gestation and ART were dichotomized to yes/no variables.

Labor induction and aspirin use were studied as possible explanations for changes in preeclampsia prevalence over time. Induction of labor was dichotomized as yes/no. Population-based data on aspirin use among women age 20-39 years were taken from the Norwegian Prescription Database, using the Anatomic Therapeutic Chemical (ATC) code B01A C06 for acetylsalicylic acid 75 mg, the dose recommended in Norway during the study period for preeclampsia prevention in high-risk women. Only aggregate data was available, reported as use per 1000 women.

IBM SPSS Statistics for Windows version 27.0.0.0 was used for the analysis. We used descriptive statistics to determine the prevalence of preeclampsia and gestational hypertension, according to maternal characteristics, gestational age at delivery and use of labor induction. Logistic regression analysis was performed to estimate the crude odds ratios (OR) with 95% confidence intervals (CIs) of preeclampsia. Using multivariate logistic regression analysis, we assessed the independent association of time periods in 4-year increments to preeclampsia, with women delivering in 1999-2002 as the reference group.

Adjustments were made for maternal age, parity, twin gestation, ART, country of birth, diabetes, chronic hypertension and 1st-trimester smoking.

Results

Main findings

Characteristics of the study population are reported in Table 1. Overall, the proportion of women with risk factors for preeclampsia increased during the study. Giving birth at advanced age (≥ 35 years) increased over the study period from 14.5% in 1999-2002 to 20.4% in 2014-2018 (Table 1). The proportion of nulliparous women increased, and women with higher parity decreased. Use of assisted reproduction increased, while 1st-trimester smoking decreased by 80% between the first and last time periods. Labor induction more than doubled in the study population from 1999-2002 (10.9%) to 2015-2018 (22.2%) (Table 1).

Of the 1 153 227 deliveries in the study population, 3.4% (n = 39 165) were affected by preeclampsia and 1.7% (n = 19 937) were affected by gestational hypertension (Table 2). The prevalence of preeclampsia was highest in the first time period in 1999-2002 (4.3%, CI 4.23, 4.44) with decreasing prevalence across successive time periods to 2.7% (CI 2.62, 2.75) in 2015-2018. Gestational hypertension prevalence had a transient increase from 1.5% (CI 1.42, 1.52) in 1999-2002 to 2.0% (CI 1.90, 2.01) in 2007-2010, and then progressively decreased to 1.6% (CI 1.55, 1.65) in 2015-2018.

Table 3 reports prevalence of preeclampsia by maternal and pregnancy characteristics and risk factors. Preeclampsia prevalence consistently decreased in all subgroups and time periods. Table 4 reports crude (OR) and adjusted odds ratios (aORs) for preeclampsia in all five time periods. After adjustment for risk factors for preeclampsia (maternal age, parity, twin pregnancy, ART, maternal country of birth, diabetes, chronic hypertension and smoking), a 44% decrease in the risk of preeclampsia (aOR = 0.56, 95%CI 0.54, 0.58) was

observed in 2015-2018 compared to years 1999-2002. This adjustment only slightly changed the OR from the univariate analysis (OR = 0.61, 95%CI 0.59, 0.63), suggesting that these risk factors did not explain the reduction in preeclampsia prevalence.

Figure 1 juxtaposes the prevalence of hypertensive diseases of pregnancy (total, preeclampsia and gestational hypertension) with risk for preeclampsia over the same time periods to illustrate the temporal decreasing trend.

Maternal age

Preeclampsia prevalence reduced in all maternal age groups. Among women ≥ 35 years old, preeclampsia decreased 30% from 4.2% at the start to 2.9% at the end of the study period (Table 1 and 3).

Parity

Preeclampsia prevalence declined 38% in nulliparous women (6.4% in 1999-2002 versus 4.0% in 2015-2018) (Table 3). There was a 43% decrease in preeclampsia among primiparous women (3.0 % in 1999-2002 versus 1.7% in 2015-2018) and a 37% decrease in multiparous women (2.7% in 1999-2002 versus 1.7% in 2015-2018).

Gestational age

Decreased prevalence of preeclampsia in both term and preterm deliveries over time was observed, with the highest prevalence in time period 1999-2002 (<34 weeks: 21.1%, 34-36 weeks: 14.8%, 37-44 weeks: 3.5%) and the lowest prevalence in time period 2015-2018 (<34 weeks: 17.7%, 34-36 weeks: 11.6%, 37-44 weeks: 2.1%) (Table 3).

Multiple gestation and assisted reproduction

The prevalence of preeclampsia decreased by approximately one-third among women with twin gestations (13.6% versus 9.1%) and women with singleton pregnancies (4.1% versus

2.6%) over the study period (Table 3). There was a similar reduction in preeclampsia prevalence among women with pregnancies resulting from assisted reproduction (7.9% versus 5.2%).

Maternal chronic diseases

Pre-gestational diabetes (type 1 and 2 diabetes) remained low and stable during the study period (Table 1). Preeclampsia prevalence among women with type 1 or type 2 diabetes was reduced from the first to the last time period by 35% and 45%, respectively (Table 3). Gestational diabetes increased from 0.7% at the study start to 4.9% at the study end (Table 1), but in these women, the prevalence of preeclampsia was significantly reduced (52%) over time. The prevalence of chronic hypertension was low during all study periods (< 1%), and preeclampsia among women with chronic hypertension decreased 31% throughout the study period, from 21.4% in 1999-2002 to 14.8% in 2015-2018.

Socioeconomic risk factors

The proportion of foreign-born women giving birth in Norway almost doubled during the study period (16.5% in 1999-2002 versus 30.2% in 2015-2018) (Table 1). The prevalence of preeclampsia decreased among both Norwegian-born and immigrant women, by 36% and 39%, respectively (Table 3). There was a decreasing trend of preeclampsia prevalence among both smokers and non-smokers during the study period, as well as among women with missing data for smoking.

Aspirin

Aggregated data from the Norwegian Prescription Database showed an increase in aspirin prescriptions among women younger than 40 years old from 2004 to 2018 (Figure 2). In 15-19 year-old women, a 146% increase in aspirin prescriptions from 2004 (0.35 per 1000

women) to 2018 (0.86 per 1000 women) was observed. Aspirin prescriptions increased by 65%, 80%, 70% and 29% among women 20-24, 25-29, 30-34, and 35-39 years old, respectively.

Discussion

Principal findings

In the present study with a 20-year population-based data of 1 153 227 women, preeclampsia prevalence decreased 37% between the first and last four-year time increments. This trend was observed despite an increasing proportion of high-risk parturients. Advanced maternal age and assisted reproduction, both risk factors for preeclampsia, increased during the study period. Conversely, 1st-trimester smoking, which is inversely associated with preeclampsia, decreased. After adjustment for known risk factors associated with preeclampsia, preeclampsia risk was reduced by 44% during the study period, indicating that the observed population changes could not explain the decreasing risk of preeclampsia.

A previous Norwegian study using MBRN data showed an increase in preeclampsia prevalence from 1967 to 1999 and a decreasing trend from 2000 to 2010 [19]. The latter is in line with our findings of a further decreasing preeclampsia prevalence. A novel finding in our study is that we observed that the reduction in preeclampsia prevalence occurred in all subgroups of women with known risk factors, despite that the proportion of high-risk women increased over time. Globally, preeclampsia prevalence increased during our study period [20]. In low and middle-income countries, preeclampsia rates are reported to be higher than in high-income countries such as Norway [21]. Preeclampsia prevalence in non-European countries with high socioeconomic indices and comprehensive national healthcare systems observe conflicting results. Our findings differ from a Canadian study that observed a doubling of preeclampsia prevalence from 1989 to 2012 [22]. In line with our findings,

however, an Australian study found a decreasing prevalence of preeclampsia between 2000 and 2008 [23].

Changes in clinical routines such as increased use of labor induction regardless of indication could partially explain the reduction of preeclampsia prevalence in late gestation, but not in the earlier gestations where induction of labor is rarely used. Labor induction for pregnancies > 41 weeks gestational age has been shown to reduce the risk of adverse perinatal outcomes, including preeclampsia [24, 25], and has become standard care in the past decade [26]. Norway has not implemented elective labor induction at 39 weeks in low-risk nulliparous women, despite studies showing decreased risk of Cesarean delivery [27], maternal morbidity and perinatal mortality [28] compared to expectant management. We observed that the temporal increase in labor induction corresponded with a temporal decreased prevalence of preeclampsia.

The transient increase in gestational hypertension paralleling the reduced preeclampsia prevalence seen in the early years of the study, could indicate that the hypertensive disorder of pregnancy phenotype shifted from the more severe form (preeclampsia) to the clinically less severe form (gestational hypertension). However, gestational hypertension prevalence at the end of the study was similar to the study start (net increase of 6.7%), whereas preeclampsia prevalence continued to fall. This suggests a more profound effect across the hypertensive disorder group, where less women were affected, and with a less severe phenotype.

Similar to current NICE guidelines [29], Norwegian national guidelines since 2014 [30] have recommended prenatal low-dose aspirin starting at the end of the first trimester for preeclampsia prevention in high-risk pregnancies. As far back as 1998 [31], aspirin was mentioned in the Norwegian guidelines for preeclampsia prevention in parous women with a previous history of preeclampsia. It is thus likely that aspirin has been used in high-risk pregnancies before the 2014 recommendation, but at an unknown frequency.

Aspirin 75 mg-dose is only available by prescription in Norway. Low-dose aspirin is used for prevention of cardiovascular diseases in high-risk populations [32], but women of reproductive age rarely take aspirin for this indication [33]. Aspirin used for pain, fever and rheumatologic illnesses are usually prescribed at higher doses. We interpret the increased prescriptions of 75 mg aspirin daily to women < 40 years old in Norway from 2004 to 2018 is likely due to increased preeclampsia aspirin prevention, although specific indications for aspirin use were not available.

Decreased preeclampsia prevalence in the preterm groups may be associated with increased aspirin prescriptions in women of reproductive age in the study period. However, the Norwegian recommendations have targeted parous women with previous obstetric complications, and thus probably cannot explain the 38% reduction of preeclampsia prevalence among the nulliparous women in our study. Although the specific pathophysiologic effects of aspirin in preventing especially early-onset preeclampsia remain unknown, a recent paper suggests that efficient aspirin prophylaxis delays the metabolic clock of gestation in high-risk women [34].

Mean systolic and diastolic blood pressures have decreased among women in Norway in all age groups over the past decades, despite a greater prevalence of overweight/obesity and diabetes in the population [35, 36]. The cause of this trend is unknown, but an association between health, wellbeing, and socioeconomic status in Norway has been reported [37]. It has been speculated that general health improvement over time, such as dietary changes including reduced use of salt, may explain this trend [36]. General improvement in health behavior with more focus on diet, physical activity and smoking cessation may also have had an overall positive effect on maternal health during our study period. A general improvement in health resulting in fewer hypertensive complications may represent an unmeasurable confounder in our study.

Strengths and limitations

The strength of this study is its large population-based dataset of 1 153 227 deliveries, including information on the main risk factors for preeclampsia. MBRN data are considered suitable for research [38] with validated variables [39]. For the multivariate regression analysis, we included biologic and socioeconomic exposure variables previously known to be associated with hypertensive disorders of pregnancy [9, 13, 15]. The risk of information bias is low, as all deliveries in Norway are registered in the MBRN with standardized recording of pregnancy and birth outcomes. MBRN still uses a classic definition of preeclampsia, which is an added strength of this large patient-based epidemiological study, as the classification of hypertensive disorders of pregnancy did not change over the study period. Updated definitions of preeclampsia that include signs of preeclampsia-associated organ dysfunction in the absence of proteinuria [14, 40] were not applicable in this study, as these data were not available. Women with preeclampsia without proteinuria were thus registered as gestational hypertension in the MBRN. We analyzed gestational hypertension in our study population and observed a minimal net positive change in prevalence during the total study period.

Sixty-five percent of deliveries lacked BMI data, since the MBRN only started collecting data on pre-pregnancy height and weight in 2006. As such, BMI was not included in the analyses in our study, although it is a known risk factor for both early and late-onset preeclampsia [41].

Clinical implications

To interpret our findings in a clinical context, we investigated the temporal trends of aspirin prescriptions and labor induction during the study period. During our study, there was a parallel increase in aspirin prescriptions among women < 40 years old and an increase in labor induction. Both interventions – aspirin and labor induction – may improve maternal and

fetal health, but the optimal risk/benefit balance and targeted patient groups for preventing preeclampsia with these interventions merit further research. We suggest that future studies on elective labor induction should also investigate temporal changes in preeclampsia prevalence.

Conclusion

During the 20-year study period, we observed a decreasing trend in preeclampsia prevalence and risk regardless of gestational age group at delivery, parity, maternal age, maternal chronic disease, and socioeconomic indices. The observed demographic changes would expectedly have increased the overall prevalence of preeclampsia; delivering women were older, had lower parity, and higher rates of assisted reproduction and gestational diabetes. Other preeclampsia risk factors such as pre-gestational diabetes, chronic hypertension and twin gestation remained relatively stable during the study period.

In conclusion, we found that measurable epidemiological changes could not account for the reduced preeclampsia risk in the present study. Changes in clinical routines may partly explain the reduction of preeclampsia prevalence, namely aspirin use for parous women and labor induction in term pregnancies. General health improvements on a population level may also have affected the results of this study.

Author Contribution

Kristina Baker Sole declares that she participated in the conception and design of the research, data collection, data analysis and interpretation, drafting of the article and critical revision of the article, and that she has seen and approved the final version, and submitted it.

Anne Cathrine Staff declares that she participated in the conception and design of the research, data interpretation, drafting of the article and critical revision of the article, and that she has seen and approved the final version.

Sari Räisänen declares that she participated in the design of the research and planning of the analyses, interpretation of the results, drafting of the article and critical revision of the article, and that she has seen and approved the final version.

Katariina Laine declares that she has been the senior study supervisor, participated in the conception and design of the research, data collection, data analysis and interpretation, drafting of the article and critical revision of the article, and that she has seen and approved the final version.

Declaration of Interests:

Kristina Baker Sole: None
Anne Cathrine Staff: None
Sari Räisänen: None
Katariina Laine: None

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Table 1. Characteristics of study population, per time period (n=1 153 227 deliveries).

	1999-2002 n=226 117 % (n)	2003-2006 n=225 205 % (n)	2007-2010 n=238 502 % (n)	2011-2014 n=235 687 % (n)	2015-2018 n=227 716 % (n)
Age, years					
<20	2.6 (5776)	2.1 (4792)	2.3 (5555)	1.6 (3741)	1.0 (2299)
20-24	15.4 (34 792)	14.2 (31 953)	14.7 (35 119)	13.9 (32 759)	10.9 (24 883)
25-29	35.0 (79 228)	31.9 (71 733)	31.0 (73 933)	31.7 (74 807)	32.7 (74 562)
30-34	32.4 (73 368)	34.6 (77 832)	32.7 (77 884)	33.1 (78 121)	35.0 (79 620)
35-39	12.5 (28 374)	14.8 (33 400)	16.3 (38 832)	16.2 (38 243)	16.7 (38 025)
≥ 40	2.0 (4579)	2.4 (5495)	3.0 (7179)	3.4 (8016)	3.7 (8327)
Parity					
0	40.2 (90 853)	41.2 (92 869)	42.5 (101 304)	42.3 (99 649)	42.4 (96 551)
1	35.6 (80 498)	35.7 (80 408)	35.4 (84 519)	36.6 (86 287)	37.1 (84 590)
≥ 2	24.2 (54 766)	23.1 (51 928)	22.1 (52 679)	21.1 (49 751)	20.5 (46 575)
Twin gestation	1.8 (4103)	1.8 (4130)	1.7 (4069)	1.6 (3833)	1.6 (3586)
Assisted reproduction	1.6 (3603)	2.2 (4955)	2.8 (6625)	3.1 (7362)	4.0 (9222)
Diabetes					
Type 1	0.4 (949)	0.5 (1068)	0.5 (1120)	0.5 (1090)	0.4 (981)
Type 2	0.2 (432)	0.3 (705)	0.4 (929)	0.3 (824)	0.4 (806)
Gestational	0.8 (1774)	0.9 (2044)	1.4 (3437)	2.8 (6614)	4.9 (11 236)
Chronic hypertension	0.7 (1483)	0.5 (1016)	0.6 (1388)	0.6 (1345)	0.5 (1189)
Country of birth					
Norway	83.4 (188 692)	81.4 (183 379)	78.2 (186 419)	73.1 (172 375)	69.8 (158 954)
Other	16.6 (37 425)	18.6 (41 826)	21.8 (52 083)	26.9 (63 312)	30.2 (68 762)
Smoking, 1st trimester					
No	64.7 (146 208)	67.3 (151 572)	72.7 (173 341)	78.3 (184 569)	87.2 (198 671)
Sometimes	2.2 (4900)	1.7 (3797)	1.4 (3440)	1.1 (2702)	0.7 (1688)
Daily	18.1 (40 990)	12.8 (28 726)	9.5 (22 584)	6.5 (15 244)	3.3 (7433)
Missing	15.0 (34 019)	18.3 (41 110)	16.4 (39 137)	14.1 (33 172)	8.7 (19 924)
Labor induction	10.9 (24.693)	13.6 (30 594)	16.3 (38 828)	20.0 (47 064)	22.2 (50 649)

Table 2. Prevalence of hypertensive disorders in pregnancy in the study population, per time period (n = 1 152 227 deliveries).

	1999-2002 % (n) CI[a]	2003-2006 % (n) CI	2007-2010 % (n) CI	2011-2014 % (n) CI	2015-2018 % (n) CI
Preeclampsia	4.3 (9755) CI 4.23-4.44	3.8 (8561) CI 3.72-3.89	3.4 (8121) CI 3.33-3.47	2.8 (6613) CI 2.74-2.87	2.7 (6115) CI 2.62-2.75
Gestational hypertension	1.5 (3327) CI 1.42-1.52	1.8 (4128) CI 1.78-1.89	2.0 (4665) CI 1.90-2.01	1.8 (4169) CI 1.71-1.82	1.6 (3648) CI 1.55-1.65
Preeclampsia and gestational hypertension	5.8 (13 082) CI 5.69-5.88	5.6 (12 689) CI 5.53-5.72	5.4 (12 786) CI 5.27-5.45	4.6 (10 782) CI 4.45-4.66	4.3 (9763) CI 4.20-4.37

[a] CI: 95% confidence interval

Table 3. Prevalence of preeclampsia (%) in the subgroups of women in time periods (n = 1 152 227 deliveries).

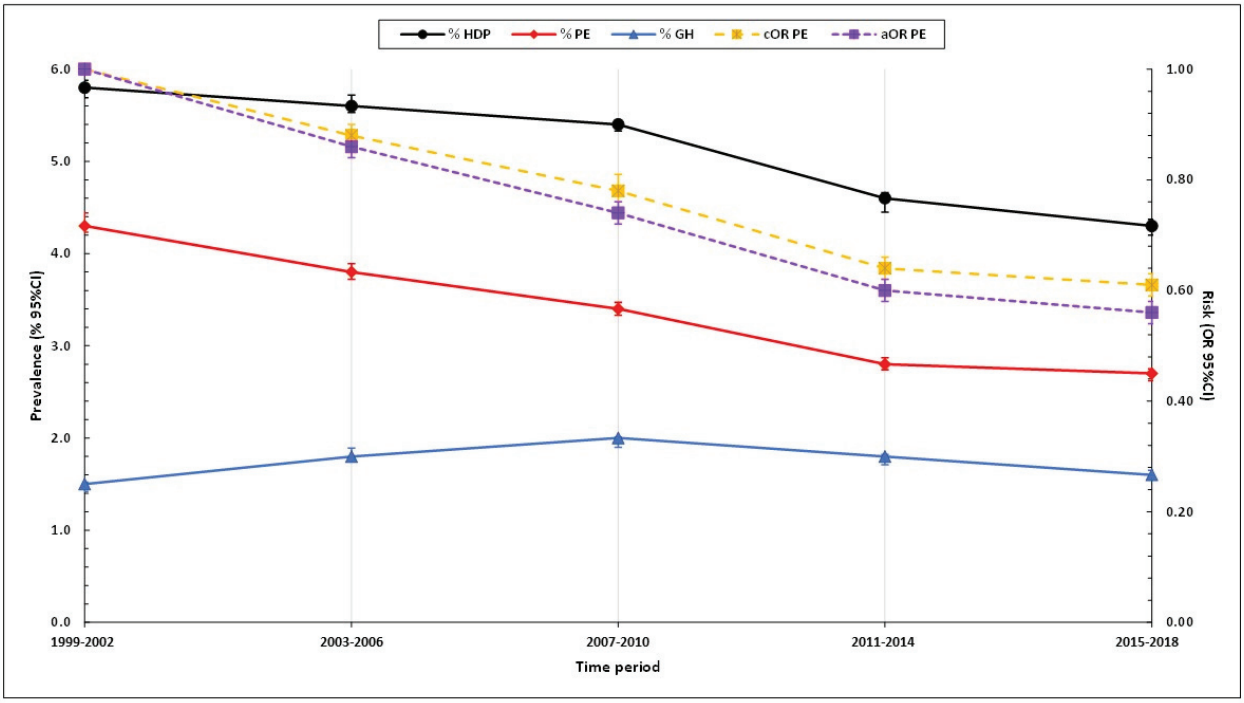
	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
Age, years					
<20	5.2 (302)	5.2 (250)	4.9 (270)	5.2 (194)	4.5 (103)
20-24	5.0 (1740)	4.5 (1446)	3.9 (1379	3.5 (1149)	3.3 (818)
25-29	4.4 (3458)	3.8 (2736)	3.3 (2472)	2.7 (2013)	2.7 (2007)
30-34	3.9 (2868)	3.4 (2623)	3.1 (2383)	2.4 (1860)	2.3 (1828)
35-39	4.1 (1163)	3.8 (1254)	3.4 (1332)	2.7 (1050)	2.7 (1021)
≥ 40	4.9 (224)	4.6 (252)	4.0 (285)	4.3 (347)	4.1 (338)
Parity					
0	6.4 (5820)	5.5 (5147)	4.8 (4892)	4.1 (4116)	4.0 (3855)
1	3.0 (2437)	2.7 (2135)	2.4 (2053)	1.9 (1603)	1.7 (1471)
≥ 2	2.7 (1498)	2.5 (1279)	2.2 (1176)	1.8 (894)	1.7 (789)
Gestational age, weeks					
≤34	21.1 (963)	21.1 (914)	19.4 (854)	19.2 (756)	17.7 (633)
34-36	14.8 (1490)	14.0 (1395)	12.5 (1276)	11.1 (1037)	11.6 (1053)
37-44	3.5 (7302)	3.0 (6252)	2.7 (5991)	2.2 (4820)	2.1 (4429)
Singleton gestation	4.1 (9197)	3.6 (8049)	3.3 (7682)	2.7 (6208)	2.6 (5788)
Twin gestation	13.6 (558)	12.4 (512)	10.8 (439)	10.6 (405)	9.1 (327)
Assisted reproduction	7.9 (285)	7.4 (366)	6.5 (430)	4.9 (361)	5.2 (483)
Diabetes					
Type 1	19.1 (181)	14.0 (150)	14.3 (160)	13.0 (142)	12.4 (122)
Type 2	11.1 (48)	7.5 (53)	10.4 (97)	7.3 (60)	6.1 (49)
Gestational	9.9 (175)	8.9 (181)	7.0 (240)	5.3 (352)	4.8 (542)
Chronic hypertension	21.4 (318)	21.8 (221)	20.7 (287)	17.1 (230)	14.8 (176)
Country of birth					
Norway	4.5 (8409)	4.0 (7269)	3.6 (6699)	3.0 (5156)	2.9 (4591)
Other	3.6 (1346)	3.1 (1292)	2.7 (1422)	2.3 (1457)	2.2 (1524)
Smoking, 1st trimester					
No	4.5 (6591)	3.9 (5881)	3.6 (6196)	2.9 (5373)	2.7 (5437)
Sometimes	3.7 (181)	3.4 (130)	2.8 (95)	3.0 (81)	2.2 (37)
Daily	3.5 (1427)	3.3 (953)	3.0 (671)	2.5 (379)	2.1 (154)
Missing	4.6 (1556)	3.9 (1597)	3.0 (1159)	2.4 (780)	2.4 (487)

Table 4. Risk of preeclampsia in time periods, crude and adjusted odds ratios (n = 1 152 227 deliveries).

	Crude OR (95%CI)[a]	Adjusted[b] OR (95%CI)
Time period		
1999-2002	Ref	Ref
2003-2006	0.88 (0.85-0.90)	0.86 (0.83-0.89)
2007-2010	0.78 (0.76-0.81)	0.74 (0.72-0.77)
2011-2014	0.64 (0.62-0.66)	0.60 (0.58-0.62)
2015-2018	0.61 (0.59-0.63)	0.56 (0.54-0.58)

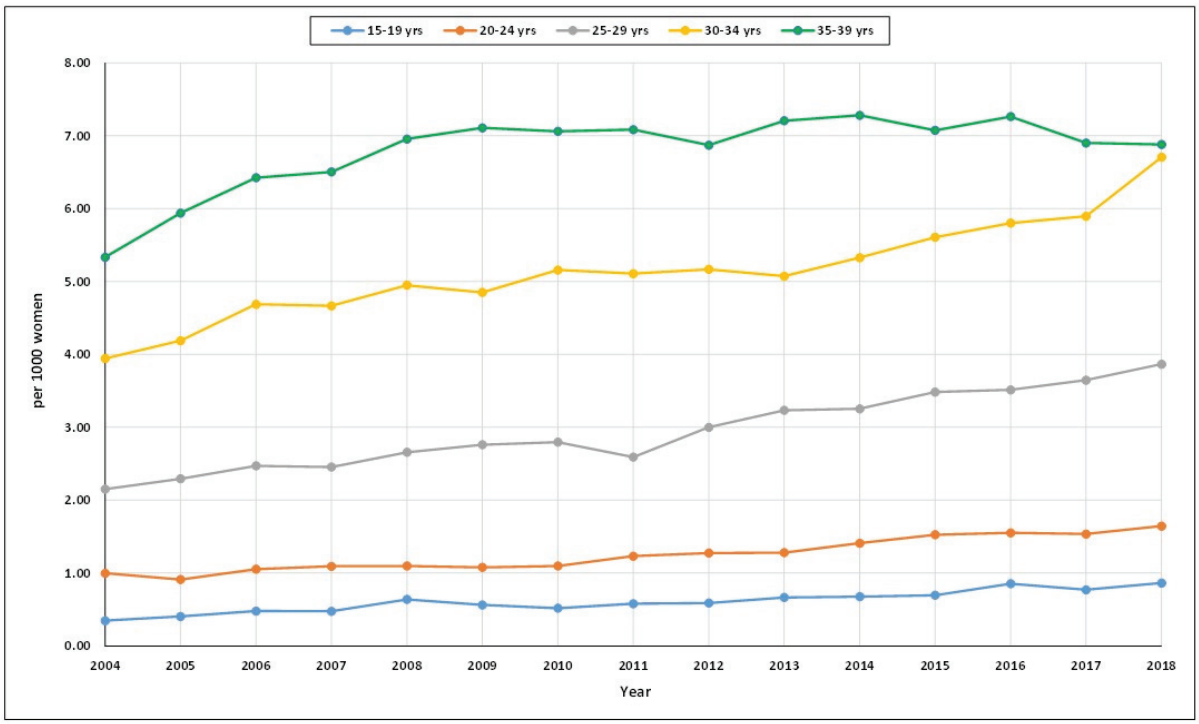
[a] OR (95%CI): Odds ratio (95% confidence interval)
[b] Adjusted for maternal age, parity, twin gestation, assisted reproduction, maternal country of birth, diabetes, chronic hypertension, 1st-trimester smoking

Figure 1. Prevalence of hypertensive disorders of pregnancy (total, preeclampsia, gestational hypertension) and risk of preeclampsia, per time period (n = 1 152 227 deliveries).



%: percent, OR: odds ratio, 95% CI: 95% confidence interval, cOR: crude odds ratio, aOR: adjusted odds ratio (adjusted for maternal age, parity, twin gestation, assisted reproduction, maternal country of birth, diabetes, chronic hypertension, 1st-trimester smoking), HDP: hypertensive disorders of pregnancy (preeclampsia and gestational hypertension), PE: preeclampsia. GH: gestational hypertension.

Figure 2. Aspirin prescriptions among women in Norway by age group.



yrs: years old