MONASH University

The role of maternal characteristics in the prognosis of preeclampsia

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BMedSc (Hons) – MD/PhD candidate

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Dedication

To whom should I dedicate this thesis? It could be to the hundreds of thousands of women who develop preeclampsia around the world each year. It could be to my family who supported me; or my supervisor, Ben; it could even be to myself, for keeping on going through thick and thin.

But instead of dedicating this to a person, I want to use this space to express gratitude and remorse towards, and sorrow for, Aboriginal and Torres Strait Islander people, the traditional owners of this land, and their ancestors and future descendants. I have learned a profound amount through this thesis, developing personal and professional skills from which I will reap rewards throughout my life. But I have done so on stolen lands, and the trauma of colonisation still runs deep. This thesis was written predominantly on the lands of the Wurundjeri people of the Kulin Nation, with some work done on the lands of the Turrbal clan.

Publications during enrolment

The following peer-reviewed journal articles were published during PhD candidature, as part of this thesis.

1. Tanner MS, De Guingand D, Reddy M, Rowson S, Rolnik DL, Da Silva Costa F, et al. The effect of preexisting medical comorbidities on the preeclamptic phenotype: A retrospective cohort study. *Hypertens*. 2021;40:336-345
2. Tanner MS, Malhotra A, Davey M-A, Wallace EM, Mol BW, Palmer KR. Maternal and neonatal complications in women with medical comorbidities and preeclampsia. *Pregnancy Hypertension*. 2022;27:62-68
3. Tanner MS, Davey M-A, Mol BW, Rolnik DL. The evolution of the diagnostic criteria of preeclampsia- eclampsia. *AJOG*. 2022;226: S835:845

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2. Tanner MS, Reddy M, Palmer KR, Davey M-A, Mol BW. The association of maternal characteristics with blood pressure variation through pregnancy.

The following peer-reviewed journal article was published during PhD candidature, outside of this thesis.

1. Palmer KR, Tanner M, Davies-Tuck M, Rindt A, Papacostas K, Giles ML, Brown K, Diamandis H, Fradkin R, Stewart AE, Rolnik DL, Stripp A, Wallace EM, Mol BW, Hodges RJ. Widespread implementation of a low-cost telehealth service in the delivery of antenatal care during the COVID-19 pandemic: an interrupted time-series analysis. The Lancet. 2021;398(10294):41-52. doi:10.1016/S0140- 6736(21)00668-1.

Thesis including published works declaration

I hereby declare that this thesis contains no material that has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes three original papers (Chapters Two, Three and Six) published in peer reviewed journals and two submitted publications (Chapters One and Four). Chapter Five has been written as a paper to be submitted. The core theme of the thesis is the association between maternal characteristics and the diagnosis and prognosis of preeclampsia. The ideas, development and writing up of the papers in the thesis were the principal responsibility of myself, the student, working within the Department of Obstetrics and Gynaecology at the School of Clinical Science, under the supervision of Professor Ben W. Mol.

(The inclusion of co-authors reflects the fact that the work came from active collaboration among researchers and acknowledges input into team-based research.)

I have renumbered sections of submitted or published papers to ensure consistency.

Student name: Michael Tanner

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Ben Mol

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To Kirsten, who gave me the courage to open my wings and fly; and to Ben, who kept me from flying too close to the sun.
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To Mum and Dad, who believed in me.
To Sarah and Alex, for the joy you found for me.
To Jacqueline, for protecting me from the isolation of 2021.
And to myself, for never giving up.

Preamble

"Science may provide the most useful way to organize empirical, reproducible data, but its power to do so is predicated on its inability to grasp the most central aspects of human life: hope, fear, love, hate, beauty, envy, honor, weakness, striving, suffering, virtue."
Paul Kalanithi, *When Breath Becomes Air*

"Deep in the human unconscious is a pervasive need for a logical universe that makes sense. But the real universe is always one step beyond logic."
Frank Herbert, *Dune*

There are few things that humans were unequivocally born to do. One of these is to tell stories.

A thesis is a story. Two stories, in fact. The first is the story of the research, which is a story of how the world works. The second is my story; the story of how my thinking has developed over the past three years.

Science can forget its role in telling stories. And the past two years have put me at risk of doing the same. This thesis is heavily data-driven. Partly this is due to me playing to my strengths and passion; partly it was born of necessity, from spending two-thirds of an entire year in lockdown in Melbourne.

I learned well how to tell the story of numbers. Over the past two years, I spent far more time interrogating data than talking to people. This thesis charts a course through the muddy waters of assumption and fact that shape how we think about preeclampsia. It offers a map; but if we look only at the map, we forget that each datapoint is a person, with their own stories to tell. Science falls into this trap. As a reminder, to myself as much as to you, to not make the same mistake, I have infused this thesis with humanity where I can. I hope you appreciate it.

Abstract

Maternal and perinatal mortality rates have plunged in the past 200 years. But pregnancy is still not risk-free. One of the most damaging complications is preeclampsia, the onset of hypertension and organ dysfunction in the second half of pregnancy. It annually contributes to, or is directly responsible for, 50,000 maternal and 500,000 neonatal deaths worldwide.

Despite a catastrophic health burden, the exact cause of preeclampsia remains elusive. This has stymied attempts to develop a reliable diagnostic test, or predict who is likely to suffer complications from the syndrome. Clinical judgement remains the mainstay of diagnosis and plays a major role in treatment decisions, decisions that can have serious ramifications for women and their babies. If pregnancy is left to continue, an expectant mother might suffer eclamptic seizures or develop organ failure; but a premature induction of labour can lead to lifelong complications for the newborn.

For many years, preeclampsia was diagnosed by the onset of hypertension and proteinuria. The 21st century saw an evolution in how we diagnose preeclampsia, with other organ dysfunction – haematological, neurological, hepatic, renal, uteroplacental – being sufficient, alongside hypertension, for a diagnosis. This shift recognizes that preeclampsia is a heterogenous syndrome that does not merely affect the maternal vascular system and the placenta.

This change in diagnostic criteria has trade-offs. Even with a narrower definition, the diagnostic criteria for preeclampsia was subjective, particularly if a woman had preexisting hypertension or proteinuria. Broadening the criteria exacerbates this subjectivity, increasing the potential for false positive diagnoses. And a diagnosis of preeclampsia itself is still not a particularly informative guide of a woman's prognosis. A more inclusive definition of preeclampsia makes the criteria yet more subjective, and subsequently less useful for determining prognosis.

This thesis explores in detail these hypothetical limitations in the diagnosis of preeclampsia.

The early chapters compare, among women with preeclampsia, the association between vascular comorbidities – chiefly hypertension, diabetes mellitus and obesity – and biomarker levels, severity of the syndrome, and the rate of complications.

These comorbidities are increasingly prevalent in pregnancy, and make diagnosing

preeclampsia particularly challenging. We found that the presence of preexisting comorbidities meant women diagnosed with preeclampsia had a milder syndrome. They had less of an elevation in biomarkers which correspond with both clinical severity and the likelihood of complications; less dysregulation in other markers of organ function; and suffered fewer complications. However, their neonates tended to have worse outcomes. We surmised that these comorbidities could lead to clinicians diagnosing preeclampsia, and subsequently recommending interventions such as an induction of labour at a lower threshold.

I then pivot to examining the association between blood pressure and body mass index as continuous variables and the diagnosis and prognosis of preeclampsia. We found that we could attribute to these baseline characteristics significant differences in the trajectory of blood pressure throughout pregnancy.

“What does that mean for outcomes from preeclampsia?” we asked. We then showed that these differences in baseline characteristics lead to significant differences in outcomes. The higher a woman’s blood pressure and body mass index at baseline, the less likely she was to suffer a complication after being diagnosed with preeclampsia.

This questions how effective, or useful, the existing criteria are for diagnosing preeclampsia. This thesis finishes with a critical appraisal of the evidence used over the past 70 years to develop and update guidelines for preeclampsia. It was clear that the current thresholds are based more on consensus and simplicity than any relationship they have with the likelihood of complications. We argue instead for an approach to studying and diagnosing preeclampsia that is rooted in two key questions: what is the prognosis of a woman? And how can treatment help?

Background

Maternal mortality has plummeted in the rich world over the past century. In 1920 in Australia, one in 200 women and one in 15 children could expect to die during the puerperium or first year of life.[1] Now those numbers are approximately one in 20,000 and one in 300.[1] This is an extraordinary achievement, a wonder of modern medicine. However, such good outcomes remain aspirational in much of the Global South – that is, for most of the world – and even many regions in rural Australia and America. And so 300,000 women[2] and 5 million infants[3] still perish on a yearly basis.

One of the leading causes of maternal mortality is Hypertensive Disorders of Pregnancy (HDoP), in particular preeclampsia. Preeclampsia is diagnosed following the onset of hypertension and organ dysfunction after 20 weeks of pregnancy.[4] It affects between 3 and 8% of pregnancies, contributing to more than 50,000 maternal and 500,000 perinatal deaths worldwide per year.[5,6] Many more women suffer serious morbidity. Maternal complications are due to eclampsia; stroke, due to uncontrolled hypertension; or organ dysfunction, such as acute kidney injury or pulmonary oedema.[7] Fetal troubles arise due to growth restriction, stillbirth, and the many sequelae of prematurity.[7]

Science and its antecedents have tussled for millenia with the cause of preeclampsia, since the time of Hippocrates.[8] Is it a toxin released from the placenta? An electrolyte imbalance? A disease of the kidney, or the endothelium, or the cardiovascular system? The picture has become clearer, but the precise aetiology of preeclampsia, and subsequently our clinical understanding of the syndrome, needs elucidating.

What we do know is that preeclampsia develops due to impaired remodelling of the spiral arteries that supply blood to the developing placenta and fetus.[9] In normal fetal development, during the first weeks of pregnancy, the extravillous cytotrophoblast, descendant of the trophoblast, invades the myometrium and replaces the smooth muscle and endothelium that lines maternal spiral arteries (Figure 1). These vessels become wider and they lose their vasoactive capabilities. They become low-resistance, high-diameter vessels that anastomose with endometrial veins, bringing blood into the intervillous space. Oxygen, nutrients and waste can thus diffuse back and forth across the thin syncytiotrophoblast.[10,11] In women who are subsequently diagnosed with preeclampsia, this remodelling is impaired. It is not clear why. The immune system has been implicated; natural killer cells may play a role.[12] Whatever the underlying cause, the impaired blood vessel development means, first, that these spiral arteries do not become the high capacity vessels that they should; and second, they retain vasoactive capabilities.[13] This can lead to fluctuating levels of oxygen in the intervillous space; ischemia, then reperfusion, and repeat.

The result initially is oxidative stress, and the release of reactive oxygen species into maternal circulation. And then comes the release of anti-angiogenic proteins from the syncytiotrophoblast,[14] proteins that enter maternal circulation and dysregulate endothelial

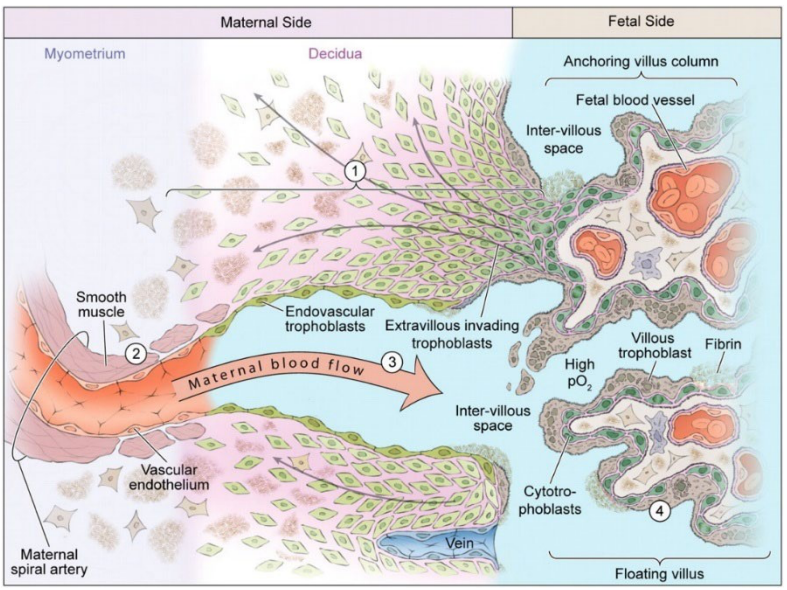

Figure 1. Normal placental development. Extravillous trophoblasts remodel maternal spiral arteries, increasing maternal blood flow to and oxygen concentration in, the inter-villous space. Cytotrophoblasts proliferate, forming the syncytiotrophoblast which becomes the interface between maternal and fetal circulations. From Menkhorst et al (2016)[10]

function. The mechanism linking the release of these proteins to the hypoxia-reperfusion injuries remains a matter of debate, but one proposal is that oxidative stress results in increased syncytiotrophoblast apoptosis.[15]

These anti-angiogenic proteins are central to the maternal syndrome of preeclampsia. The major culprits are soluble fms-like tyrosine kinase-1 (sFLT-1) and soluble endoglin (sEng),[16] which can bind to and sequester placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), key regulators of endothelial function (Figure 2).[17] We can refer generally to this as angiogenic imbalance – an excess of anti- and shortage of pro-angiogenic proteins.

It was in 2003 that Maynard et al provided persuasive evidence tying angiogenic imbalance, particularly mediated by sFLT-1, to the preeclamptic phenotype of hypertension, proteinuria and oedema.[18] In vitro studies found impaired angiogenesis in the serum of women diagnosed with preeclampsia, angiogenesis that could be worsened by the addition of sFLT-1, but relieved by the addition of PlGF. Many other groups have over the past two decades demonstrated the importance of this imbalance to the phenotype of preeclampsia, culminating in major prospective studies,[19,20] moving towards using the ratio as a diagnostic test for preeclampsia.

The key effect of angiogenic imbalance and the release of reactive oxygen species is to cause widespread maternal endothelial dysfunction, culminating in vasoconstriction, hypertension and organ dysfunction.[21,22] Endothelial dysfunction is a broad term, but generally refers to a decrease in bioavailable nitric oxide – a key vasodilator and regulator of endothelial function – and an imbalance between vasodilators such as nitric oxide (NO) and prostacyclin, and vasoconstrictors such as endothelin-1 (ET-1), angiotensin-II and thromboxane A2.[23]

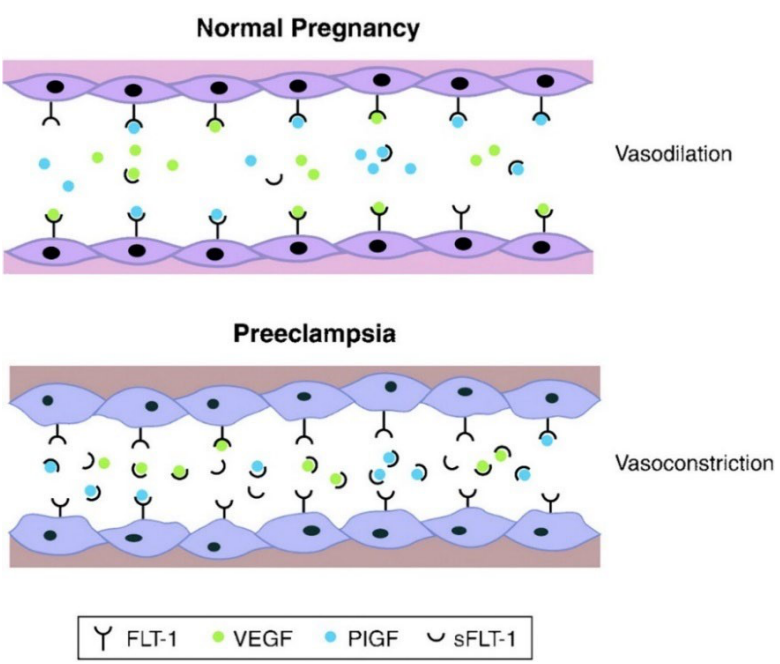

Figure 2: sFLT-1 binds to and sequesters PlGF and VEGF, reducing their bioavailability. From Shibuya et al (2013)[17]

Beyond the imbalance in vasoconstrictors and vasodilators, endothelial dysfunction leads to inflammation; increased blood vessel

permeability and plasma leakage; alterations in coagulation factors, leading to hypercoagulability and microthrombus formation; et cetera.[24] This leads to more widespread organ dysfunction –the kidneys, liver, brain – and can worsen uteroplacental perfusion, creating a vicious cycle.

This widespread endothelial dysfunction is the hallmark of the maternal phase of preeclampsia. The contribution of placental and maternal factors to preeclampsia can vary. The relationship between the placenta and maternal haemodynamics is bidirectional (Figure 3).[25]

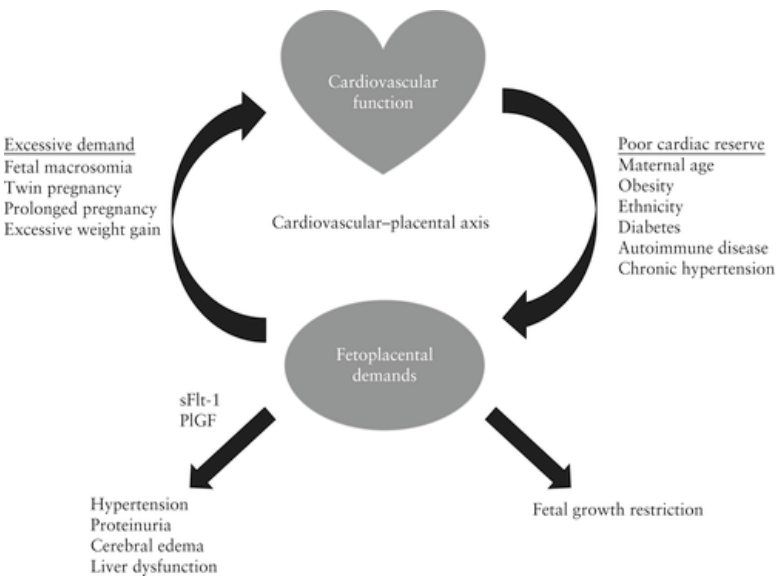

Figure 3: The interplay between the maternal cardiovascular system and the placenta. From Thilaganathan et al (2018)[25]

Placental insufficiency can lead to maternal endothelial dysfunction; but so too can a suboptimal haemodynamic adaptation to pregnancy cause impaired trophoblast invasion and spiral artery remodelling.

HDoP, and particularly preeclampsia, worsen during pregnancy. The only cure is delivery of the placenta and, necessarily, the fetus.[26] Aspirin reduces the incidence of preterm preeclampsia,[27] but once the syndrome is present, the only management is to attempt to safely prolong pregnancy. The aim is to improve neonatal outcomes while avoiding excessive risk to maternal health – preventing severe hypertension, monitoring for worsening health, and aiming to deliver the baby at a time which maximises both maternal and neonatal outcomes. However, it is particularly difficult to ascertain when complications are imminent, and thus timing delivering relies predominantly on clinical acumen. Research is ongoing into predicting preeclampsia and its complications, with the sFLT-1: PlGF ratio[28] and with the fullPIERS algorithm, which uses clinical features to determine the likelihood of complications[29] – but neither is yet widely used.

There remains no diagnostic test for preeclampsia. The sFLT-1: PlGF ratio holds promise – it is typically elevated weeks before the onset of clinical preeclampsia[30] – and is gradually being incorporated into guidelines for managing preeclampsia.[31] However, diagnosis remains largely based on clinical evaluation and organ function, via assessment of blood pressure, proteinuria, platelet counts, liver enzymes and so forth.

While preeclampsia was defined for many years as the onset of hypertension and proteinuria, in recent decades the diagnostic criteria have been updated to reflect the systemic nature of preeclampsia.[26,32] Hepatic, haematological, neurological, renal, or placental dysfunction, in conjunction with hypertension, can be sufficient for a diagnosis. However, the absence of a more precise understanding of the cause of preeclampsia, and the subsequent challenge to develop an effective diagnostic test, poses several challenges to the diagnosis of preeclampsia.

First is the variable presentation of preeclampsia. Preeclampsia is commonly subdivided into early- and late-onset preeclampsia, based on whether it develops before or after 34 weeks gestation. However, these two subtypes represent different disease processes. Early-onset preeclampsia is more severe, and the earlier it develops the more

serious it tends to be. Most complications from preeclampsia arise following the early-onset subgroup. The late-onset syndrome tends to be milder, often arising close to term and requiring less intensive management.[33]

This reflects differences in pathophysiology. Early-onset preeclampsia is associated with marked angiogenic imbalance (Figure 4), and generally involves a low-output, high-resistance state, with placental insufficiency and fetal growth restriction common complications. In contrast, the late-onset subtype is more closely tied to maternal characteristics, such as obesity, is associated with a high-output, low-resistance vascular system, and is not usually associated with fetal growth restriction.[34-36] However, these differences are not mutually exclusive, and occur on a continuous scale; the earlier the syndrome develops the more severe it is. Dividing women into a binary of early- or late-onset does not account for this.

These differences in pathophysiology are particularly relevant when considering the association of angiogenic imbalance with the severity of preeclampsia. A prospective study of women presenting with suspected preeclampsia found that 11 of 13 women who went on to suffer severe maternal complications had a sFLT-1: PlGF ratio greater than 15 times higher than the median;[37] another study of women diagnosed with preeclampsia found that all complications occurred in women with a sFlt-1: PlGF ratio greater than 85.[38] Correlations have also been established between the sFlt-1: PlGF ratio and the development of severe preeclampsia;[39] likelihood of complications such as stillbirth;[40] a need for imminent delivery;[41] length of hospital stay for both mothers and neonates;[42] as well as biochemical markers, such as lower platelet counts,[41] higher uric acid[43] and ALT[41], more proteinuria.[42]

The second challenge to the diagnosis of preeclampsia is that the signs and symptoms – particularly following the expansion of the diagnostic criteria to include other organ dysfunction beyond proteinuria – are not specific. Changes in blood pressure and proteinuria, in particular, are common during pregnancy, particularly for women with preexisting hypertension, obesity or diabetes mellitus.

Some 13% of women with chronic hypertension in one study had proteinuria prior to pregnancy.[44] Diabetic nephropathy, with the subsequent presence of proteinuria, is an increasingly common complication of diabetes

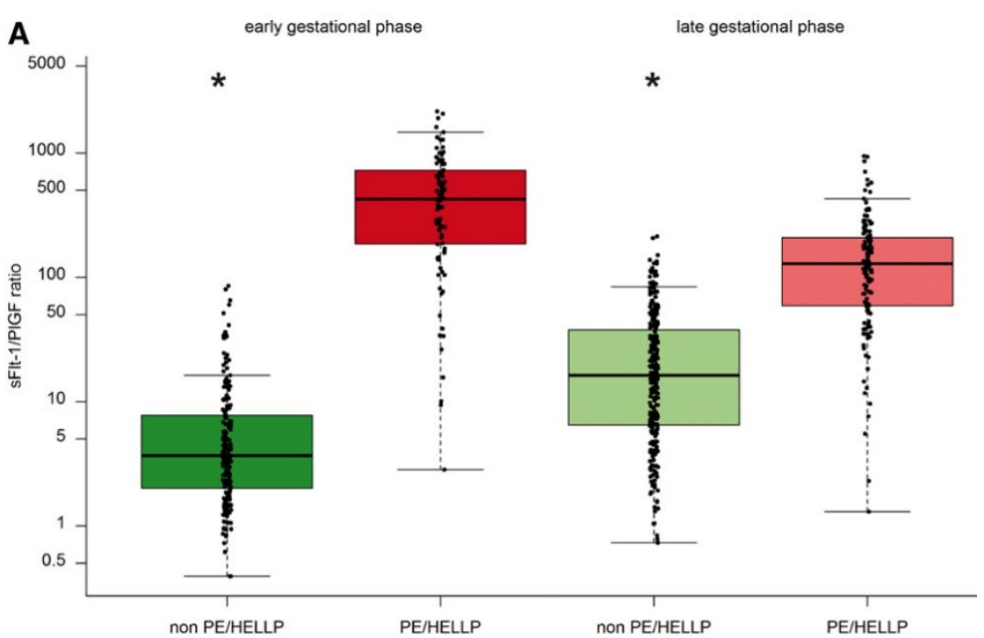

Figure 4. The sFLT-1: PlGF ratio in early- and late-onset preeclampsia. From Verlohren et al (2012)[45]

mellitus; and even in the absence of overt nephropathy, diabetes is associated with an exaggerated rise in proteinuria during pregnancy.[45] Obesity increases the likelihood of developing physiological proteinuria in pregnancy, particularly after 33 weeks gestation;[46] and hypertension and proteinuria are commonly present in women with CKD.[47] This muddies the picture, making a clinical diagnosis challenging.

These comorbidities are major risk factors for a diagnosis of preeclampsia: preeclampsia develops in as many as 20% of pregnancies with pre-existing hypertension, diabetes or chronic kidney disease, while obesity and gestational diabetes are associated with a two- to threefold increased risk.[48-53]

The challenge of accurate diagnosis, and the possibility of overdiagnosis, could account for some of this risk. But another contributing factor is that these comorbidities are associated with endothelial dysfunction, the common final pathway in all preeclampsia, prior to pregnancy.

The sustained elevation of systemic blood pressure in hypertension leads to premature endothelial cell aging, reducing its vasodilating capacity.[54] Chronic hypertension is also associated with increased levels of asymmetric dimethylarginine (ADMA), a competitive eNOS inhibitor.[55]

Hyperglycaemia is associated with increased expression of ET-1 and downregulation eNOS13, as well as increased levels of reactive oxygen species and oxidative stress in the maternal endothelium.[56] And besides insulin resistance, obesity is also associated with increased activation of the renin-angiotensin system, contributing to vasoconstriction.[57] And obesity is associated with reduces activity of eNOS, independent of hypertension.[57] Finally, CKD is associated with oxidative stress and higher ADMA concentrations, independent of hypertension.[55,58]

Endothelial dysfunction is the final common pathway of preeclampsia. And as these comorbidities are associated with endothelial dysfunction prior to pregnancy, a milder degree of placental insufficiency and the resulting sequelae may result in preeclampsia developing. A rise in circulating anti- angiogenic proteins is observed in normal pregnancies;[59] this normal occurrence may, for women with these comorbidities, be sufficient to produce the pre-eclamptic phenotype.[60] But what does it mean for the severity and prognosis of preeclampsia, if the underlying pathological changes are milder?

A better characterisation of the clinical phenotype and prognosis of women with comorbidities who develop preeclampsia is important for several reasons.

First, these comorbidities are increasingly prevalent and developing younger in life. Thus they are complicating a greater number of pregnancies, particularly in high and middle income countries. In 2014-2015 in Australia, pre-gestational diabetes complicated 1% and gestational diabetes 10% of pregnancies.[61] In the United States, the prevalence of chronic hypertension has increased rapidly, from 0.1% in 1970 to 1.5% in 2010.[62] Some 45% of new Australian mothers in 2018 were overweight or obese;[63] and while it is less common, CKD affects about 1/750 pregnancies and is on the rise, as diabetes and diabetic nephropathy develop earlier in society.[64]

Second, comorbidities are associated with a range of adverse pregnancy outcomes. Chronic hypertension is associated with a greater than two-fold increase in the odds of fetal and neonatal mortality, severe preeclampsia and placental abruption; a three-fold increase in odds of prematurity; and greater than four-fold increases in birthweight <10th centile and respiratory distress syndrome.[65] Pre-gestational and gestational diabetes are associated with

increases in stillbirth rates, as well as preterm delivery, preeclampsia, NICU admission, fetal growth restriction, and respiratory distress syndrome.[66-69] Both obesity and CKD increase the likelihood of preterm birth and NICU admission.[70-72]

These ramifications of these challenges in the diagnosis and prognosis of preeclampsia have been little studied. Guidelines remain vague when suggesting diagnostic criteria for women with preexisting hypertension and proteinuria, with little evidence to guide decisions.

This thesis aims to fill that gap.

Chapter one consists of a longitudinal cohort study, where we sample blood from women across pregnancy and, among women who proceeded to develop preeclampsia, compared levels of sFLT-1 and PlGF between women with and without comorbidities.

Chapter Two compares, among women with preeclampsia, the clinical phenotype and outcomes of women between those with and without comorbidities.

Chapter Three builds on the findings of Chapter Two, by comparing the frequency of complications from preeclampsia on a much bigger scale.

Chapter Four changes course, to look at the effect of baseline blood pressure and body mass index – as continuous variables, and not restricted to women with a diagnosed comorbidity – on the course of blood pressure during pregnancy. And Chapter Five extends this work, by looking once more at the rate of complications from preeclampsia, but again treating baseline blood pressure and BMI as continuous predictors.

Finally, Chapter Six is a literature review; an evaluation of how the diagnostic criteria of preeclampsia changed across the 20th and early 21st centuries. We critically appraise the evidence that guided diagnostic evolution over the years, and suggest directions for studying and classifying preeclampsia. Finally, the discussion synthesizes and elaborates on these findings.

In summary, this thesis comprehensively explores the role of maternal characteristics in the diagnosis and prognosis of preeclampsia. It contributes knowledge to identifying women at risk of developing preeclampsia (Chapters One and Four); to refining the diagnostic criteria of preeclampsia (All Chapters, but specifically Chapter Six); to understanding the severity of preeclampsia (Chapter Two); to evaluating the likelihood of maternal complications (Chapters Two, Three and Five)and neonatal complications (Chapter Three).

Chapter One

"Sometimes a small change could make all the difference."
— Cynthia D'Aprix Sweeney, *The Nest*

Introduction

In recent decades, one of the most exciting discoveries in women's health was that of the role of sFLT-1 in preeclampsia. When Maynard et al showed that administering sFLT-1 to rats resulted in the development proteinuria and hypertension,[18] the world finally had a suspect for the "toxin", long dubbed "Factor X", so long thought to be responsible for preeclampsia.[73]

The imbalance between sFLT-1 and PlGF is associated with the severity of preeclampsia; and the overwhelming majority of (and in some studies, all) women who suffer complications have a substantial angiogenic imbalance. Thus it is unsurprising that the sFLT-1: PlGF ratio has received considerable scrutiny for a potential role in diagnosing or predicting both preeclampsia and its complications.

Two other trends were converging as research into the sFLT-1: PlGF ratio exploded. First, the diagnostic criteria for preeclampsia were broadening, culminating in a criteria which no longer requiring proteinuria.[8] Second, the number of pregnant women with obesity, and other metabolic risk factors such as essential hypertension and diabetes mellitus, was increasing rapidly.[61,62,64]

However, sparse research has evaluated the sFLT-1: PlGF ratio in women with comorbidities. We hypothesised that, compared to those women without comorbidities, a lower elevation of this ratio would lead to a diagnosis of preeclampsia. Thus we undertook a cohort study to compare the sFLT-1: PlGF ratio between women who develop preeclampsia with and without comorbidities.

The effect of comorbidities on the sFLT-1: PlGF ratio in preeclampsia

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Abstract

Research indicates that soluble fms-like tyrosine kinase 1 (sFLT-1) and placental growth factor (PLGF) have diagnostic and prognostic significance for women with preeclampsia. However, sparse research has studied these biomarkers in women with preexisting comorbidities such as chronic hypertension, diabetes mellitus, systemic lupus erythematosus and chronic kidney disease. We undertook a prospective longitudinal cohort study to compare the sFLT-1: PlGF ratio between women with and without comorbidities who did and did not go on to develop preeclampsia. We found that women with comorbidities may develop preeclampsia with a milder elevation in sFLT-1: PlGF than do women without comorbidities. This has clinical and research implications.

Introduction

Preeclampsia affects 2-5% of pregnancies, causing significant maternal and perinatal morbidity and mortality (1).

The pathogenesis of preeclampsia remains incompletely understood. Its characteristic hypertension and organ-dysfunction arise secondary to widespread endothelial dysfunction and vasoconstriction (2).

Evidence increasingly suggests a role for the angiogenic biomarkers soluble fms-like tyrosine kinase-1 (sFLT-1) and placental growth factor (PlGF), which are, respectively, increased and decreased in preeclampsia (3). sFLT-1 is released from the ischemic placenta, antagonising and sequestering the pro-angiogenic PLGF and vascular endothelial growth factor, contributing to endothelial dysfunction (4).

Vascular risk factors, including medical comorbidities such as chronic hypertension, diabetes mellitus, chronic kidney disease and systemic lupus erythematosus, increase the risk of women developing preeclampsia (5-9).

There is sparse evidence guiding the clinical diagnosis of preeclampsia when preexisting hypertension and/or proteinuria are present, as is common for women with these comorbidities, due to the diagnostic challenge preeclampsia poses. Similarly, there is limited research evaluating how useful sFLT-1 and PlGF, which are entering clinical decision making guidelines (10), are in the diagnosis of preeclampsia for these women. Women with vascular risk factors are prone to pre-existing endothelial dysfunction. They thus may develop clinical preeclampsia with a milder imbalance between sFLT-1 and PlGF (11).

While several studies (12,13) have demonstrated that, among women with these comorbidities, these biomarkers are elevated when preeclampsia develops, sparse research has compared the magnitude of their elevation between women with and without comorbidities. Data from studies on women without vascular risk factors, which forms the basis for new guidelines, may not be applicable for women with comorbidities. We undertook a prospective cohort study to compare the sFLT-1: PlGF ratio between women with and without comorbidities, who did and did not develop preeclampsia.

Methods

We performed a longitudinal observational study at a tertiary hospital in Melbourne, Australia, between 2017 and 2019. We recruited women with a singleton pregnancy without congenital abnormalities attending a maternal-fetal medicine clinic to evaluate novel biomarkers for preeclampsia. Following written informed consent, we collected serum samples at multiple time periods throughout pregnancy: 15-20 weeks, 24-29 weeks, and 33-37 weeks' gestation. A minimum 4ml of whole blood was collected into ethylenediaminetetraacetic acid (EDTA) vacutainer tubes (Beckton Dickinson, Oakville, ON, USA). The samples were centrifuged at 1200g for 20 minutes and the serum collected and aliquoted prior to storage at -80°C until they were analysed. sFLT-1 and PlGF concentrations were determined on the B.R.A.H.M.S KRYPTOR Compact PLUS (Thermo Fisher Scientific, Waltham, MA, USA), an automated immunoassay analyser, as per the manufacturer's instructions. Ethics approval was granted by Monash Health human research ethics committee (No. 19397).

We compared biomarker levels between women with and without comorbidities, which included chronic hypertension, diabetes mellitus, chronic renal disease, or systemic lupus erythematosus.

Statistical Analysis

Descriptive statistics were computed for all data, with dichotomous outcomes presented as

a number (%). Continuous outcomes are displayed as mean (standard deviation) or median (interquartile range).

We compared the sFLT-1: PlGF in each gestational period between women with and without comorbidities and between women who did and did not develop preeclampsia at any stage during their pregnancy, using two-way analysis of variance with Tukey's post hoc adjustment. Statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using *R* version 4.0.2

Results

A total of 123 women provided at least two blood samples and were included in the final analysis. Of these, 34 women (28%) had preexisting medical comorbidities. There were no significant differences in baseline demographics between women with and without comorbidities.

Fourteen (41.2%) women with comorbidities and six (6.7%) without comorbidities developed preeclampsia (Relative Risk (RR) 3.76, 95% CI 2.29 to 6.18). Of the women with comorbidities who developed preeclampsia, seven (50%) had preexisting hypertension, six (43%) had CKD, two (14%) had type 1 diabetes, and one (7%) had Type 2 diabetes.

The sFLT-1: PlGF ratio was higher in all three gestational age windows in women who subsequently developed preeclampsia compared to those who did not (Figure 1). This was statistically significant between 24-29 weeks, and between 33-37 weeks ($P<0.001$).

Between 24- and 29-weeks gestation and 33-37 weeks gestation, the sFLT-1: PlGF ratio tended to be higher among women who developed preeclampsia without comorbidities compared to those who developed preeclampsia with comorbidities, though the differences were not significant ($p = 0.44$ and $p = 0.26$ respectively) (Table 1).

Discussion and Conclusion

In this prospective observational study, we have shown that the sFLT-1: PlGF ratio is higher in women who develop preeclampsia than in those who do not. However, among women diagnosed with preeclampsia, it may be less elevated in women with comorbidities than it is among women without comorbidities. Furthermore, several women without comorbidities developed an elevated ratio without developing preeclampsia, indicating an ability to tolerate angiogenic imbalance. No women with comorbidities developed a high ratio without doing so. Thus the sFLT-1: PlGF ratio may, for women with comorbidities, risk inadvertently ruling out preeclampsia.

This has clinical and research implications. Angiogenic biomarkers are being incorporated into clinical practice guidelines (10). However, few studies have evaluated whether established cut-offs are appropriate for women with comorbidities.

Clinical practice guidelines in any field commonly use a single cut-off to guide practice. However, research used to develop cut-offs and guide their incorporation into clinical practice has largely been undertaken in women without comorbidities. A single cut-off based off research in women at low-risk of preeclampsia, stringently applied to women with comorbidities, may miss women at risk of developing preeclampsia and subsequent complications.

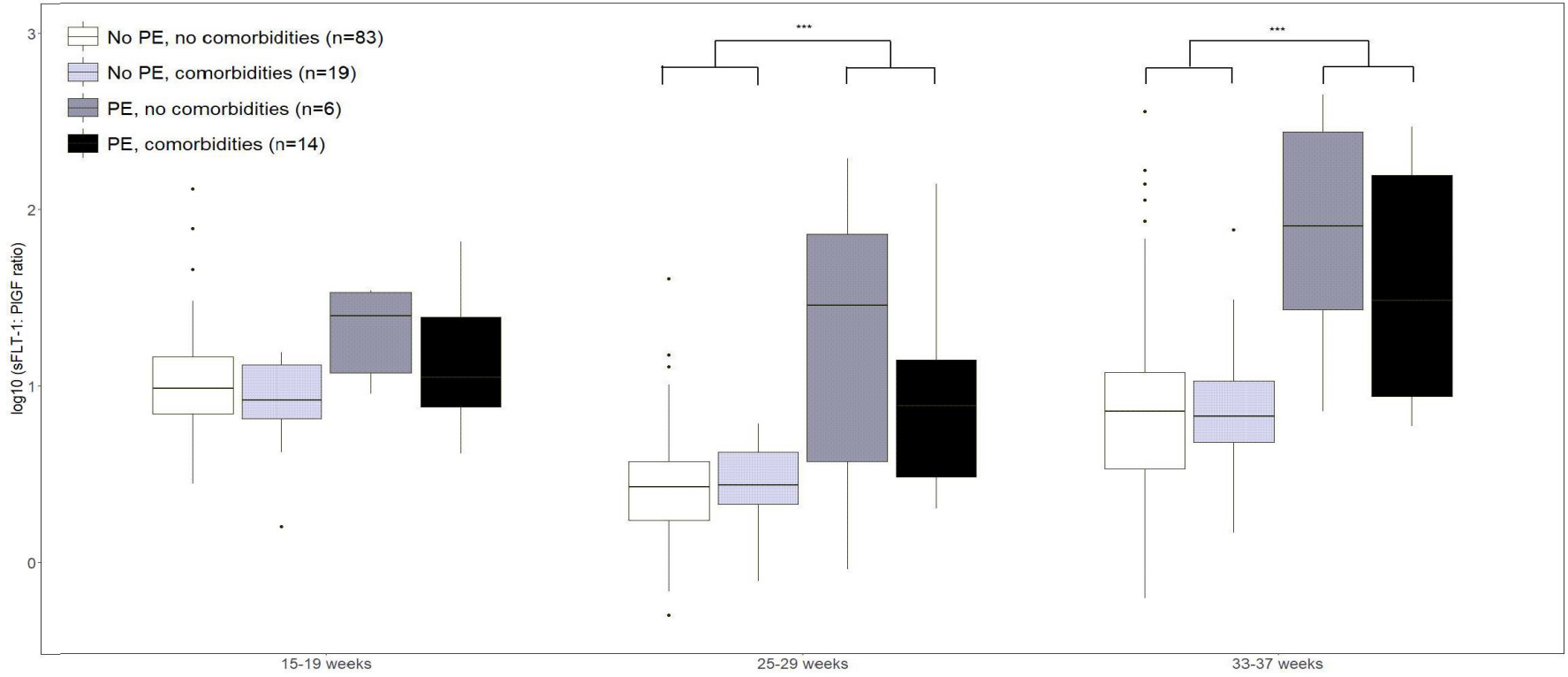
This study is limited by the small number of women who developed preeclampsia. However, our findings accord with the underlying pathophysiology of preeclampsia and our hypothesis that preexisting endothelial dysfunction may lower the threshold for angiogenic imbalance to trigger clinical preeclampsia. This warrants both further research, and caution when interpreting sFLT-1, PlGF and the sFLT-1: PlGF ratio in women with comorbidities.

Table 1. Baseline demographics and sFLT-1: PlGF ratios

	No preeclampsia, no comorbidities (n = 83)	No preeclampsia, comorbidities (n = 19)	Developed preeclampsia, no comorbidities (n = 6)	Developed preeclampsia, comorbidities (n = 14)	P value
Baseline demographics					
Age	33.1 (5.6)	34.3 (5.3)	35.6 (6.9)	31.0 (4.1)	0.50
BMI	30.3 (9.6)	30.6 (8.5)	32.0 (10.4)	32.7 (7.6)	0.44
Nulliparous	26 (31.3%)	9 (47.4%)	3 (50%)	6 (40%)	0.81
Current smoker	5 (6.0%)	0 (0%)	0 (0%)	0 (0%)	0.77
sFLT-1: PlGF ratio					
15-19 weeks	9.63 (6.89 – 14.54) (n = 54)	7.95 (5.22 – 13.02) (n = 11)	24.76 (11.77 – 33.62) (n = 5)	11.18 (7.54 – 24.34) (n = 9)	0.11
25-29 weeks	2.66 (1.72 – 3.72) (n = 75)	2.74 (2.12 – 4.17) (n = 19)	28.42 (3.70 – 72.04) (n = 5)	7.78 (3.14 – 14.04) (n = 14)	<0.001
33-37 weeks	7.14 (3.38 – 11.86) (n = 75)	6.69 (4.76 – 10.57) (n = 17)	80.27 (26.85 – 273.47) (n = 5)	50.5 (8.71 – 155.73) (n = 12)	<0.001

Data given as mean (standard deviation), median (interquartile range), or number (%). Numbers in parentheses refer to the number of women giving samples at each gestational window. P values calculated with two-way ANOVA with Tukey's post-hoc correction.

Figure 1. sFLT-1: PlGF ratios across gestation.



sFLT-1: PlGF ratios across gestation in women with and without comorbidities, and with and without preeclampsia. *Errors bars* represent the median; *boxes*, the interquartile range (IQR); *whiskers*, the range of the median ± 1.5 times the IQR; *dots*, outliers. *** indicates P < 0.001, calculated with two-way ANOVA, comparing women with and without preeclampsia.

References

1. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2019;133(1):e1-e25.
2. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi J-M. Pre-eclampsia: pathophysiology, diagnosis, and management. Vasc Health Risk Manag. 2011;7:467-74.
3. Redman CW, Sargent IL. Pre-eclampsia, the placenta and the maternal systemic inflammatory response--a review. Placenta. 2003;24 Suppl A:S21-7.
4. Suzuki H, Ohkuchi A, Matsubara S, Takei Y, Murakami M, Shibuya M, et al. Effect of recombinant placental growth factor 2 on hypertension induced by full-length mouse soluble fms-like tyrosine kinase 1 adenoviral vector in pregnant mice. Hypertension. 2009;54(5):1129-35.
5. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ (Clinical research ed). 2005;330(7491):565-.
6. Seely EW, Ecker J. Chronic Hypertension in Pregnancy. Circulation. 2014;129(11):1254-61.
7. Weissgerber TL, Mudd LM. Preeclampsia and diabetes. Current diabetes reports. 2015;15(3):9-.
8. Schneider S, Freerksen N, Röhrig S, Hoeft B, Maul H. Gestational diabetes and preeclampsia – Similar risk factor profiles? Early Human Development. 2012;88(3):179-84.
9. Roberts JM, Bodnar LM, Patrick TE, Powers RW. The Role of Obesity in Preeclampsia. Pregnancy hypertension. 2011;1(1):6-16.
10. National Institute for Health and Care Excellence. PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio). 2016.
11. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. The New England journal of medicine. 2006;355(10):992-1005.
12. Powers RW, Jeyabalan A, Clifton RG, Van Dorsten P, Hauth JC, Klebanoff MA, et al. Soluble fms-Like tyrosine kinase 1 (sFlt1), endoglin and placental growth factor (PlGF) in preeclampsia among high risk pregnancies. PLoS ONE 5(10):e13263.
13. Nzelu D, Biris D, Karampitsakos T, Nicolaides KK, Kametas NA. First trimester serum angiogenic and anti-angiogenic factors in women with chronic hypertension for the prediction of preeclampsia. American Journal of Obstetrics & Gynecology.222(4):374.e1-.e9.
14. Tanner MS, Davey MA, Mol BW, Rolnik DL. The evolution of the diagnostic criteria of preeclampsia-eclampsia. Am J Obstet Gynecol. 2022;226(2s):S835-s43.

Summary

While this was a study with promising results, there were too few women to draw any sure conclusions, nor determine whether what we saw was a signal, or merely noise.

We can, however, conclude that this is a question that should be explored further. Our results, insufficient as they are to draw conclusions, would appear to support our hypothesis – that women with comorbidities would be diagnosed with preeclampsia with a relatively low sFLT-1: PLGF ratio. And such a result is biologically plausible. But it will be for others to pose the follow-up questions: to test our conclusions on a larger scale; to further explore the influence of specific comorbidities; and to evaluate the prognostic potential of these biomarkers.

While it is a significant investment to conduct a large prospective study, there is lower hanging fruit to pick. Rare is the woman for whom preeclampsia is not diagnosed clinically. And we know that the degree of imbalance in sFLT-1 and PlGF relates closely to the severity of preeclampsia. Thus evaluating the association between the presence of comorbidities and the clinical picture and outcome of preeclampsia is valuable. If the sFLT-1: PlGF ratio truly is lower in women with comorbidities, then we would expect to see these women diagnosed with preeclampsia with only a mild clinical syndrome.

Studying this hypothesis also gives useful clinical information. Diagnosing preeclampsia when the syndrome is only mild may lead to unnecessary intervention and neonatal harm due to early delivery. The association between comorbidities and the severity of preeclampsia has been unsatisfactorily answered, particularly considering the rising prevalence of vascular risk factors in pregnancy.

It is here we turn to Chapter Two.

Chapter Two

" 'If I ever have to go to hospital, madam,' one of the midwives calmly tells her, 'I want to be seen last. Because that means everyone else there is sicker than me.'"
Adam Kay, *This is Going to Hurt: Secret Diaries of a Junior Doctor*

Introduction

The sFLT-1: PlGF ratio is a useful tool – but does it just tell us what we already know? If a woman has severe preeclampsia, you can often tell – if she is diagnosed at 28 weeks gestation with a skyrocketing high blood pressure, headache, falling platelets and increasing proteinuria, you know it is severe. If it is diagnosed at 37 weeks with a slight increase in blood pressure, it probably isn't.

Preeclampsia is still diagnosed, and treatment decisions made, using primarily clinical judgement. Thus identifying associations between comorbidities and the clinical course of preeclampsia is valuable. We undertook a retrospective cohort study of women who were diagnosed with preeclampsia. We compared severity of and outcomes from the syndrome between women with and without comorbidities, evaluating signs and symptoms, laboratory markers, and maternal and neonatal outcomes.

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The effect of preexisting medical comorbidities on the preeclamptic phenotype: a retrospective cohort study

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The effect of preexisting medical comorbidities on the preeclamptic phenotype: a retrospective cohort study

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ABSTRACT

Objective: To compare the effect of comorbidities on the phenotype and outcomes of preeclampsia.

Methods:A matched retrospective cohort study of women delivering at a tertiary maternity center following a diagnosis of preeclampsia. We collected data on signs and symptoms, biochemical markers, and maternal and perinatal outcomes.

Results: We studied 474 women; 158 women with and 316 without comorbidities. Compared to women without comorbidities, women with comorbidities delivered earlier. They suffered fewer maternal but more neonatal complications.

Conclusion: Women with comorbidities receive earlier intervention than women without comorbidities, which may lead to fewer maternal complications but worse neonatal outcomes.

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Preeclampsia; hypertension; angiogenic; complications; comorbidities

Introduction

Preeclampsia, characterized by hypertension and organ dysfunction in pregnancy, remains a leading cause of maternal and perinatal morbidity and mortality (1). The maternal syndrome results from widespread endothelial dysfunction, secondary to placental insufficiency and the release of anti-angiogenic and pro-inflammatory proteins and reactive oxygen species.

Medical comorbidities such as chronic hypertension, preexisting diabetes mellitus, systemic lupus erythematosus (SLE), chronic kidney disease (CKD), and anti-phospholipid syndrome (APLS) are associated with an increased likelihood of adverse maternal or neonatal outcomes in pregnancy, including an increased risk of preeclampsia (2–6). All are associated with preexisting endothelial dysfunction (7–11), which has been proposed as a mechanism explaining their increased risk of developing preeclampsia (12). Preexisting endothelial dysfunction could mean that a lesser degree of placental insufficiency and its sequelae, particularly angiogenic imbalance, is required to trigger the clinical syndrome.

Angiogenic biomarkers are entering practice to guide clinical decision-making for women with preeclampsia (13). Chief among these are the anti-angiogenic soluble fms-like tyrosine kinase-1 (sFLT-1), and the pro-angiogenic placental growth factor (PlGF). Dysregulation of these biomarkers correlates with the severity of preeclampsia, including biochemical tests (14–16) and frequency of complications (17,18). However, evidence is sparse for women at high-risk of developing the disease. Powers et al. (19) studied these biomarkers in women at high-risk of preeclampsia, including women with hypertension and diabetes. Though women who developed preeclampsia developed dysregulated biomarkers, these changes were milder than those seen in women at low-risk of preeclampsia. If women with comorbidities develop preeclampsia with mild changes in these biomarkers, this may have implications for the severity of disease. However, minimal research has assessed either the severity or prognosis of preeclampsia between women with and without comorbidities.

As these comorbidities are increasingly common (20–22), understanding how they alter the clinical picture and outcomes of preeclampsia is crucial. Evidence guiding management of the disease – including timing delivery and application of emerging biomarkers – is overwhelmingly generated in women without these comorbidities, and may not be generalizable to women with comorbidities. We undertook a matched cohort study to compare the clinical phenotype of

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preeclampsia between women with and without comorbidities.

Methods

Women with a pregnancy complicated by preeclampsia who delivered at a single tertiary referral center between 2011 and 2018 were identified from Birthing Outcome System (BOS) (Melbourne Clinical and Translational Sciences [MCATS], Melbourne, Australia) records. Clinicians routinely enter data regarding maternal characteristics and antenatal and neonatal diagnoses, interventions and complications.

Women with a prepregnancy diagnosis of chronic hypertension, diabetes mellitus, SLE, CKD, or APLS were identified and matched for maternal age and body mass index (BMI) in a 1:2 ratio with women without any of these comorbidities. We selected a matched cohort to facilitate a detailed record review of a smaller subset of patients. Matching on age and BMI also led to more balanced groups at baseline for in other characteristics, such as parity. CKD was defined as a prepregnancy estimated glomerular filtration rate <60 ml/min/1.73 m^2, or a diagnosed pathology (e.g. Goodpasture's disease, IgA nephropathy) with a creatinine >80 μmol/L at pregnancy booking. Diagnoses of preeclampsia were confirmed through record review, using the 2014 International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria (23), as this was the guideline in use for most of the study period. Women with preexisting proteinuria or hypertension required another feature of organ dysfunction to meet the definition of preeclampsia (23) . For women with multiple pregnancies complicated by preeclampsia in the study period, the first pregnancy was selected.

Data regarding maternal demographics, clinical presentation, biochemical markers of disease, and maternal and neonatal outcomes were extracted from medical records. Maternal demographics included age, BMI, parity, aspirin use, and whether women smoked through pregnancy. Age and BMI were recorded at booking visit, most commonly between 12 and 16 weeks gestation. Women at our center are routinely offered aspirin if they are at high risk of preeclampsia due to a past history of preeclampsia, medical comorbidities, family history of preeclampsia, age >40 years, BMI >35 $km/^2$, nulliparity, or having a multiple pregnancy. Clinical data included signs and symptoms that were documented in the week prior to delivery, the highest systolic and diastolic blood pressure (mmHg), and anti-hypertensive medication requirements. Biochemical markers recorded included creatinine (μmol/L), alanine transaminase (ALT) (IU/L), platelet count (x 10^9/L), uric acid (μmol/L) and urine protein: creatinine ratio (uPCR) (mg/mmol). The most extreme measurement in the week prior to delivery was recorded. Maternal outcomes included gestation at diagnosis of preeclampsia and gestation at delivery, length of stay post-partum, development of HELLP syndrome, and any severe complications; defined as a composite of at least one of eclampsia, placental abruption, acute pulmonary edema, acute kidney injury, and intensive care unit (ICU) admission. Gestation at diagnosis was recorded as when a woman first met the diagnostic criteria for preeclampsia.

Perinatal outcomes included birthweight, stillbirth, and need for admission to and length of stay in special-care nursery (SCN) or neonatal ICU (NICU). Subgroup analysis was performed for early-onset (diagnosed prior to 34 weeks' gestation) and late-onset (diagnosed from 34 weeks' gestation onwards) preeclampsia.

Statistical analysis

Descriptive statistics were computed for all data, with dichotomous outcomes presented as a number (%). Continuous outcomes were assessed for normality with the Shapiro-Wilk test, and are displayed as mean (standard deviation) or median (interquartile range) for continuous outcomes. Dichotomous outcomes were compared using conditional logistic regression, controlling for maternal age and BMI. Where necessary, bootstrap resampling was used to produce a robust estimate. P values for the differences in continuous outcomes were determined using generalized estimating equations, with the matching strata as a random effect. Statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study participants

There were 1180 women with a recorded diagnosis of preeclampsia who delivered during the study period. Of these, 158 women with medical comorbidities met the criteria for preeclampsia, and once matched with 316 controls, 474 women were included in the analysis. Overall, 181 (38%) women had early-onset preeclampsia (91 with and 90 without comorbidities), and 293 (62%) had late-onset disease (67 with and 226 without comorbidities). The cohorts of women with and

without comorbidities were comparable at baseline (Table 1). Chronic hypertension was the most common medical comorbidity, with 67.7% of women having a preexisting diagnosis (Table 1).

Table 1. Baseline demographics of the study population. Data expressed as mean (SD), median (IQR), or number (%). SLE = Systemic Lupus Erythematosus; APLS = antiphospholipid syndrome; CKD = chronic kidney disease.

Demographics	Women with comorbidities (n = 158)	Women without comorbidities (n = 316)
Age (years)	33.6 (5.0)	32.6 (5.4)
BMI (kg/m^2)	32.6 (8.2)	32.5 (8.4)
Current smoker (yes/no)	12 (7.6%)	26 (8.2%)
Nulliparous	74 (46.8%)	161 (50.9%)
Aspirin use	28 (17.7%)	14 (4.4%)
Comorbidities		
Hypertension	107 (67.7%)	0 (0%)
Type 1 Diabetes	27 (17.1%)	0 (0%)
Type 2 Diabetes	31 (19.6%)	0 (0%)
CKD	7 (4.4%)	0 (0%)
SLE/APLS	14 (8.9%)	0 (0%)
Ethnicity		
Caucasian	101 (71.6%)	200 (63.3%)
South East Asian	15 (9.5%)	27 (8.5%)
South Asian	22 (13.9%)	50 (15.8%)
Other/not specified	20 (12.6%)	39 (12.3%)

Maternal and perinatal outcomes

Tables 2 and 3 display maternal and perinatal complications and data on diagnosis and delivery of women with and without comorbidity.

Diagnosis and delivery

Women with comorbidities were diagnosed with preeclampsia at a median (interquartile range) of 33.2 (30.3– 36.2) weeks, compared to women without comorbidities who were diagnosed at 36.9 (33.4– 38.7) weeks ($p < 0.001$). Those without comorbidities also delivered earlier, at 35.0 (31.6– 37.1) weeks compared to 37.4 (35.2– 39.1) weeks. Women with comorbidities were less likely to be induced (40.5% vs 58.2%, aOR 0.48 (0.32– 0.71)) than women without comorbidities but were more likely to have a prelabor cesarean section (55.1% vs 32.3%, aOR 2.56 (1.72– 3.79) (Table 2).

Among women diagnosed with early-onset preeclampsia, there were no significant differences between those with and without comorbidities in gestation at delivery or labor onset. Conversely, among women diagnosed with late-onset preeclampsia, women with comorbidities delivered earlier (37.1 (1.7) vs 38.6 (2.3) weeks, $p < 0.001$); were less likely to be induced (52.2% vs 70.4%, aOR 0.46 (0.26–0.81)); and more likely to have a prelabor cesarean section (38.8% vs 18.6%, aOR 3.20 (1.70– 6.01)) (Table 3).

Complications

Fourteen women without comorbidities suffered severe complications from preeclampsia, compared to just one woman with a comorbidity (aOR 7.30, 95% CI 1.63–

Table 2. Maternal and neonatal outcomes. Results expressed as n (%) or mean (SD); ICU = intensive care unit. HELLP = haemolysis, elevated liver enzymes, low platelets. NICU = neonatal intensive care unit. Any severe adverse outcome prespecified as a composite of eclampsia, placental abruption, ICU admission, acute pulmonary edema, acute kidney injury, or maternal death within six weeks of delivery.

Outcomes	Women with comorbidities (n = 158)	Women without comorbidities (n = 316)	aOR (95% CI) or P value
Maternal outcomes			
Gestation at diagnosis (weeks)	33.2 (30.3- 36.2)	36.9 (33.4- 38.7)	<0.001
Gestation at delivery (weeks)	35.0 (31.6- 37.1)	37.4 (35.2- 39.1)	<0.001
Labor onset			
Spontaneous	7 (4.4%)	28 (8.9%)	0.48 (0.21- 1.13)
Induced	64 (40.5%)	184 (58.2%)	**0.48 (0.32– 0.71)**
No labor	87 (55.1%)	102 (32.3%)	**2.56 (1.72– 3.79)**
Complications			
HELLP Syndrome	9 (5.7%)	13 (4.1%)	1.41 (0.57- 3.34)
Placental abruption	0 (0.0%)	9 (2.8%)	NA
Eclampsia	0 (0.0%)	3 (0.9%)	NA
Acute pulmonary edema	0 (0.0%)	2 (0.6%)	NA
Acute kidney injury	0 (0.0%)	2 (0.6%)	NA
ICU admission	1 (0.6%)	3 (0.9%)	0.66 (0.03- 5.24)
Any severe adverse outcome	1 (0.6%)	14 (4.4%)	**0.14 (0.08– 0.70)**
Neonatal			
Stillbirth	6 (3.8%)	6 (1.9%)	2.06 (0.65- 6.50)
Birthweight (grams)	2305 (1368- 3222)	2860 (2026- 3455)	<0.001
Birthweight <3rd centile	30 (19.0%)	44 (13.9%)	1.44 (0.87- 2.39)
NICU stay >2 days	60 (38.0%)	41 (13.0%)	**4.57 (2.89– 7.21)**

11.11). Ten women (11%) without comorbidities who developed early-onset preeclampsia suffered any severe adverse outcome, most commonly placental abruption (n = 6). (Table 3)

Seven women (including the one woman with a comorbidity) who suffered a severe adverse outcome developed their complications prior to being diagnosed with preeclampsia. Four developed complications within a day of being diagnosed with preeclampsia. The other three developed their complications two, four, seven and eight days after diagnosis.

Perinatal outcomes

Six women in each cohort had a stillbirth (aOR 2.06, 95% CI 0.65– 6.50). All occurred in women with early onset preeclampsia (6.6% (women with comorbidities) vs 6.7% (women without comorbidities), aOR 0.99 (0.31– 3.19)).

Women with comorbidities gave birth to smaller babies, with a birthweight of 2305 (1368–3222) grams compared to 2860 (2026–3455) grams for women without comorbidities (Table 2). However following subgroup analysis, birthweights were not significantly different between women with and without comorbidities in either the early- or late-onset cohorts (Table 3). There were also no significant differences in the number of babies born below the 3rd centile to mothers with and without co-morbidities overall (Table 2), or in the early-onset or late-onset groups (Table 3).

Babies born to mothers with comorbidities were more likely to require NICU admission for more than two days than were those born to mothers without comorbidities (38.0% vs 13.0%, aOR 4.57 (2.89– 7.21)) (Table 2). This was limited to the early-onset cohort, where 62.6% of babies born to mothers with comorbidities required prolonged admission, compared to 35.6%

Table 3. Subgroup analysis of maternal and neonatal outcomes. Results expressed as n (%) or mean (SD); ICU = intensive care unit. HELLP = haemolysis, elevated liver enzymes, low platelets. NICU = neonatal intensive care unit. Any severe adverse outcome prespecified as a composite of eclampsia, placental abruption, ICU admission, acute pulmonary edema, acute kidney injury, or maternal death within six weeks of delivery. Outcomes adjusted for age and BMI with conditional logistic regression or linear mixed effects models.

	Early-onset preeclampsia			Late-onset preeclampsia		
Outcomes	**Women with comorbidities (n = 91)**	**Women without comorbidities (n = 90)**	**aOR (95% CI) or P value**	**Women with comorbidities (n = 67)**	**Women without comorbidities (n = 226)**	**aOR (95% CI) or P value**
Maternal						
Gestation at diagnosis (weeks)	30.6 (4.9)	30.8 (4.1)	0.20	36.6 (1.4)	37.9 (1.8)	<0.001
Gestation at delivery (weeks)	32.3 (5.6)	32.1 (4.2)	0.85	37.1 (1.7)	37.9 (1.8)	
Labor onset	1 (1.1%)				38.6 (2.3)	<0.001
Spontaneous	29 (31.1%)	3 (3.4%)	0.26 (0.03-2.55)	6 (9.0%)	25 (11.1%)	
Induced	61 (67.8%)	25 (28.4%)	1.22 (0.63-2.34)	35 (52.2%)	159 (70.4%)	0.69 (0.27-1.80)
No labor	8 (8.8%)	60 (68.2%)	0.94 (0.50-1.79)	26 (38.8%)	42 (18.6%)	0.46 (0.26-0.81)
Complications	0 (0%)	11 (12.2%)		1 (1.5%)	2 (0.9%)	3.20 (1.70-6.01)
HELLP	0 (0%)	6 (6.6%)		0 (0%)	3 (1.3%)	
Syndrome	0 (0%)	2 (2.2%)		0 (0%)	1 (<0.01%)	
Placental abruption	0 (0%)	2 (2.2%)	0.69 (0.26-1.81)	0 (0%)	0 (0%)	
Eclampsia	0 (0%)	1 (1.1%)	0.00 (0 - ∞)	0 (0%)	1 (<0.01%)	1.70 (0.15-19.01)
Acute pulmonary edema		2 (2.2%)	0.00 (0 - ∞)	1 (1.5%)	1 (<0.01%)	
Acute kidney injury		10 (11.0%)	0.00 (0 - ∞)	1 (1.5%)	4 (1.8%)	NA
ICU admission	6 (6.6%)		0.00 (0 - ∞)			NA
Any severe adverse outcome	1630 (891)	6 (6.7%)	0.00 (0 - ∞)			NA
Neonatal	27 (29.7%)	1538 (721)	0.00 (0 - ∞)	0 (0%)	0 (0%)	NA
Stillbirth	57 (62.6%)	20 (22.2%)		3218 (704)	3132 (654)	0.29 (0.09-1.09)
Birthweight (grams)		32 (35.6%)		3 (4.5%)	21 (9.3%)	
Birthweight <3rd centile				3 (4.5%)	9 (4.0%)	0.42 (0.04-4.35)
NICU stay >2 days			0.99 (0.31-3.19)			
			0.43			
			1.37 (0.70-2.69)			NA
			2.12 (1.16-3.89)			0.44
						0.50 (0.14-1.75)
						1.00 (0.20-4.95)

of those born to mothers without comorbidities (aOR 2.12, 95% CI 1.16– 3.89) (Table 3).

Maternal clinical phenotype

Tables 4 and 5 display data on biochemical markers and signs and symptoms of preeclampsia.

Signs/symptoms

Women with comorbidities developed more signs and symptoms of preeclampsia than did women without comorbidities, including abdominal pain (25.9% vs 16.8%), edema (39.9% vs 16.8%), clonus (20.9% vs 8.5%), and nausea (12.0% vs 6.0%). They were less likely to be diagnosed without any clinical features (17.1% vs 28.0%) (Table 4).

Women with comorbidities developed higher systolic blood pressures, with a median peak of 170.0 mmHg (IQR 160.0– 180.0) compared to 160.0 (150.0– 170.0) for women without comorbidities ($p < 0.001$). Median diastolic blood pressures were equal, but diastolic blood pressures overall tended to be higher in women with comorbidities (100.0 mmHg (95.0– 110.0) for women with comorbidities compared to 100.0 (90.0– 104.0) for those without ($p < 0.001$)) (Table 4).

In women with early-onset preeclampsia, most signs and symptoms occurred with similar frequency between those with and without comorbidities, though women with comorbidities were more likely to experience edema (44.0% vs 24.0%) and nausea (9.0% vs 4.9%). There were no significant differences in highest systolic or diastolic blood pressure (Table 5).

Among women with late-onset disease, those with comorbidities were more likely to develop signs and symptoms such as abdominal pain (22.4% vs 10.2%), edema (34.3% vs 13.7%), clonus (19.4% vs 4.4%) and nausea (14.3% vs 8.9%). They were also less likely to have no clinical features (13.4% vs 35.0%).

Biochemical markers

There were no significant differences in ALT, platelets, uPCR or uric acid between women with and without comorbidities, though women with comorbidities had higher creatinine (67.0 (56.0– 82.0) µmol/L compared to 58.0 (52.0– 72.5)) (Table 4).

However, among women with early-onset preeclampsia, women without comorbidities developed significantly lower platelet counts, higher uPCR and higher uric acid levels compared to women with comorbidities. In the late-onset cohort, there were no significant differences in any markers except creatinine, which was higher in women with comorbidities ($p < 0.001$) (Table 5).

For both cohorts of women, higher platelet counts and lower ALT, uPCR, uric acid, creatinine, and blood pressure, both systolic and diastolic, were all significantly associated with a later gestation at delivery (all $p < 0.01$).

However, when comparing women who delivered at the same gestational age, women with comorbidities had higher platelet counts (estimated difference +12.8 $x10^9$/L, 95% CI 1.0 to 24.7, $p = 0.03$), lower uric acid (−22.2 µmol/L, 95% CI −42.7 to −1.7, $p < 0.001$), lower

Table 4. Clinical and biochemical features of preeclampsia. Results expressed as median (IQR) or n (%). uPCR = urine protein: creatinine ratio; ALT = alanine transaminase. P values calculated with linear mixed effects models. Odds Ratios adjusted for age and BMI with conditional logistic regression (aOR).

	Women with comorbidities (n = 158)	Women without comorbidities (n = 316)	aOR (95% CI) or P value
Biochemical markers			
Creatinine (µmol/L)	67.0 (56.0- 82.0)	58.0 (52.0- 72.5)	**<0.001**
ALT (IU/L)	17.0 (12.0- 26.0)	17.0 (12.0- 31.0)	0.16
Platelets ($x10^9$/L)	197.0 (152.0- 229.0)	188.0 (146.0- 242.0)	0.97
uPCR (mg/mmol)	0.07 (0.04- 0.27)	0.07 (0.04- 0.20)	0.64
Uric acid (µmol/L)	370.0 (316.0- 434.0)	382.0 (323.0- 452.0)	0.43
Clinical features			
Headache	90 (57.0%)	153 (48.4%)	**1.42 (0.97– 2.09)**
Visual disturbance	31 (19.6%)	68 (21.5%)	0.88 (0.55- 1.41)
Abdominal pain	41 (25.9%)	53 (16.8%)	**1.74 (1.09– 2.75)**
Edema	63 (39.9%)	53 (16.8%)	**3.45 (2.25– 5.34)**
Clonus	33 (20.9%)	27 (8.5%)	**2.72 (1.56– 4.73)**
Nausea	19 (12.0%)	19 (6.0%)	**2.11 (1.08– 4.10)**
Vomiting	9 (5.7%)	14 (8.9%)	1.33 (0.56- 3.14)
No clinical features	27 (17.1%)	87 (28%)	**0.54 (0.34– 0.88)**
Blood Pressure			
Highest systolic (mmHg)	170.0 (160.0- 180.0)	160.0 (150.0- 170.0)	**<0.001**
Highest diastolic (mmHg)	100.0 (95.0- 110.0)	100.0 (90.0- 104.0)	**<0.001**

Table 5. Subgroup analysis of clinical and biochemical features of preeclampsia. Results expressed as median (IQR) or n (%). uPCR = urine protein: creatinine ratio; ALT = alanine transaminase. P values calculated with linear mixed effects models. Odds Ratios adjusted for age and BMI with conditional logistic regression (aOR).

	Early-onset preeclampsia			Late-onset preeclampsia		
Biochemical markers	**Women with comorbidities (n = 91)**	**Women without comorbidities (n = 90)**	**aOR (95% CI) or P value**	**Women with comorbidities (n = 67)**	**Women without comorbidities (n = 226)**	**aOR (95% CI) or P value**
Creatinine (μmol/L)	65.0 (52.2- 78.8)	67.0 (57.0- 83.0)	0.12	64.0 (54.5- 82.0)	57.0 (48.0- 70.0)	<0.001
ALT (IU/L)	21.0 (14.0- 31.5)	25.0 (16.0- 78.0)	0.14	16.0 (10.5- 23.0)	15.0 (11.0- 24.0)	0.88
Platelets ($x10^9$/L)	193.0 (146.5- 225.5)	162.5 (119.2- 206.8)	0.01	202.0 (172.0- 242.5)	201.0 (154.2- 246.0)	0.86
uPCR (mg/mmol)	0.07 (0.04- 0.29)	0.18 (0.06- 0.45)	0.001	0.07 (0.04- 0.24)	0.06 (0.04- 0.13)	0.49
Uric acid (μmol/L)	383.0 (320.0- 445.0)	421.0 (358.5- 483.5)	0.03	353.0 (313.8- 423.0)	368.0 (309.0- 438.0)	0.54
Clinical features						
Headache	60 (65.9%)	62 (68.9%)	1.00 (0.52- 1.94)	30 (44.8%)	91 (40.3%)	1.16 (0.66- 2.01)
Visual disturbance	20 (22.0%)	27 (30%)	0.68 (0.34- 1.35)	11 (16.4%)	41 (18.1%)	0.78 (0.37- 1.66)
Abdominal pain	26 (28.6%)	30 (33.3%)	0.83 (0.44- 1.57)	15 (22.4%)	23 (10.2%)	2.46 (1.16- 5.19)
Edema	40 (44.0%)	22 (24.4%)	2.91 (1.46- 5.80)	23 (34.3%)	31 (13.7%)	3.31 (1.74- 6.29)
Clonus	20 (22.0%)	17 (18.9%)	1.30 (0.61- 2.73)	13 (19.4%)	10 (4.4%)	6.05 (2.40- 15.25)
Nausea	13 (14.4%)	8 (8.9%)	1.58 (0.60- 4.13)	6 (9.0%)	11 (4.9%)	1.92 (0.67- 5.54)
Vomiting	8 (8.9%)	7 (7.8%)	0.88 (0.30- 2.60)	2 (3.0%)	6 (3.0%)	1.13 (0.22- 5.74)
No clinical features	18 (19.8%)	8 (8.9%)	2.34 (0.94- 5.79)	9 (13.4%)	79 (35.0%)	0.28 (0.13- 0.59)
Blood Pressure						
Highest systolic (mmHg)	170.0 (160.0- 188.8)	170.0 (160.0- 180.0)	0.23	166.5 (150.0- 170.0)	160.0 (153.8- 180.0)	0.002
Highest diastolic (mmHg)	100.0 (100.0- 110.0)	100.0 (98.0- 110.0)	0.65	100.0 (90.0- 100.0)	100.0 (90.0- 100.0)	0.25

ALT (−5.4 IU/L, 95% CI −9.9 to −0.8, p = 0.02) and lower uPCR (−0.05 mg/mmol, 95% CI −0.10 to 0, p = 0.05), but higher systolic blood pressures (+5.3 mmHg, 95% CI 1.8 to 8.3, p = 0.003) and higher creatinine (+6.0 µmol/L, 95% CI 2.4 to 9.6, p = 0.001).

Discussion

Main findings

We compared the phenotype of preeclampsia between women with and without comorbidities and found several important differences. Compared to women without comorbidities, women with comorbidities were diagnosed and delivered at an earlier gestational age and were more likely to have a prelabor cesarean section. They also suffered fewer maternal complications. Neonatal complications were comparable between women with and without comorbidities, though neonates born to women with comorbidities were more likely to be admitted to the NICU. Finally, at time of delivery, women with comorbidities had less severe disease biochemically, demonstrated by higher platelet counts, and lower uric acid, ALT and urine PCR, though their blood pressures were higher. Finally, women with comorbidities had more signs and symptoms of preeclampsia recorded.

Interpretation

The low rate of complications for women with comorbidities is likely to be a result of closer monitoring during pregnancy, as well as earlier intervention. This is a success for the management of these women. This intervention also may not cause a significant increase in neonatal harm, as among neonatal outcomes only NICU admission in the early-onset cohort was significantly different. However, we did not study other key neonatal complications associated with prematurity, such as respiratory distress syndrome.

Our findings highlight that preeclampsia is commonly severe when it develops in women without comorbidities. This underscores importance of developing and improving screening tools for women who appear to be at low risk of developing preeclampsia, as well as improving the monitoring of these women when preeclampsia does develop, as they are at highest risk of complications.

However, our work also raises questions regarding the diagnosis of preeclampsia in women with comorbidities. Preeclampsia poses a diagnostic dilemma when women have preexisting hypertension or proteinuria. Diagnostic criteria (24–26) in these instances are nonspecific and based on low-quality evidence. Considering the relatively milder disease phenotype these women appear to have, clinicians may be diagnosing preeclampsia, and intervening, leading to earlier delivery, at a lower clinical threshold for women when they have comorbidities.

The high prevalence of symptoms – particularly among women with late-onset preeclampsia – suggests that clinicians may be relying on symptoms such as edema and abdominal pain to diagnose preeclampsia. However, these symptoms are common in uncomplicated pregnancies, such that in the year 2000, edema was removed from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy diagnostic criteria (27), and subsequent guidelines from other groups (28).

Earlier intervention is undoubtedly a major contributor to the low occurrence of complications seen in women with comorbidities. However, as demonstrated by the high rate of NICU admission, this comes with the prospect of neonatal harm. The question that arises is whether pregnancy could be safely prolonged without compromising maternal health. The phenotype – particularly their biochemical markers of disease – of women with comorbidities being milder at time of delivery could indicate a lower threshold for intervention – perhaps reflecting a higher level of clinician concern owing to the presence of comorbidities.

The benefits of prolonging pregnancy at very preterm gestations are equivocal, and it may, in some cases, be safe to do so without risking maternal health, thus avoiding unnecessary neonatal harm.

For women diagnosed at or near term, current guidelines recommend delivery at 37 weeks' gestation for women with mild preeclampsia (13,29,30). The HYPITAT trial (31) demonstrated that this reduced maternal morbidity without compromising neonatal outcomes.

Among women without preeclampsia, compared to delivery at 39 or more weeks' gestation, early term birth is associated with increased neonatal mortality (32) and morbidity, including NICU admission, sepsis, respiratory disease (33,34), and poorer neurodevelopmental outcomes (35). If women with comorbidities are at low risk of complications, then delivery at 37 weeks' gestation may be causing undue neonatal harm.

Sparse research has compared the outcomes of preeclampsia between women with and without comorbidities. Tuuli et al. compared outcomes between women with preeclampsia superimposed on chronic hypertension and *de novo* preeclampsia (36). They found similar rates of complications, but more intervention-related events such as early delivery and cesarean sections.

Our study agrees with these findings, but by virtue of its sample size, provides a more detailed analysis by gestation at delivery, and looks at the effect of diabetes and obesity, not merely hypertension.

Neither the severity of preeclampsia nor its prognosis have previously been compared between women with and without comorbidities. However, our findings appear to be in line with existing literature. Powers et al. (19) have reported higher sFLT-1 and lower PlGF in women with hypertension or diabetes who develop preeclampsia compared to those that don't, but these changes are more modest than other studies evaluating women at low-risk. Furthermore, an elevated sFLT-1: PlGF ratio has been linked to lower platelet counts (14), higher uric acid (15) and ALT (14), more proteinuria (16), and an increased risk of complications (17,18) – in short, a more severe disease phenotype.

Existing literature thus suggests that, compared to women at low-risk, women at high-risk of preeclampsia may develop disease with a lower sFLT-1: PlGF ratio, which would translate into a milder disease phenotype. Our findings – particularly the low incidence of complications and mild biochemical picture seen in women with comorbidities – reflect this.

Strengths and limitations

Our study has limitations.

The comorbidities we have assessed are heterogenous; however, they share underlying characteristics – endothelial dysfunction prior to pregnancy, and a predisposition to hypertension and/or proteinuria that makes the diagnosis of preeclampsia challenging.

While the potentially most important finding of our study was the lower frequency of complications in women with comorbidities, there were only 15 cases of severe adverse outcome across the cohorts, meaning further research should be undertaken before firm conclusions are drawn.

Our in-depth record review is a strength. It offers a highly detailed clinical picture of preeclampsia across different cohorts. Research into preeclampsia commonly uses routinely collected data, which does not allow for our detailed analysis. This detail has enabled us to identify important areas for further research, particularly around crucial questions such as the timing of delivery. With medical comorbidities increasingly prevalent in pregnancy, better understanding the phenotype of preeclampsia is crucial to guide both management and further research.

Conclusion

Our research has identified important areas for further investigation. It is crucial that the risk of complications from preeclampsia and the severity of the disease phenotype be compared between women with and without comorbidities on a larger scale. If our findings hold true across larger populations, then research aimed toward redefining diagnostic criteria for women with comorbidities and revision of the recommendations around timing of birth would be warranted. Correspondingly, improving the screening of women thought to be at low risk of developing preeclampsia and their subsequent monitoring is important, as it is clear these are the women at highest risk of complications. Furthermore, the implementation of the sFLT-1: PlGF ratio into clinical guidelines must proceed with caution in women with preexisting medical comorbidities, as these women appear to have less angiogenic imbalance compared to women without comorbidities. The use of existing sFLT-1: PlGF ratios for ruling out preeclampsia may inadvertently miss at-risk women with comorbidities. Further prospective research is also needed given the reduced risk of serious complications seen in this population.

Disclosure statement

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Data sharing

The data underlying this project are available from the corresponding author on reasonable request.

Contribution to authorship

Conceptualisation: KRP, EMW. Methodology: MST, KRP, EMW. Data collection: MST, DDG, SR, MR. Statistical analysis: MST, DLR. Data interpretation: MST, DLR, KRP.

Manuscript draft: MST. Manuscript review and editing: MST, DDG, MR, SR, DLR, FCS, BWM, EMW, KRP, MAD.

Ethics approval

This research was approved by the Monash Health human research and ethics committee (HREC no. 19,397).

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References

[1] AbouZahr C. Global burden of maternal death and disability. Br Med Bull. 2003;67(1):1–11.
[2] Yanit KE, Snowden JM, Cheng YW, et al. The impact of chronic hypertension and pregestational diabetes on pregnancy outcomes. Am J Obstet Gynecol. 2012;207 (4):333.e1-.e6.
[3] Clowse ME, Jamison M, Myers E, et al. A national study of the complications of lupus in pregnancy. Am J Obstet Gynecol. 2008;199(2):127 e1–6.
[4] Kendrick J, Sharma S, Holmen J, et al. Kidney disease and maternal and fetal outcomes in pregnancy. Am J Kidney Dis. 2015;66(1):55–59.
[5] Saccone G, Berghella V, Maruotti GM, et al. Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. Am J Obstet Gynecol. 2017;216 (5):525e1–e12 .
[6] Bartsch E, Medcalf KE, Park AL, et al. High risk of pre-eclampsia identification G. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;353:i1753.
[7] Dharmashankar K, Widlansky ME. Vascular endothelial function and hypertension: insights and directions. Curr Hypertens Rep. 2010;12(6):448–455.
[8] Mak A, Ny K, Schwarz H, et al. Endothelial dysfunction in systemic lupus erythematosus – a case-control study and an updated meta-analysis and meta-regression. Sci Rep. 2017;7(1):7320.
[9] Velásquez M, Rojas M, Abrahams VM, et al. Mechanisms of endothelial dysfunction in antiphospholipid syndrome: association with clinical manifestations. Front Physiol. 2018;9(1840). DOI:10.3389/fphys.2018.01840
[10] Avogaro A, Albiero M, Menegazzo L, et al. Endothelial dysfunction in diabetes: the role of reparatory mechanisms. Diabetes Care. 2011;34(Suppl 2):S285–S90.
[11] Malyszko J. Mechanism of endothelial dysfunction in chronic kidney disease. Clin Chim Acta. 2010;411(19–20):1412–1420.
[12] Levine RJ, Lam C, Qian C, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N Engl J Med. 2006;355(10):992–1005.
[13] National Institute of Health Care and Excellence. Hypertension in pregnancy: diagnosis and management (NG133). NICE guideline. 2019.
[14] Verlohren S, Herraiz I, Lapaire O, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. Am J Obstet Gynecol. 2012;206(1):58.e1-.e8.
[15] Doherty A, Carvalho JCA, Drewlo S, et al. Altered hemodynamics and hyperuricemia accompany an elevated sFlt-1/PlGF ratio before the onset of early severe Preeclampsia. J Obstet Gynaecology Canada. 2014;36 (8):692–700.
[16] Pinheiro CC, Rayol P, Gozzani L, et al. The relationship of angiogenic factors to maternal and neonatal manifestations of early-onset and late-onset preeclampsia. Prenat Diagn. 2014;34(11):1084–1092.
[17] Rana S, Powe CE, Salahuddin S, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected Preeclampsia. Circulation. 2012;125 (7):911–919.
[18] Rana S, Schnettler WT, Powe C, et al. Clinical characterization and outcomes of preeclampsia with normal angiogenic profile. Hypertens. 2013;32(2):189–201.
[19] Powers RW, Jeyabalan A, Clifton RG, et al. Soluble fms-Like tyrosine kinase 1 (sFlt1), endoglin and placental growth factor (PlGF) in preeclampsia among high risk pregnancies. PLoS ONE. 2010;5(10):e13263.
[20] Ananth CV, Duzyj CM, Yadava S, et al. Changes in the prevalence of chronic hypertension in pregnancy, United States, 1970 to 2010. Hypertension. 2019;74 (5):1089–1095.
[21] Ward MC, Agarwal A, Bish M, et al. Trends in obesity and impact on obstetric outcomes in a regional hospital in Victoria, Australia. Aust NZ J Obstetrics Gynaecol. 2020;60(2):204–211.
[22] Coton SJ, Nazareth I, Petersen I. A cohort study of trends in the prevalence of pregestational diabetes in pregnancy recorded in UK general practice between 1995 and 2012. BMJ Open. 2016;6(1):e009494.
[23] Tranquili AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensivedisorders of pregnancy: a revised statement from the ISSHP. Pregnancy Hypertens. 2014;4 (2):97–104.
[24] Brown M, Magee L, and Kenny L, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2018; 13:28-29 .
[25] Townsend R, O'Brien P, Khalil A. Current best practice in the management of hypertensive disorders in pregnancy. Integr Blood Press Control. 2016;9:79–94.
[26] American College of Obstetricians and Gynaecologists. ACOG practice bulletin No. 203: chronic hypertension in pregnancy. Obstetrics Gynecol. 2019;133(1):e29.

[27] Report of the National High Blood Pressure Education Program working group on high blood pressure in pregnancy. Am J Obstet Gynecol. 2000;183(1):S1–s22.
[28] Bell MJ. A historical overview of preeclampsia-eclampsia. J Obstet Gynecol Neonatal Nurs. 2010;39(5):510–518.
[29] Ananth C, Vintzileos A. Medically indicated preterm birth: recognizing the importance of the problem. Clin Perinatol. 2008;35(1):53–67. viii.
[30] Lowe SA, Bowyer L, Lust K, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Aust N Z J Obstet Gynaecol. 2015;55(5):1–29.
[31] Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet. 2009;374(9694):979–988.
[32] Reddy U, Ko C-W WM. Early term births (37-38 weeks) are associated with increased mortality. Am J Clin Exp Obstet Gynecol. 2006;195(6):S202.
[33] Parikh LI, Reddy UM, Männistö T, et al. Neonatal outcomes in early term birth. Am J Obstet Gynecol. 2014;211(3):265.e1-.e11.
[34] Tita ATN, Jablonski KA, Bailit JL, et al. Neonatal outcomes of elective early-term births after demonstrated fetal lung maturity. Am J Clin Exp Obstet Gynecol. 2018;219(3):296.e1-.e8.
[35] Murray S, Shenkin S, McIntosh K, et al. Long term cognitive outcomes of early term (37-38 weeks) and late preterm (34-36 weeks) births: a systematic review [version 1; peer review: 1 approved, 2 approved with reservations]. Wellcome Open Res. 2017;2(101):101.
[36] Tuuli MG, Rampersad R, Stamilio D, et al. Perinatal outcomes in women with preeclampsia and superimposed preeclampsia: do they differ? Am J Obstet Gynecol. 2011;204(6):508.e1-.e7.

Summary

To sum up, among women with preeclampsia, most complications occurred in women without preexisting comorbidities. Women without comorbidities with early-onset preeclampsia were at highest risk of complications, and tended to have more dysregulated laboratory markers, particularly platelets, liver enzymes and uric acid. Hypertension and proteinuria were the exception, which is perhaps to be expected given many women had chronic hypertension or renal disease. Finally, and importantly, there was a correlation between gestation at diagnosis and how severe the preeclampsia ultimately was; but among women diagnosed at the same gestation, women with comorbidities had a milder syndrome.

There are two important paths forward here. First, our key finding of the low rate of complications from preeclampsia seen in women with comorbidities warrants further study. We showed a big effect size, but the absolute numbers were small. We need to confirm whether this holds true on a large scale. And if it does, what does that say about who we are diagnosing with preeclampsia?

And so we move to Chapter Three.

Chapter Three

"Doctors?" said Ron, looking startled. "Those Muggle nutters that cut people up?"
J.K. Rowling, *Harry Potter and the Order of the Phoenix*

Introduction

Women with comorbidities suffer fewer complications from preeclampsia than do women who develop preeclampsia *de novo*. Is it true? It seems counterintuitive given comorbidities are associated with a higher risk of other complications in pregnancy. However, it fits with our original hypothesis: that women who have comorbidities will be diagnosed with preeclampsia at a lower threshold, biochemically or clinically or both.

Our finding warrants investigation on a larger scale. Further, we did not study an adequate range of neonatal outcomes. Managing preeclampsia is about balancing risks to mother and fetus, not merely minimising risks to the mother. Thus we used whole of state data from the *Victorian Perinatal Data Collection* to assess the association between maternal comorbidities and complications from preeclampsia. We hypothesised that among women with preeclampsia, those with comorbidities would have better outcomes, but their neonates would suffer worse outcomes.

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Maternal and neonatal complications in women with medical comorbidities and preeclampsia

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ABSTRACT

Objectives: To evaluate how medical comorbidities – chronic hypertension, pre-gestational or gestational diabetes and obesity – influence maternal and neonatal complications from preeclampsia.
Study design: We undertook a retrospective cohort study of women delivering in Victoria, Australia, between 2009 and 2017. We compared the likelihood of having a maternal complication before delivery or neonatal complication after birth between women with and without comorbidities. We used causal mediation analysis for neonatal outcomes to separate the effects of comorbidities and of prematurity on morbidity.
Main outcome measures: Pregnancy complications (eclampsia; haemolysis, elevated liver enzymes, low platelets syndrome; placental abruption; stillbirth) and neonatal complications (respiratory distress syndrome; neonatal sepsis; a 5-minute APGAR < 5; neonatal intensive care unit admission).
Results: Women with comorbidities delivered at a median (interquartile range) of 37.0 (36.0–39.0) weeks gestation, earlier than women without comorbidities (38.0 (36.0–39.0) weeks, $p < 0.001$). Women with comorbidities were less likely than those without to suffer any pregnancy complication prior to delivery (adjusted relative risk 0.78, 95% confidence interval 0.72–0.86); however, their neonates suffered more respiratory distress syndrome (aRR 1.43, 95% CI 1.31–1.57), neonatal sepsis (aRR 1.42, 95% CI 1.17–1.72) and NICU admission (aRR 1.37, 95% CI 1.23–1.53). Earlier delivery was a major contributor to worse neonatal outcomes.
Conclusions: Medical comorbidities are associated with earlier delivery among women with preeclampsia. This is associated with fewer maternal complications, but worse neonatal outcomes.

1. Introduction

Medical comorbidities – chiefly chronic hypertension, pregestational and gestational diabetes mellitus and obesity – are increasingly prevalent in pregnancy [1–3]. These comorbidities are associated with adverse pregnancy outcomes: in particular, a markedly increased risk of preeclampsia. This ranges from a 1.5 fold increased risk for women with gestational diabetes, to a threefold increase for women with obesity; to up to 20% of pregnant women with chronic hypertension developing superimposed preeclampsia [4–8].

Preeclampsia is characterised by hypertension and organ dysfunction, arising secondary to widespread endothelial dysfunction and oxidative stress [9]. Endothelial dysfunction – characterised by reduced bioavailability of nitric oxide (NO), a molecule which is crucial for vascular homeostasis – is often present prior to pregnancy in women with medical comorbidities. This is largely secondary to reduced expression of endothelial nitric oxide synthase (eNOS), the key enzyme for NO production [10–12]. These comorbidities are also associated with increased release of reactive oxygen species, contributing to widespread oxidative stress [13–15]. This preexisting endothelial dysfunction and oxidative stress are thought to underscore the increased risk of developing preeclampsia, potentially via reducing the degree of angiogenic imbalance required for preeclampsia to develop [16].

These comorbidities also make a diagnosis of preeclampsia challenging, due to preexisting hypertension and/or proteinuria, or exaggerated exaggerated increases in proteinuria during pregnancy [17].

Given the susceptibility of women with these comorbidities to being diagnosed with preeclampsia and the increasing prevalence of these

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conditions in pregnancy, we evaluated the influence of these comorbidities on maternal and neonatal outcomes in pregnancies complicated by preeclampsia.

2. Methods

We conducted a retrospective cohort study of pregnancies complicated by preeclampsia between 2009 and 2017 in Victoria, Australia. Data was sourced from the Victorian Perinatal Data Collection – a surveillance system that collects data including maternal demographics, obstetric procedures and complications and perinatal morbidity and mortality – on all births after 20 weeks' gestation or, if gestation is not known, >400 g birthweight in Victoria.

We compared outcomes between women that had a diagnosis of chronic hypertension, pregestational or gestational diabetes mellitus or obesity against women who developed preeclampsia without these comorbidities.

2.1. Exposures

The Victorian Perinatal Data collection uses ICD-10 coding for recording medical comorbidities and pregnancy complications. Women in our cohort were identified using ICD-10 codes for preeclampsia (O14), chronic hypertension (I10-14, O10-11) and pregestational or gestational diabetes mellitus (E10-14, O24.0-O24.4, O24.9). Obesity was defined as a body mass index >30 kg/m^2, based off self-reported weight at time of conception. We excluded women with preexisting chronic kidney disease or systemic lupus erythematosus, as these tend to be poorly documented on a population level.

We assessed basic demographic data (age, BMI, region of birth, smoking status, parity); gestation at delivery and mode of birth; and maternal and neonatal morbidity and mortality.

2.2. Outcomes

Antenatal complications included were haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome (O14.2), placental abruption (O45); eclampsia (O15); a need for high dependency care; stillbirth; and birthweight below the third centile. High dependency care includes both women receiving such care on the labour ward, as well as traditional high dependency unit or intensive care unit admission. We report stillbirth and low birthweight as antenatal outcomes as they arise due to an insult during pregnancy, and the risk of each developing increases as pregnancy continues. Birthweight centiles were calculated using local population charts [18]. We also report a composite of severe pregnancy complications – HELLP syndrome, eclampsia, placental abruption, or stillbirth.

For neonatal outcomes, we focused on a core set of common outcomes that occur at both term and preterm gestations that are likely to be accurately captured on a population level. These included neonatal sepsis (P36), respiratory distress syndrome (P22.0, P22.8, P22.9, P96.8), NICU admission and a 5-minute APGAR score lower than 5.

2.3. Statistical analysis

Descriptive statistics were computed for baseline demographics and compared between groups using Poisson regression. Dichotomous outcomes are presented as number and percentage; continuous outcomes as median (interquartile range (IQR)) or mean (standard deviation (SD)) as appropriate. For statistical analyses, missing data was imputed by multiple imputation with chained equations. Due to a large proportion of women with gestational diabetes mellitus (GDM) not being diagnosed until 28 weeks' gestation, as well as the limited number of women delivering in the second trimester, we restricted our analyses to women delivering after 28 weeks' gestation. As some women had more than one comorbidity, all regression analyses adjust for the presence of other comorbidities.

2.4. Pregnancy complications

For women with pre-eclampsia, we calculated adjusted relative risks between the presence of co-morbidities and specified maternal outcomes using modified Poisson regression, with age, BMI, country of birth, smoking status, parity and other comorbidities considered as confounders. We performed subgroup analysis of women delivering between 28–32, 33–36, and 37 or more weeks' gestation.

2.5. Neonatal complications

We calculated raw relative risks for each neonatal outcome. We then used causal-mediation analysis to separate the effects of gestation at delivery and maternal comorbidities on neonatal outcomes.

Causal mediation involves segmenting the overall effect of an exposure (in this study, maternal comorbidities), into a natural direct effect and a natural indirect effect.

The natural direct effect (NDE) is the effect of the exposure when keeping the mediator at the level it would have been at without the exposure (19). For example, the increase in risk of neonatal morbidity as a result of having a comorbidity, if gestation at delivery was the same as it would have been without a comorbidity.

The natural indirect effect (NIE) is the difference in the risk of the outcome if all subjects were exposed, and the mediator was set to the value it would take if unexposed. In our study, that is the difference in risk between women with comorbidities who deliver at a given gestational age, compared to their risk if they had delivered at the gestational age they would have if they did not have a comorbidity.

Thus, the NDE reflects the effect on neonatal morbidity due to maternal comorbidities, and the NIE the effect on neonatal morbidity of the earlier gestation at birth due to these comorbidities. Relative risks for each of these two can be calculated.

The proportion of increased morbidity that is due to preterm birth can be calculated by [20]:

$$\%mediated\ by\ prematurity = \frac{\left[RR_{NDE}(RR_{NIE}-1)\right]}{RR \quad *RR-1_{NDE}} *100$$

We performed these analyses using the *medflex* package [21]. Further details regarding causal mediation analysis can be found online [19,21–23].

All statistical tests were two tailed, and a p value of <0.05 was considered statistically significant. Analyses were performed in *R* version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study population

A total of 17,824 women with preeclampsia were included in the study. Of these, 9,898 (55.5%) had no comorbidities; 1790 (10.0%) had chronic hypertension; 2,363 (13.3%) had pregestational or gestational diabetes mellitus and 5,772 (32.4%) had obesity. A total of 7,926 (44.5%) of women had at least one comorbidity.

There was missing data for BMI (1753 women (9.6%)), parity (109 women (0.6%)), smoking (2888 women (15.9%)), and maternal age (6 women (0.03%)).

3.2. Baseline demographics

Baseline demographics of study participants are in Table 1. Maternal hypertension and diabetes were associated with older maternal age (both p < 0.001); maternal hypertension, diabetes and obesity were associated with a higher BMI (all p < 0.001). Women with comorbidities

Table 1
Baseline demographics by co-morbidity status for the study population. Data given as mean ± standard deviation, median (interquartile range), or number (proportion). *P < 0.001, ψP < 0.05 compared to women without a comorbidity.

Demographics	No comorbidity (n = 9,898)	Chronic Hypertension (n = 1,790)	Diabetes Mellitus (n = 2,363)	Obesity (n = 5,772)	Any comorbidity (n = 7,926)
Age (years)	30.2 ± 5.7	32.2 ± 5.7*	32.4 ± 5.6*	30.6 ± 6.0	31.0 ± 5.9*
BMI (kg/m^2)	24.3 (22.1 – 26.8)	28.8 (24.6 – 34.4)*	30.5 (25.5 – 36.6)*	34.8 (32.0 – 38.9)*	33.0 (30.1 – 37.4) *
Nulliparous (%)	6,976 (70.5%)	1,018 (57.4%)*	1,356 (57.9%)*	3,337 (57.4%)*	4610 (58.2%)*
Smoking (%)	423 (4.3%)	74 (4.8%)	99 (4.8%)ψ	337 (6.9%)*	413 (5.2%)*
Region of birth					
Australia	6780 (69.1%)	1,276 (71.3%)	1,453 (61.5%)	4,655 (80.6%)	5914 (74.6%)
Europe	456 (4.6%)	69 (3.9%)	97 (4.1%)	178 (3.1%)	268 (3.4%)
South Asian	855 (8.7%)	133 (7.4%)	311 (13.2%)*	242 (4.2%)	558 (7.0%)
Oceania	258 (2.6%)	53 (3.0%)	101 (4.3%)*	287 (5.0%)	333 (4.2%)
South East/East Asia	770 (7.8%)	139 (7.8%)	231 (9.8%)*	142 (2.5%)	415 (5.2%)
Africa/middle east	522 (5.3%)	90 (5.0%)	134 (5.7%)*	193 (3.4%)*	327 (4.1%)
Americas	95 (1.0%)	27 (1.5%)ψ	28 (1.2%)	51 (0.9%)ψ	80 (1.0%)
Other/unspecified	79 (0.8%)	3 (0.2%)	8 (0.3%)	24 (0.4%)*	31 (0.4%)
Gestation at delivery					
Weeks	38.0 (36.0 – 39.0)	37.0 (34.0 – 38.0)*	37.0 (35.0 – 38.0)*	37.0 (36.0 – 39.0)	37.0 (36.0 – 39.0)*
28 – 32 weeks	661 (6.7%)	306 (17.1%)*	169 (7.2%)	341 (5.9%)	626 (7.9%)*
33 – 36 weeks	2406 (24.3%)	581 (32.5%)*	858 (36.3%)*	1451 (25.1%)	2163 (27.3%)*
37+ weeks	6831 (69.0%)	903 (50.4%)	1336 (56.5%)	3980 (69.0%)ψ	5137 (64.8%)
Caesarean section					
Total (%)	5103 (51.6%)	1188 (66.4%)	1613 (68.3%)	3458 (59.9%)	4885 (61.6%)*
< 37 weeks (%) ‡	2311 (23.3%)	734 (41.0%)	829 (35.1%)	1416 (24.5%)	2229 (28.1%)*

were less likely to be nulliparous (58.2% vs 80.5%, p < 0.001) than those without comorbidities, while mothers with obesity were more likely to smoke (6.9% vs 4.3%, p= 0.03). Compared to women without comorbidities, women with obesity were more likely to be born in Australia (80.6% vs 69.1%, p < 0.001) or Oceania (5.0% vs 2.6% p < 0.001); women with chronic hypertension in the Americas (1.5% vs 1.0%, p < 0.001). Women with diabetes were significantly less likely to be born in Australia (61.5% vs 69.1%) and more likely to be born in South (13.2% vs 8.7%) or South-East Asia (9.8% vs 7.8%) (all p < 0.001).

Women with hypertension and diabetes delivered at a median (IQR) gestational age of 37.0 (34.0 – 38.0) weeks and 37.0 (35.0 – 38.0) weeks respectively, both significantly earlier than women without comorbidities (38.0 (36.0 – 39.0) weeks' gestation)). Obesity was not associated with earlier gestation at delivery (median (IQR) 37.0 (36.0 – 39.0) weeks).

Chronic hypertension significantly increased the risk of birth prior to 33 weeks' gestation (aRR 3.27, 95% CI 2.86 – 3.73) and before 37 weeks' gestation (1.52, 1.42 – 1.64). Maternal diabetes increased the risk of preterm birth (aRR 1.32, 95% CI (1.22 – 1.40)), while obesity reduced the likelihood (0.94, 0.89 – 0.99). Hypertension (aRR 1.15, 95% CI 1.08 – 1.22), diabetes (1.15, 1.10 – 1.22) and obesity (1.12, 1.08 –1.17) were all associated with increased caesarean section rates. Maternal hypertension and diabetes were also associated with a higher risk of a caesarean prior to 37 weeks' gestation (aRR 1.61, 95% CI 1.49 – 1.75 and 1.33, 1.23 – 1.44 respectively)).

4. Pregnancy complications

Fig. 1 and Table 2 compare the occurrence of complications between women without comorbidities and with each comorbidity; Fig. 2 and Table S1 compare women with any comorbidity against women without comorbidities.

A total of 797 (10.0%) of women with a comorbidity suffered the composite antenatal outcome, compared to 1236 (12.5%) of women without comorbidities (aRR 0.78, 95% CI 0.72 – 0.86). This was largely due to lower rates of HELLP syndrome (aRR 0.70, 95% CI 0.62 – 0.79) and placental abruption (0.61, 0.45 – 0.82) among women with a

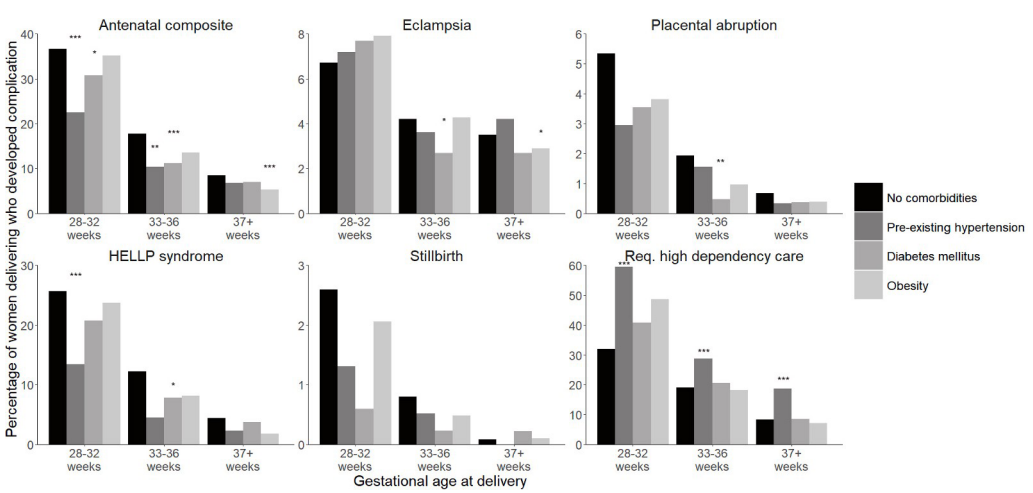

Fig. 1. Proportion of women with pre-eclampsia delivering who suffered complication prior to delivery, displayed by gestational age at delivery. Women without comorbidities in black. * indicates P < 0.05; ** indicates P < 0.01; *** indicates P < 0.001, compared to women without that comorbidity. Adjusted relative risks and confidence intervals for each comparison are in Table 2.

Table 2

Antenatal outcomes for women with pre-eclampsia and each comorbidity. Relative risks calculated with Poisson regression, adjusted for age, BMI, country of birth, smoking status, and parity. HELLP; haemolysis, elevated liver enzymes, low platelets syndrome. Composite antenatal outcome defined as one or more of eclampsia, stillbirth, placental abruption, or HELLP syndrome.

	No comorbidity (n = 9898)	Hypertension (n = 1790)		Diabetes (n = 2363)		Obesity (n = 5772)	
	N (%)	N (%)	aRR (95% CI)	N (%)	aRR (95% CI)	N (%)	aRR (95% CI)
Eclampsia							
Total	382 (3.9%)	81 (4.5%)	**1.27 (1.01 – 1.59)**	72 (3.0%)	**0.77 (0.61 – 0.98)**	204 (3.5%)	0.90 (0.76 – 1.06)
28 – 32 weeks	44 (6.7%)	22 (7.2%)	1.06 (0.94 – 1.19)	13 (7.7%)	1.12 (0.62 – 2.01)	27 (7.9%)	1.01 (0.90 – 1.12)
33 – 36 weeks	100 (4.2%)	21 (3.6%)	0.91 (0.58 – 1.42)	23 (2.7%)	**0.61 (0.39 – 0.95)**	62 (4.3%)	1.10 (0.80 – 1.52)
37+ weeks	239 (3.5%)	38 (4.2%)	1.27 (0.92 – 1.77)	36 (2.7%)	0.79 (0.56 – 1.11)	115 (2.9%)	**0.78 (0.62 – 0.97)**
Placental abruption							
Total	126 (1.3%)	21 (1.2%)	1.13 (0.72 – 1.77)	15 (0.6%)	**0.57 (0.33 – 0.97)**	42 (0.7%)	**0.63 (0.43 – 0.91)**
28 – 32 weeks	35 (5.3%)	9 (2.9%)	0.61 (0.30 – 1.23)	6 (3.6%)	0.86 (0.36 – 2.06)	13 (3.8%)	0.80 (0.40 – 1.57)
33 – 36 weeks	47 (2.0%)	9 (1.6%)	1.14 (0.57 – 2.29)	<5 (<0.5%)	**0.29 (0.11 – 0.81)**	14 (1.0%)	0.65 (0.37 – 1.14)
37+ weeks	46 (0.7%)	<5 (<0.3%)	0.57 (0.18 – 1.81)	5 (0.4%)	0.66 (0.26 – 1.66)	15 (0.4%)	0.57 (0.31 – 1.04)
HELLP Syndrome							
Total	760 (7.7%)	88 (4.9%)	**0.74 (0.59 – 0.91)**	152 (6.4%)	1.04 (0.88 – 1.23)	272 (4.7%)	**0.66 (0.57 – 0.75)**
28 – 32 weeks	170 (25.6%)	41 (13.4%)	**0.44 (0.31 – 0.63)**	35 (20.7%)	0.87 (0.58 – 1.30)	81 (23.8%)	0.98 (0.72 – 1.32)
33 – 36 weeks	296 (12.3%)	26 (4.5%)	**0.43 (0.29 – 0.63)**	67 (7.8%)	**0.79 (0.61 – 0.99)**	119 (8.2%)	**0.77 (0.63 – 0.95)**
37+ weeks	301 (4.4%)	21 (2.3%)	0.69 (0.45 – 1.07)	50 (3.7%)	1.31 (0.98 – 1.76)	72 (1.8%)	**0.44 (0.34 – 0.56)**
Stillbirth							
Total	42 (0.4%)	7 (0.4%)	1.06 (0.48 – 2.31)	6 (0.3%)	0.65 (0.28 – 1.51)	18 (0.3%)	0.89 (0.48 – 1.66)
28 – 32 weeks	17 (2.6%)	<5 (<1.5%)	0.58 (0.20 – 1.68)	<5 (<3.0%)	0.26 (0.04 – 1.94)	7 (2.1%)	1.07 (0.39 – 2.94)
33 – 36 weeks	19 (0.8%)	<5 (<0.5%)	0.83 (0.25 – 2.73)	<5 (<0.5%)	0.33 (0.08 – 1.41)	7 (0.5%)	0.81 (0.35 – 1.87)
37+ weeks	6 (0.1%)	0 (0%)	NA	<5 (0.5%)	2.45 (0.64 – 9.33)	<5 (<0.1%)	0.93 (0.26 – 3.35)
Composite antenatal							
Total	1236 (12.5%)	190 (10.6%)	0.93 (0.81 – 1.07)	241 (10.2%)	0.90 (0.79 – 1.03)	526 (9.1%)	**0.76 (0.69 – 0.84)**
28 – 32 weeks	242 (36.6%)	69 (22.5%)	**0.61 (0.57 – 0.64)**	52 (30.8%)	**0.92 (0.87 – 0.98)**	120 (35.2%)	1.00 (0.96 – 1.04)
33 – 36 weeks	426 (17.7%)	60 (10.3%)	**0.66 (0.51 – 0.84)**	96 (11.2%)	**0.69 (0.56 – 0.85)**	197 (13.6%)	0.87 (0.74 – 1.03)
37+ weeks	578 (8.5%)	61 (6.8%)	0.94 (0.73 – 1.21)	93 (7.0%)	1.02 (0.83 – 1.25)	209 (5.3%)	**0.63 (0.54 – 0.73)**
Birthweight <3rd centile							
Total	556 (5.6%)	96 (5.4%)	1.14 (0.93 – 1.40)	94 (4.0%)	**0.75 (0.61 – 0.93)**	214 (3.7%)	**0.79 (0.67 – 0.92)**
28 – 32 weeks	36 (5.5%)	16 (5.2%)	0.99 (0.57 – 1.70)	8 (4.7%)	0.88 (0.43 – 1.81)	16 (4.7%)	0.84 (0.47 – 1.50)
33 – 37 weeks	159 (6.6%)	32 (5.5%)	0.99 (0.69 – 1.43)	41 (4.8%)	0.78 (0.56 – 1.10)	60 (4.1%)	**0.73 (0.54 – 1.00)**
37 + weeks	363 (5.3%)	48 (5.3%)	1.23 (0.93 – 1.64)	45 (3.4%)	**0.67 (0.50 – 0.91)**	138 (3.5%)	**0.76 (0.63 – 0.93)**
HDU admission							
Total	1245 (12.6%)	518 (28.9%)	**2.48 (2.25 – 2.73)**	359 (15.2%)	1.12 (1.00 – 1.26)	712 (12.3%)	0.82 (0.75 – 0.90)
28 – 32 weeks	212 (32.1%)	182 (59.5%)	**1.71 (1.43 – 2.04)**	166 (48.7%)	0.99 (0.77 – 1.27)	69 (40.8%)	1.11 (0.91 – 1.34)
33 – 36 weeks	459 (19.1%)	167 (28.7%)	**1.61 (1.36 – 1.91)**	264 (18.2%)	1.07 (0.90 – 1.28)	176 (20.5%)	0.83 (0.71 – 0.96)
37+ weeks	574 (8.4%)	169 (18.7%)	**2.51 (2.12 – 2.96)**	282 (7.1%)	1.04 (0.85 – 1.27)	114 (8.5%)	0.73 (0.63 – 0.84)

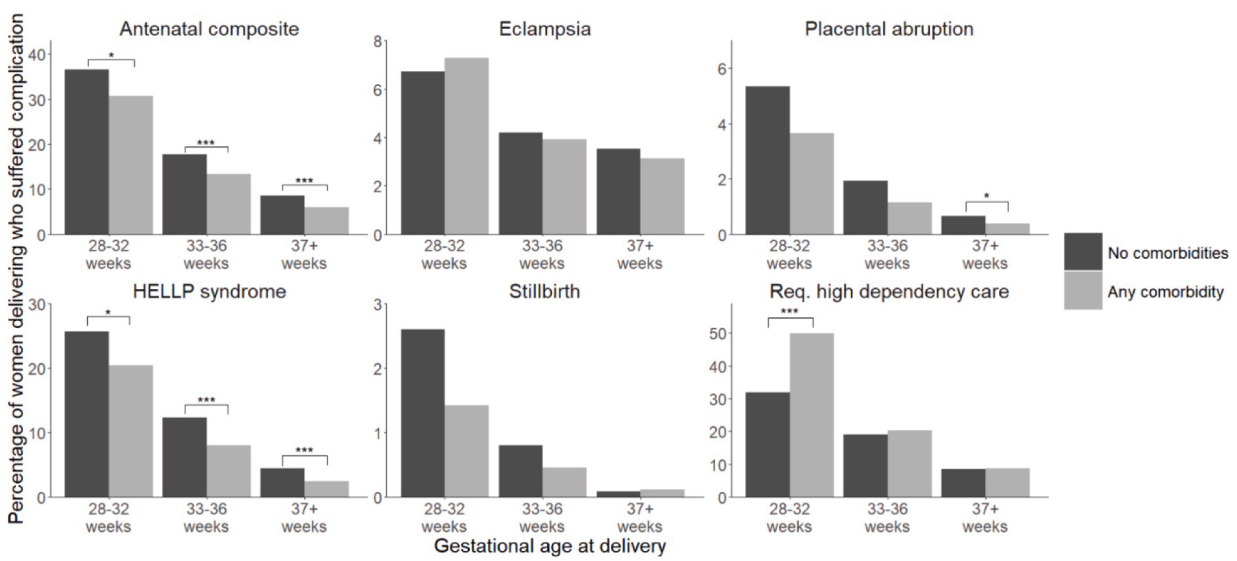

Fig. 2. Proportion of all women with pre-eclampsia delivering who suffered complication prior to delivery, displayed by gestational age at delivery. Antenatal composite outcome refers to any of eclampsia, placental abruption, HELLP syndrome and stillbirth. * indicates P < 0.05; *** indicates P < 0.001, compared to women with no comorbidity. Adjusted relative risks ratios and confidence intervals for each comparison are in Table S1.

comorbidity. Stillbirth and eclampsia rates did not differ significantly between women with and without comorbidities.

For women with chronic hypertension there was no significant difference in the antenatal composite outcome overall, but those who delivered preterm were significantly less likely to have suffered the antenatal composite outcome – largely due to low rates of HELLP

syndrome – and in contrast, they were more likely to develop eclampsia. Chronic hypertension was also associated with a greater rate of high dependency care.

Similarly, women with diabetes who delivered preterm were less likely to have suffered a complication prior to birth. They had lower rates of eclampsia and placental abruption at all gestational ages, while there was no significant difference in stillbirth, HELLP syndrome, or need for high dependency care compared to women without comorbidities.

In contrast, obesity was associated with fewer complications among women delivering at term, but not at preterm gestations. They had significantly lower rates of placental abruption and HELLP syndrome overall, and lower rates of eclampsia at term. They were also no more likely to require high dependency care.

Women with obesity or diabetes were less likely to deliver a baby with a birthweight below the 3rd centile, while there was no significant difference for women with hypertension.

4.1. Neonatal outcomes

Raw relative risks for neonatal outcomes for mothers with each co-morbidity are shown in Table S2. Maternal hypertension was associated with increased rates of respiratory distress syndrome (RR 2.04, 95% CI 1.82 – 2.29), sepsis (2.09, 1.64 – 2.67) and NICU admission (3.37, 2.98 – 3.82). Diabetes was also associated with more respiratory distress syndrome (RR 1.35, 95% CI 1.20 – 1.52), sepsis (1.51, 1.18 – 1.93) and NICU admission (1.26, 1.09 – 1.47). Obesity was associated with an increased likelihood of respiratory distress syndrome (RR 1.23, 95% CI 1.12 – 1.36), but not sepsis or NICU admission.

Causal mediation analysis of neonatal outcomes is shown in Table 3.

After adjustment for confounders ($RR_{Total\ effect}$), maternal hypertension was associated with an increased risk of RDS (aRR 1.95, 95% CI 1.74 – 2.20), neonatal sepsis (2.08, 1.62 – 2.67), and NICU admission (3.30, 2.91 – 3.75). This was predominantly mediated through preterm birth, with 81%, 59% and 78% of the increase in risk, respectively, attributable to earlier gestation at birth. The likelihood of a low APGAR score was significantly increased (RR_{NIE} 1.39, 95% CI 1.27 – 1.52) by the earlier gestation at birth associated with hypertension, but not by the presence of hypertension itself (RR_{NDE} 0.73, 95% CI 0.47 – 1.16).

Diabetes was similarly associated with increased rates of RDS (aRR 1.25, 95% CI 1.10 – 1.41) and sepsis (1.44, 1.12 – 1.86), with 33.7% and 24.4% of the increase attributable to earlier gestation at birth. Earlier delivery also increased the likelihood of a low APGAR score (RR_{NIE} 1.11, 95% CI 1.08 – 1.14), but diabetes itself did not (RR_{NDE} 0.68, 95% CI 0.44 – 1.07).

Maternal obesity increased the likelihood of respiratory distress syndrome, purely a result of the natural direct effect. Maternal obesity did not significantly affect the likelihood of neonatal sepsis, NICU admission or a low APGAR score.

Table 3
Neonatal outcomes for women with pre-eclampsia and co-morbidities compared with no co-morbidity: Causal mediation analysis results. RR, relative risk; NDE, natural direct effect: the effect of maternal comorbidities independent of gestation at delivery; NIE, natural indirect effect, the effect of gestation at delivery independent of comorbidities. Relative risks adjusted for age, BMI, ethnicity, parity and smoking status.

Perinatal morbidity – causal mediation analysis	Respiratory distress syndrome	Neonatal sepsis	NICU admission	5-minute APGAR <5
No comorbidities (n = 9,898)				
N (%)	889 (9.0%)	195 (2.0%)	598 (6.0%)	110 (1.1%)
Hypertension (n = 1,790)				
N (%)	354 (19.8%)	79 (4.4%)	343 (19.2%)	21 (1.2%)
$RR_{Total\ effect}$	**1.95 (1.74 – 2.20)**	**2.08 (1.62 – 2.67)**	**3.30 (2.91 – 3.75)**	1.02 (0.65 – 1.61)
RR_{NDE}	**1.18 (1.08 – 1.29)**	**1.45 (1.15 – 1.84)**	**1.59 (1.44 – 1.75)**	0.73 (0.47 – 1.16)
RR_{NIE}	**1.65 (1.55 – 1.77)**	**1.43 (1.33 – 1.54)**	**2.06 (1.86 – 2.28)**	**1.39 (1.27 – 1.52)**
% mediated by gestation at delivery	81%	59%	78%	100%
Diabetes (n = 2,363)				
N(%)	327 (13.8%)	78 (3.3%)	203 (8.6%)	22 (0.9%)
$RR_{Total\ effect}$	**1.25 (1.10 – 1.41)**	**1.44 (1.12 – 1.86)**	1.12 (0.96–1.31)	0.76 (0.48 – 1.19)
RR_{NDE}	**1.16 (1.04 – 1.28)**	**1.33 (1.04 – 1.69)**	**1.19 (1.05 – 1.35)**	0.68 (0.44 – 1.07)
RR_{NIE}	**1.07 (1.01 – 1.13)**	**1.08 (1.05 – 1.12)**	0.94 (0.85 – 1.05)	**1.11 (1.08 – 1.14)**
% mediated by gestation at delivery	34%	24%	0%	100%
Obesity (n = 5,772)				
N(%)	688 (11.9%)	151 (2.6%)	366 (6.3%)	66 (1.1%)
$RR_{Total\ effect}$	**1.11 (1.01 – 1.23)**	1.04 (0.84 – 1.28)	0.98 (0.87 – 1.12)	1.20 (0.87 – 1.66)
RR_{NDE}	**1.18 (1.09 – 1.29)**	1.08 (0.88 – 1.32)	1.01 (0.92 – 1.12)	1.21 (0.88 – 1.66)
RR_{NIE}	0.96 (0.92 – 1.01)	0.97 (0.94 – 1.00)	0.95 (0.87 – 1.04)	0.98 (0.94 – 1.03)
% mediated by gestation at delivery	0%	0%	0%	0%
Any comorbidity (n = 7,926)				
N (%)	1021 (12.9%)	222 (2.8%)	656 (8.3%)	90 (1.1%)
$RR_{Total\ effect}$	**1.41 (1.29 – 1.54)**	**1.49 (1.23 – 1.81)**	**1.37 (1.22 – 1.53)**	1.00 (0.76 – 1.31)
RR_{NDE}	**1.29 (1.20 – 1.39)**	**1.38 (1.11 – 1.61)**	**1.22 (1.11 – 1.33)**	0.93 (0.71 – 1.22)
RR_{NIE}	**1.10 (1.05 – 1.14)**	**1.08 (1.04 – 1.10)**	**1.12 (1.04 – 1.21)**	**1.07 (1.05 – 1.10)**
% mediated by gestation at delivery	31%	23%	40%	0%

5. Discussion

5.1. Main findings

We have assessed on a population level the association between medical comorbidities and maternal and neonatal complications for women with preeclampsia. This is the largest study exploring this relationship to date. We have shown that among women diagnosed with preeclampsia, the presence of comorbidities is associated with fewer maternal complications, but poorer neonatal outcomes. This discrepancy likely arises, at least in part, due to women with comorbidities receiving a greater degree of intervention than those without comorbidities – demonstrated by earlier gestation at birth, a higher caesarean section rate, and more frequent receipt of high dependency care. Our causal mediation analysis shows that this earlier gestation at delivery is a major driver of the increase in neonatal morbidity. Given these differences in outcomes, existing literature regarding the management of preeclampsia may not represent best practice when women have preexisting hypertension, obesity, or pregestational or gestational diabetes.

5.2. Interpretation

The challenge of managing preeclampsia is balancing the needs of the neonate through minimising prematurity against the increased risk

to the mother associated with prolonging pregnancy.

Given the major contribution of preterm delivery to neonatal morbidity in our cohort, marked neonatal improvements may be seen by prolonging gestation. Further research should investigate whether this is safe for mothers in some circumstances. There is currently sparse research comparing the severity of preeclampsia between women with and without comorbidities. Given the relatively small number of complications seen in women with comorbidities – particularly among women delivering preterm – it may be safe to prolong pregnancy for some women without unduly compromising maternal health. However, the higher rates of intervention and the more frequent need for high dependency care could equally indicate a more severe clinical picture, or a lower threshold to initiate delivery or closer monitoring, and so there remains insufficient data to recommend such an approach.

Improvements in care could also be made for women with preeclampsia in the late preterm period. The HYPITAT trial [24] suggested that for women with mild hypertensive disease at or beyond 36 weeks' gestation, induction of labour instead of expectant management reduced maternal complications without increasing neonatal morbidity. However, the significant contribution of prematurity to poor neonatal outcomes, combined with the lower likelihood of maternal complications for women with comorbidities, may mean prolonging pregnancy further could improve neonatal outcomes in some cases.

The potential benefits of prolonging pregnancy in women with preeclampsia and these co-morbidities are also reflected in the relatively low rate of complications associated with placental insufficiency – stillbirth, a birthweight below the third centile, and placental abruption. Diabetes and obesity are associated with an increased risk of both stillbirth and fetal growth restriction, and chronic hypertension is associated with all three [5,25,26] – yet these relationships appear muted, or reversed, among women with preeclampsia. These complications arise due to a combination of maternal and placental factors [27,28]. As the contribution from maternal characteristics is likely to be greater in women with comorbidities than in those without, our results may indicate milder placental pathology in women with comorbidities. A less hostile placental environment for these women would also explain the greater improvements their neonates see with prolonging gestation.

5.3. Strengths and limitations

Strengths of our research include the large sample size, the elimination of selection bias as a result of the population nature of the dataset, and data collection in the Victorian Perinatal Data Collection has been well validated [29]. We have also untangled the effects of comorbidities and prematurity on neonatal outcomes, highlighting important areas for further research and improvements to clinical practice. However, our work has limitations.

Population level data requires outcomes and medical conditions to be accurately recorded, but this cannot be verified. As such, complications such as HELLP syndrome are based only off diagnostic codes, not laboratory-confirmed criteria. This is also a challenge regarding the diagnosis of preeclampsia; women with comorbidities are susceptible to having a diagnosis of preeclampsia recorded, but fail to meet a strict research definition of the disease. However, this renders our findings pragmatic, more closely reflecting clinical decision making than would a stricter definition.

We have also analysed gestational diabetes together with pregestational diabetes. This was a limitation of the population-level data and also required the censorship of women delivering prior to 28 weeks, women with the most severe forms of preeclampsia. This does not unduly detract from our conclusions. There is typically less clinical equipoise when women develop preeclampsia so early in pregnancy, and the question of whether it is safe to prolong pregnancy in women with comorbidities is less relevant than it is for women who develop preeclampsia later in pregnancy.

Finally, our work cannot comment on the prospective risk of complications from preeclampsia, information that is more useful to clinicians faced with a woman with preeclampsia. Further research is needed to determine to what extent our findings are due to a milder clinical phenotype, and to what extent they result from closer monitoring and more intervention.

6. Conclusion

We have undertaken a large, population-based study of women with preeclampsia to compare the likelihood of maternal and neonatal complications between women with and without comorbidities. We found that women with comorbidities receive earlier iatrogenic intervention, and this leads to fewer maternal but more neonatal complications. Further research should determine whether and in what circumstances pregnancy can safely be prolonged for women with comorbidities, in order to improve neonatal outcomes.

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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Contribution to authorship

MST undertook data analysis and interpretation, and wrote and revised the manuscript. EMW and KRP conceived and designed the study, and assisted with project co-ordination. KRP, BMW and MAD assisted with data analysis and interpretation and manuscript preparation. AM assisted with interpretation and manuscript preparation. All authors contributed to the final manuscript.

Ethical approval

Ethics approval was provided by the Monash Health Human Research Ethics Committee (#57363) on February 4, 2020.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2021.12.006.

References

[1] C.V. Ananth, C.M. Duzyj, S. Yadava, M. Schwebel, A.T.N. Tita, K.S. Joseph, Changes in the prevalence of chronic hypertension in pregnancy, United States, 1970 to 2010, Hypertension 74 (5) (2019) 1089–1095.

[2] M.C. Ward, A. Agarwal, M. Bish, R. James, F. Faulks, J. Pitson, et al., Trends in obesity and impact on obstetric outcomes in a regional hospital in Victoria, Australia, Aust. N. Z. J. Obstet. Gynaecol. 60 (2) (2020) 204–211.

[3] S.J. Coton, I. Nazareth, I. Petersen, A cohort study of trends in the prevalence of pregestational diabetes in pregnancy recorded in UK general practice between 1995 and 2012, BMJ Open. 6 (1) (2016), e009494.

[4] K. Duckitt, D. Harrington, Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies, BMJ (Clinical Res. ed) 330 (7491) (2005) 565.
[5] E.W. Seely, J. Ecker, Chronic hypertension in pregnancy, Circulation 129 (11) (2014) 1254–1261.
[6] T.L. Weissgerber, L.M. Mudd, Preeclampsia and diabetes, Curr. Diab. Rep. 15 (3) (2015) 9.
[7] S. Schneider, N. Freerksen, S. Ro¨hrig, B. Hoeft, H. Maul, Gestational diabetes and preeclampsia – similar risk factor profiles? Early Human Dev. 88 (3) (2012) 179–184.
[8] J.M. Roberts, L.M. Bodnar, T.E. Patrick, R.W. Powers, The role of obesity in preeclampsia, Pregnancy Hypertens. 1 (1) (2011) 6–16.
[9] J. Uzan, M. Carbonnel, O. Piconne, R. Asmar, J.-M. Ayoubi, Pre-eclampsia: pathophysiology, diagnosis, and management, Vasc Health Risk Manag. 7 (2011) 467–474.
[10] Q. Li, J.-Y. Youn, H. Cai, Mechanisms and consequences of endothelial nitric oxide synthase dysfunction in hypertension, J. Hypertens. 33 (6) (2015) 1128–1136.
[11] S. Dimassi, K. Chahed, S. Boumiza, M. Canault, Z. Tabka, P. Laurant, et al., Role of eNOS- and NOX-containing microparticles in endothelial dysfunction in patients with obesity, Obesity. 24 (6) (2016) 1305.
[12] C.R. Triggle, H. Ding, A review of endothelial dysfunction in diabetes: a focus on the contribution of a dysfunctional eNOS, J. Am. Soc. Hypertens. 4 (3) (2010) 102–115.
[13] L. Rochette, M. Zeller, Y. Cottin, C. Vergely, Diabetes, oxidative stress and therapeutic strategies, Biochim. Biophys. Acta (BBA) – General Subjects 1840 (9) (2014) 2709–2729.
[14] R.M. Touyz, Reactive oxygen species, vascular oxidative stress, and redox signaling in hypertension, Hypertension 44 (3) (2004) 248–252.
[15] J.F. Keaney, M.G. Larson, R.S. Vasan, P.W.F. Wilson, I. Lipinska, D. Corey, et al., Obesity and systemic oxidative stress, Arterioscler. Thromb. Vasc. Biol. 23 (3) (2003) 434–439.
[16] R.J. Levine, C. Lam, C. Qian, K.F. Yu, S.E. Maynard, B.P. Sachs, et al., Soluble endoglin and other circulating antiangiogenic factors in preeclampsia, New England J. Med. 355 (10) (2006) 992–1005.
[17] C. Macdonald-Wallis, D.A. Lawlor, J. Heron, A. Fraser, S.M. Nelson, K. Tilling, Relationships of risk factors for pre-eclampsia with patterns of occurrence of isolated gestational proteinuria during normal term pregnancy, PLoS ONE 6 (7) (2011), e22115.
[18] T.A. Dobbins, E.A. Sullivan, C.L. Roberts, J.M. Simpson, Australian national birthweight percentiles by sex and gestational age, 1998–2007, Med. J. Aust. 197 (5) (2012) 291–294.
[19] C.V. Ananth, T.J. VanderWeele, Placental abruption and perinatal mortality with preterm delivery as a mediator: disentangling direct and indirect effects, Am. J. Epidemiol. 174 (1) (2011) 99–108.
[20] T.J. Vanderweele, S. Vansteelandt, Odds ratios for mediation analysis for a dichotomous outcome, Am. J. Epidemiol. 172 (12) (2010) 1339–1348.
[21] J. Steen, T. Loeys, B. Moerkerke, S. Vansteelandt, medflex, An R Package for Flexible Mediation Analysis using Natural Effect Models. 2017;76(11):46 2017.
[22] L. Starkopf, M.P. Andersen, T. Gerds, C. Torp-Pedersen, T. Lange, July, editors. Comparison of five software solutions to mediation analysis, 2017.
[23] L. Valeri, T. VanderWeele, Technical Report: Extending the Baron and Kenny Mediation Analysis to Allow for Exposure-Mediator Interactions: SAS and SPSS Macros, Harvard School of Public Health, Boston, MA, 2010.
[24] C.M. Koopmans, D. Bijlenga, H. Groen, S.M.C. Vijgen, J.G. Aarnoudse, D. J. Bekedam, et al., Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial, Lancet 374 (9694) (2009) 979–988.
[25] H.R. Murphy, R. Bell, C. Cartwright, P. Curnow, M. Maresh, M. Morgan, et al., Improved pregnancy outcomes in women with type 1 and type 2 diabetes but substantial clinic-to-clinic variations: a prospective nationwide study, Diabetologia 60 (9) (2017) 1668–1677.
[26] L. Poston, R. Caleyachetty, S. Cnattingius, C. Corval´an, R. Uauy, S. Herring, et al., Preconceptional and maternal obesity: epidemiology and health consequences, Lancet Diabetes Endocrinol. 4 (12) (2016) 1025–1036.
[27] A. Malhotra, B.J. Allison, M. Castillo-Melendez, G. Jenkin, G.R. Polglase, S. L. Miller, Neonatal Morbidities of Fetal Growth Restriction: pathophysiology and Impact, Front. Endocrinol. 10 (55) (2019).
[28] L. Avagliano, G.P. Bulfamante, A. Morabito, A.M. Marconi, Abnormal spiral artery remodelling in the decidual segment during pregnancy: from histology to clinical correlation, J. Clin. Pathol. 64 (12) (2011) 1064–1068.
[29] M.M. Flood, S.J. McDonald, W.E. Pollock, M.A. Davey, Data accuracy in the Victorian Perinatal Data Collection: Results of a validation study of 2011 data, Health Inf. Manage.: J. Health Inf. Manage. Assoc. Australia 46 (3) (2017) 113–126.

Supplementary data

Table S1. Maternal and neonatal outcomes for women with preeclampsia			
	No comorbidity (n = 9,898)	Any comorbidity (n = 7,926)	
Maternal	**N (%)**	**N (%)**	**aRR (95% CI)**
Eclampsia			
Total	382 (3.9%)	294 (3.7%)	0.96 (0.82 – 1.11)
28 – 32 weeks	44 (6.7%)	46 (7.3%)	1.10 (0.73 – 1.67)
33 – 36 weeks	100 (4.2%)	86 (3.9%)	0.96 (0.72 – 1.28)
37+ weeks	239 (3.5%)	161 (3.1%)	0.90 (0.73 – 1.09)
Placental abruption			
Total	126 (1.3%)	68 (0.8%)	0.61 (0.45 – 0.82)
28 – 32 weeks	35 (5.3%)	23 (3.6%)	0.69 (0.41 – 1.17)
33 – 36 weeks	47 (2.0%)	24 (1.1%)	0.61 (0.37 – 1.00)
37+ weeks	46 (0.7%)	19 (0.4%)	0.52 (0.30 – 0.89)
HELLP Syndrome			
Total	760 (7.7%)	429 (5.4%)	0.70 (0.62 – 0.79)
28 – 32 weeks	170 (25.6%)	127 (20.3%)	0.79 (0.63 – 0.99)
33 – 36 weeks	296 (12.3%)	172 (8.0%)	0.65 (0.54 – 0.78)
37+ weeks	301 (4.4%)	123 (2.4%)	0.55 (0.45 – 0.68)
Stillbirth			
Total	42 (0.4%)	25 (0.3%)	0.73 (0.45 – 1.20)
28 – 32 weeks	17 (2.6%)	9 (1.4%)	0.56 (0.25 – 1.25)
33 – 36 weeks	19 (0.8%)	10 (0.5%)	0.60 (0.28 – 1.30)
37+ weeks	6 (0.1%)	6 (0.1%)	1.33 (0.43 – 4.12)
Composite antenatal			
Total	1236 (12.5%)	797 (10.0%)	0.78 (0.72 – 0.86)
28 – 32 weeks	242 (36.6%)	192 (30.7%)	0.83 (0.68 – 1.00)
33 – 36 weeks	426 (17.7%)	286 (13.2%)	0.75 (0.64 – 0.87)
37+ weeks	578 (8.5%)	309 (6.0%)	0.71 (0.62 – 0.82)
Birthweight <3rd centile			
Total	556 (5.6%)	342 (4.3%)	0.80 (0.70 – 0.92)
28 – 32 weeks	36 (5.5%)	32 (5.1%)	0.94 (0.58 – 1.51)
33 – 37 weeks	159 (6.6%)	103 (4.8%)	0.75 (0.58 – 0.96)
37 + weeks	363 (5.3%)	205 (4.0%)	0.82 (0.69 – 0.98)
HDU admission			
Total	1245 (12.6%)	1200 (15.1%)	1.22 (1.13 – 1.33)
28 – 32 weeks	212 (32.1%)	312 (49.8%)	1.56 (1.31 – 1.86)
33 – 36 weeks	459 (19.1%)	439 (20.3%)	1.19 (1.02 – 1.40)
37+ weeks	574 (8.4%)	449 (8.7%)	1.41 (1.20 – 1.65)
Neonatal	**N (%)**	**N (%)**	**Raw RR (95% CI)**
Respiratory distress syndrome	889 (9.0%)	1021 (12.9%)	1.43 (1.31 – 1.57)
Neonatal sepsis	195 (2.0%)	222 (2.80%)	1.42 (1.17 – 1.72)
NICU admission	598 (6.0%)	656 (8.3%)	1.37 (1.23 – 1.53)
5 minute APGAR <5	110 (1.1%)	90 (1.1%)	1.00 (0.76 – 1.32)

Adjusted relative risks presented for maternal outcomes; raw relative risks for neonatal outcomes.

Table S2. Raw relative risks for each comorbidity for neonatal outcomes.							
	No comorbidity (n = 9,898)	Chronic hypertension (n = 1,790)		Diabetes mellitus (n = 2,363)		Obesity (n = 5,772)	
Outcome	**N (%)**	**N (%)**	**RR**	**N (%)**	**RR**	**N (%)**	**RR**
Respiratory distress syndrome	889 (9.0%)	354 (19.8%)	2.04 (1.82 – 2.29)	327 (13.8%)	1.35 (1.20 – 1.52)	688 (11.9%)	1.23 (1.12 – 1.36)
Neonatal sepsis	195 (2.0%)	79 (4.4%)	2.09 (1.64 – 2.67)	78 (3.3%)	1.51 (1.18 – 1.93)	151 (2.6%)	1.15 (0.94 – 1.41)
NICU admission	598 (6.0%)	343 (19.2%)	3.37 (2.98 – 3.82)	203 (8.6%)	1.26 (1.09 – 1.47)	366 (6.3%)	1.10 (0.96 – 1.26)
5 minute APGAR <5	110 (1.1%)	21 (1.2%)	1.05 (0.65 – 1.61)	22 (0.9%)	0.81 (0.50 – 1.23)	66 (1.1%)	1.21 (0.89 – 1.65)

NICU; neonatal intensive care unit.

Further analyses

Introduction

We undertook further analyses, which were not included in the published manuscript due to space reasons.

Rationale

As guidelines[35,36] routinely recommend delivery at 37 weeks for women with mild hypertension in pregnancy, we evaluated whether the presence of comorbidities influenced neonatal outcomes beyond 37 weeks. A 2019 individual patient data meta-analysis of five randomized control trials that compared maternal and neonatal outcomes between expectant management and immediate delivery, at either 34 or 36 weeks' gestation, found that immediate delivery was associated with a lower incidence of HELLP Syndrome or eclampsia (RR 0.33, 95% CI [0.15 – 0.73]), but an increased likelihood of respiratory distress syndrome (RR 1.9 [1.3 – 3.6]).

We reasoned that as women with comorbidities may have a milder phenotype of preeclampsia, their incidence of both HELLP syndrome/preeclampsia and respiratory distress syndrome would be lower, and thus it may be beneficial, if possible to do so safely, to prolong pregnancy from 37 to 38- or 39- weeks. However, to determine if this is even worth studying, it is first necessary to determine whether neonatal outcomes, such as respiratory distress syndrome, would indeed be better, as prolonging pregnancy always carries an increased risk of developing complications from preeclampsia.

Methods

We compared gestational-age specific risks of complications in the term period for women with and without comorbidities using chi-square tests for trend. Gestational age was treated as an ordered categorical variable, consisting of delivery at 37, 38, 39, or 40 or more weeks' gestational age.

Results

The proportion of neonates born at each gestational week beyond term who suffered respiratory distress syndrome, sepsis, required NICU admission or had a low APGAR score are shown in Figure 3.

For neonates born to mothers without comorbidities, delivery beyond 37 weeks' gestation was associated with less respiratory distress syndrome (χ^2 = 5.8, p = 0.02) but an increase in neonatal sepsis (χ^2 = 11.4, p < 0.001), with no significant change to either NICU admission rates (χ^2 = 2.1, p = 0.55) or low APGAR scores (χ^2 = 0.4, p = 0.54).

However, for neonates born to women with comorbidities, analysed as a group, delivery beyond 37 weeks' gestation was associated with lower rates of both RDS (χ^2 = 22.0, p < 0.001) and sepsis (χ^2 = 4.1, p = 0.04), though no change to NICU admission (χ^2 = 1.3, p = 0.26) or low APGAR scores (χ^2 = 1.2, p = 0.27).

For neonates born to women with hypertension, delivery beyond 37 weeks was associated with a significant decrease in RDS (χ^2 = 7.3, p = 0.01), but no change to sepsis (χ^2 = 0.5, p = 0.56), NICU admission (χ^2 = 2.2, p = 0.14) or low APGAR scores (χ^2 = 0.5, p = 0.47).

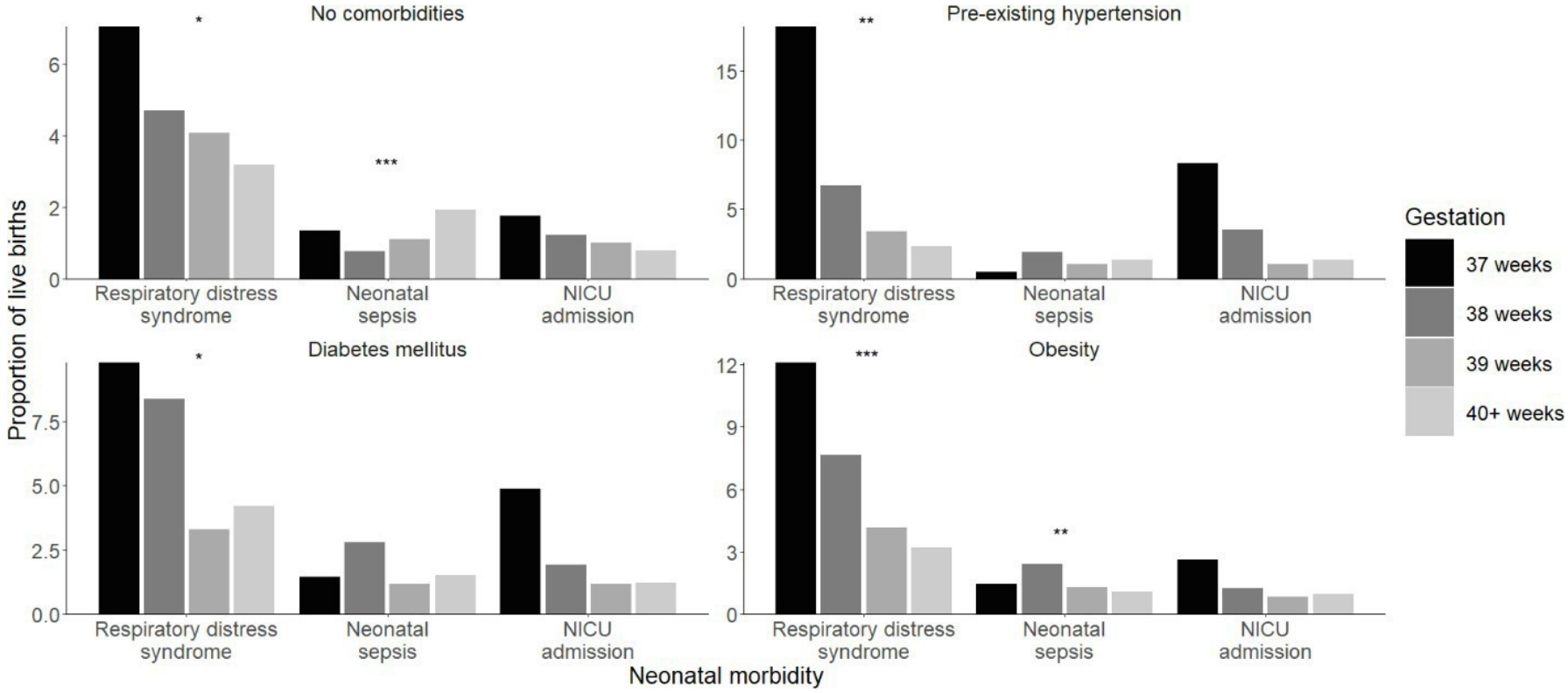
If mothers had diabetes, longer gestation was associated with less RDS (χ^2 = 5.4, p = 0.02), but no change in sepsis (χ^2 = 1.3, p = 0.25), NICU admissions (χ^2 = 0.54, p = 0.46) or low APGAR scores (χ^2 = 0.94,p = 0.33). If mothers had obesity, longer gestation was associated with a fall in both RDS (χ^2 = 25.9, p < 0.001) and sepsis (χ^2= 5.1, p = 0.02), without changing NICU admission (χ^2 = 0.5, p = 0.47) or low APGAR scores (χ^2 = 0.7, p = 0.42).

Conclusion

For mothers without comorbidities, delivering beyond 37 weeks' gestation was

associated with a minor decrease in respiratory distress syndrome, but a slight increase in neonatal sepsis. In contrast, for women with comorbidities, delivery beyond 37 weeks was associated with lower rates of respiratory distress and sepsis. Future research should assess how prolonging gestation influences maternal complications, given the potential for neonatal benefits.

Figure 3. Proportion of live births to mothers with and without comorbidities who suffered complications at term.



Neonates born at 37 weeks in black; 38 through 40+ weeks in sequentially lighter grey. * indicates $P < 0.05$, ** indicates $P < 0.01$, *** indicates $P < 0.001$, calculated using chi-square test for trend.

Summary

Studies two and three complemented each other. Where study two looked at a small cohort in great depth, study three looked at a large cohort in less detail. Across both, we found comorbidities were associated with a lower rate of complications from preeclampsia. This effect was strongest for women delivering earlier in gestation. We surmised that this could be due to clinicians intervening – either diagnosing preeclampsia, or initiating further management – at a lower threshold, due to a presumption that these comorbidities would convey an increased risk of poor outcomes. This makes sense, given the elevated risk these women face of pregnancy complications in general. However, if these women are being unnecessarily diagnosed with preeclampsia, this perception of elevated risk may be misguided. This could easily lead to unnecessary intervention.

We've spent two studies looking at complications from preeclampsia. But now to the other side of the same coin. Studying how any factor interacts with complications or prognosis must be complemented by studying how that factor interacts with diagnosis. The effect of improving prognosis must be separated from the effect of increasing the apparent prevalence of a disease or syndrome, such as preeclampsia, without having a bearing on outcomes. Imagine if, for every 1000 women, 10 developed eclampsia (the true rate is far lower). If in one population we diagnosed 100 women with preeclampsia, then the complication rate would be 10%; if in another population we diagnosed 200 women, the complication rate would be 5%. A “better prognosis” can simply mean a higher apparent prevalence of a disease/syndrome, with no bearing on complications.

And so it is that diagnosis and prognosis are intertwined. Thus in Chapter Four we studied how maternal characteristics would influence the course of blood pressure through pregnancy. Blood pressure is the central element of preeclampsia, so formed our primary outcome. We hypothesised that if, owing to maternal characteristics, there were systematic differences in the trajectory and average level of blood pressure throughout pregnancy, there would be systematic differences in the likelihood of different women being diagnosed with preeclampsia, and thus systematic differences in the prognosis for different women.

References

1. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation*. 2014;130:1003-1008
2. Thilaganathan B. Pre-eclampsia and the cardiovascular–placental axis. *Ultrasound in Obstetrics & Gynecology*. 2018;51:714-717
3. Tranquilli AL. Mid-trimester blood pressure in pregnancy. Blood pressure fall or fall of a myth? *J Hypertens*. 2011;29:658-659
4. Page EW, Christianson R. The impact of mean arterial pressure in the middle trimester upon the outcome of pregnancy. *Am J Obstet Gynecol*. 1976;125:740-746
5. MacGillivray I, Rose GA, Rowe B. Blood pressure survey in pregnancy. *Clinical science*. 1969;37:395-407
6. Loerup L, Pullon RM, Birks J, Fleming S, Mackillop LH, Gerry S, et al. Trends of blood pressure and heart rate in normal pregnancies: A systematic review and meta-analysis. *BMC Med*. 2019;17:167
7. Green LJ, Kennedy SH, Mackillop L, Gerry S, Purwar M, Staines Urias E, et al. International gestational age-specific centiles for blood pressure in pregnancy from the intergrowth-21st project in 8 countries: A longitudinal cohort study. *PLOS Medicine*. 2021;18:e1003611
8. Cheung KL, Lafayette RA. Renal physiology of pregnancy. *Advances in chronic kidney disease*. 2013;20:209-214
9. Macdonald-Wallis C, Tilling K, Fraser A, Nelson SM, Lawlor DA. Associations of blood pressure change in pregnancy with fetal growth and gestational age at delivery: Findings from a prospective cohort. *Hypertension*. 2014;64:36-44
10. Tanner MS, Davey MA, Mol BW, Rolnik DL. The evolution of the diagnostic criteria of preeclampsia-eclampsia. *Am J Obstet Gynecol*. 2022;226:S835-s843
11. Golding J, Pembrey M, Jones R. Alspac--the avon longitudinal study of parents and children. I. Study methodology. *Paediatric and perinatal epidemiology*. 2001;15:74-87
12. Villar J, Altman D, Purwar M, Noble J, Knight H, Ruyan P, et al. The objectives, design and implementation of the intergrowth-21st project. *BJOG*. 2013;120:9-26
13. Macdonald-Wallis C, Silverwood RJ, Fraser A, Nelson SM, Tilling K, Lawlor DA, et al. Gestational-age-specific reference ranges for blood pressure in pregnancy: Findings from a prospective cohort. *J Hypertens*. 2015;33:96-105
14. Shen M, Tan H, Zhou S, Smith GN, Walker MC, Wen SW. Trajectory of blood pressure change during pregnancy and the role of pre-gravid blood pressure: A functional data analysis approach. *Scientific Reports*. 2017;7:6227
15. Facca TA, Mastroianni-Kirsztajn G, Sabino ARP, Passos MT, Dos Santos LF, Famá EAB, et al. Pregnancy as an early stress test for cardiovascular and kidney disease

diagnosis. *Pregnancy hypertension*. 2018;12:169-173
16. Folkow B. The pathophysiology of hypertension. *Drugs*. 1993;46:3-7
17. Sun Z. Aging, arterial stiffness, and hypertension. *Hypertension*. 2015;65:252-256
18. Kalafat E, Perry H, Bowe S, Thilaganathan B, Khalil A. Prognostic value of maternal cardiovascular hemodynamics in women with gestational hypertension and chronic hypertension in pregnancy. *Hypertension*. 2020;76:506-513
19. Tihtonen K, Kööbi T, Huhtala H, Uotila J. Hemodynamic adaptation during pregnancy in chronic hypertension. *Hypertens Pregnancy*. 2007;26:315-328
20. Vonck S, Lanssens D, Staelens AS, Tomsin K, Oben J, Bruckers L, et al. Obesity in pregnancy causes a volume overload in third trimester. *European journal of clinical investigation*. 2019;49:e13173
21. Sarno L, Morlando M, Giudicepietro A, Carlea A, Sidhu S, Campanile M, et al. The impact of obesity on haemodynamic profiles of pregnant women beyond 34 weeks' gestation. *Pregnancy hypertension*. 2020;22:191-195
22. Schmieder RE, Messerli FH. Does obesity influence early target organ damage in hypertensive patients? *Circulation*. 1993;87:1482-1488
23. Mulder E, de Haas S, Mohseni Z, Schartmann N, Abo Hasson F, Alsadah F, et al. Cardiac output and peripheral vascular resistance during normotensive and hypertensive pregnancy – a systematic review and meta-analysis. *BJOG.* 2021; 00: 1–12.
24. Sisti G, Williams B. Body of evidence in favor of adopting 130/80 mm hg as new blood pressure cut-off for all the hypertensive disorders of pregnancy. *Medicina (Kaunas)*. 2019;55:703
25. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. 1988;158:892-898
26. Macdonald-Wallis C, Tilling K, Fraser A, Nelson SM, Lawlor DA. Established preeclampsia risk factors are related to patterns of blood pressure change in normal term pregnancy: Findings from the avon longitudinal study of parents and children. *J Hypertens*. 2011;29:1703-1711
27. Dildy GA, Cotton DB. Management of severe preeclampsia and eclampsia. *Critical Care Clinics*. 1991;7:829-850
28. National high blood pressure education program working group report on high blood pressure in pregnancy. *Am J Obstet Gynecol*. 1990;163:1691-1712
29. Management of hypertension in pregnancy: Executive summary. *Medical Journal of Australia*. 1993;158:700-702
30. North RA, Taylor RS, Schellenberg J-C. Evaluation of a definition of pre-eclampsia. *BJOG: An International Journal of Obstetrics & Gynaecology*. 1999;106:767-773
31. Levine RJ, Ewell MG, Hauth JC, Curet LB, Catalano PM, Morris CD, et al. Should the definition of preeclampsia include a rise in diastolic blood pressure of >/=15 mm

hg to a level <90 mm hg in association with proteinuria? *Am J Obstet Gynecol*. 2000;183:787-792

32. Tanner MS, De Guingand D, Reddy M, Rowson S, Rolnik DL, Da Silva Costa F, et al. The effect of preexisting medical comorbidities on the preeclamptic phenotype: A retrospective cohort study. *Hypertens*. 2021;40:336-345

33. Tanner MS, Malhotra A, Davey M-A, Wallace EM, Mol BW, Palmer KR. Maternal and neonatal complications in women with medical comorbidities and preeclampsia. *Pregnancy hypertension*. 2022;27:62-68

Chapter Four

"Highly organized research is guaranteed to produce nothing new."

— Frank Herbert, *Dune*

Introduction

In Chapters Two and Three, we demonstrated that among women diagnosed with preeclampsia, comorbidities are associated with fewer complications. This could reflect an increased likelihood of being diagnosed; a protective effect once the syndrome has set in; or both. In this chapter we examine how maternal characteristics might affect the former.

If baseline maternal characteristics have a significant effect on the normal, physiological course, using the exact same criteria for diagnosing preeclampsia would lead to some women being unnecessarily diagnosed and thought to be at risk of complications; and others not being diagnosed, despite being at high-risk, but not receiving the additional care they might require.

Instead of restricting our cohort to women with a diagnosed comorbidity – such as hypertension or obesity – we treated baseline blood pressure and BMI as continuous variables. And while we were at it, we looked at some other maternal factors – age, parity, whether or not they smoked during pregnancy, and region of birth.

Let's jump into Chapter Four.

The association of maternal characteristics with blood pressure variation through pregnancy

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Abstract

Objective: Recent work has questioned the use of 140/90mmHg as a uniform threshold to diagnose hypertension in pregnancy. Maternal characteristics may contribute to unnecessary diagnoses of hypertensive disorders of pregnancy.. Thus we evaluated the relationship between the trajectory of blood pressure during pregnancy, and maternal characteristics including blood pressure and body mass index.

Design: Retrospective cohort study.

Setting: One tertiary referral and two secondary hospitals.

Population: All women receiving antenatal care with at least one blood pressure measurement taken prior to 16 weeks gestation (n = 18,915).

Methods: We modelled blood pressure across pregnancy using mixed-effects linear spline models. We used each maternal characteristic as a stand-alone predictor and as an interaction with gestational age, to show their effects on both average blood pressure and weekly change in blood pressure.

Main Outcome Measures: Systolic and diastolic blood pressure at a given gestational age.

Results: There was an inverse correlation between baseline blood pressure and the weekly change in blood pressure in the first half of pregnancy. Blood pressure on average fell for women with higher blood pressures, and increased for women with lower blood pressures. Body mass index, age and other maternal characteristics had a smaller influence throughout pregnancy.

Conclusions: Haemodynamic adaptation to pregnancy is influenced by maternal characteristics, particularly blood pressure and body mass index. This may lead to unnecessary diagnoses of hypertensive disorders of pregnancy.

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Introduction

The maternal cardiovascular system undergoes major changes during pregnancy.[1] In the first five weeks of pregnancy, dilation of the systemic vasculature begins, leading to a fall in Systemic Vascular Resistance (SVR), reaching a nadir in the late second trimester.[1] This is accompanied by a rise in Cardiac Output (CO). These haemodynamic adaptations are crucial to ensuring adequate uteroplacental perfusion.

A suboptimal endothelial adaptation can in the second half of pregnancy manifest as hypertensive disorders of pregnancy (HDoP).[2] Endothelial dysfunction secondary to placental insufficiency results in vasoconstriction and hypertension, and when severe enough, preeclampsia. How blood pressure changes across gestation may thus be indicative of underlying pathology. Accurately characterising its trajectory may help predict the development of HDoP, or subsequent complications.

It is widely held that blood pressure declines through the first half of pregnancy, reaching its lowest point at approximately 20-24 weeks gestation.[3] However, this perspective was initially supported by only a small number of studies published in the mid-twentieth century.[4, 5] More recent research indicates that while diastolic blood pressure (DBP) does indeed fall during the first half of pregnancy, systolic blood pressure (SBP) may follow a different trajectory. A recent meta- analysis[6] and a large prospective study[7] concluded that SBP was at its lowest at around 10-12 weeks gestation, while DBP did indeed reach a nadir at 20- 21 weeks.

Other groups, however, have found that blood pressure is indeed lowest at around 20 weeks for both SBP and DBP. However, the difference between first-trimester and mid-pregnancy was approximately 1.5-2mmHg, a far cry from the 10- 15mmHg that has been reported.[6,8] Maternal characteristics have also been shown to influence the course of blood pressure through pregnancy.[9] In particular, risk factors for HDoP such as obesity and older age are associated with higher blood pressure in the first trimester, as well as greater increases in blood pressure later in pregnancy. This suggests that HDoP represents the upper end of the spectrum of endothelial adaptation to pregnancy, and resultant changes in blood pressure and endothelialfunction.[9]

We link these developments to our work that has evaluated whether a uniform blood pressure threshold (i.e. 140/90mmHg) is appropriate for a diagnosis of HDoP, specifically with relation to preeclampsia. Guidelines recommending this threshold commonly cite statistical limits, expert opinion or simplicity – not always primary data.[10] And risk factors such as hypertension and obesity, that increase the likelihood of preeclampsia, may be associated with a better maternal but worse neonatal outcome following a diagnosis. This could suggest women being diagnosed and receiving intervention at a lower clinical threshold. Thus our interest was focused on the role of blood pressure and body mass index (BMI).

We evaluated how maternal characteristics and blood pressure are associated with the trajectory of blood pressure through pregnancy. We hypothesised that the course of blood pressure through pregnancy would vary depending on a woman's baseline blood pressure (bBP), as well as her other characteristics including BMI and age.

Methods

This retrospective cohort study was undertaken at the largest maternity service provider in Melbourne, Australia. Monash Health provides maternity care across one tertiary referral and two

secondary hospitals. Data on women receiving pregnancy care is collected using the Birthing Outcomes Summary (BOS) database. During antenatal care, clinicians fill in data in 46 prespecified forms, across maternal personal and health details; pregnancy care requirements; blood pressure measurements; medical and obstetric history; and maternal and perinatal outcomes.

We used BOS database records to study all woman who gave birth at Monash Health between January 1, 2016 and December 31, 2019 to a fetus at or after 20 weeks' gestation, or greater than 400 grams birthweight if gestation at birth was unknown. We excluded women with a multiple pregnancy and pregnancies complicated by a major congenital fetal anomaly. We supplemented this data with electronic medical records where key information was missing. Ethics approval was granted by Monash Health Human Research Ethics Committee (#713135).

Outcomes

Our primary outcomes were SBP and DBP at a given gestational age in pregnancy.

Blood pressure is routinely measured and recorded by trained midwifery and obstetric staff , with an appropriately sized cuff and the woman seated. We excluded the small number of blood pressure measurements that were implausible: SBPs over 200mmHg or below 60mmHg at baseline, and DBPs over 160mmHg at any time in pregnancy, or below 35mmHg at baseline.

The predictors we used were gestational age the blood pressure was measured (weeks); maternal age (years), body mass index (kg/m^2), region of birth, smoking, parity and bBP. We only included women with a first blood pressure measurement prior to 16weeks' gestation, and used the first blood pressure available as the bBP. We then randomly selected one blood pressure reading in each two week period after 12 weeks' gestation, to ensure women with a large number of clustered measurements were not overrepresented.

Other predictors were recorded at the first antenatal visit. Smoking was categorised as either a current or non- smoker. Our database records country of birth, which we used as a proxy for ethnicity. We grouped these observations into regions: Australia/New Zealand; South and East Asia (including China); Africa; the Middle East; South and Central America; Western Europe and North America; and other. Parity was coded as nulliparous or parous. We also collected data on preexisting comorbidities (Obesity, Chronic Hypertension, Diabetes Mellitus) and HDoP.

We included women who developed HDoP, which differs from other studies. We were interested in the association between blood pressure and body mass index on a continuous scale, viewing HDoP as the upper end of the spectrum of suboptimal cardiovascular and endothelial adaptation to pregnancy. Under this approach, excluding women who developed HDoP would bias our sample, as it would preferentially exclude women with elevated blood pressure early in pregnancy, leading to an overrepresentation of women with lower blood pressures who are less likely to be diagnosed with HDoP.

Statistical analysis

We modelled weekly blood pressure change using a linear spline model relating blood pressure to gestation. Knots were at 18, 32 and 36 weeks' gestation. We identified the approximate locations of the knots by using polynomial models to graph the relationship between blood pressure and gestation, then selected the knots that minimised the log-likelihood of the model.

We then used linear mixed-effects models to analyse the association of each predictor with average blood pressure and weekly blood pressure change through pregnancy. The predictor(s) represented the fixed effects, and each woman's unique study identifier was a random effect.

We first modelled blood pressure as a function of gestation alone to calculate the weekly change in blood pressure in each period in pregnancy. We then added each predictor to the model as both a constant term and as an interaction with gestation. We scaled gestation to have a value of zero at 12 weeks, which means that the β for the constant term represents the difference associated with that predictor at 12 weeks gestation. The β for the interaction with gestation represents the association of that predictor with weekly change in blood pressure for each spline segment (<18, 18 – 32, 32 – 36, or 36+ weeks' gestation). The exception is for bBP, which we added as a constant and interaction term separately, which means the β represents the difference on average throughout pregnancy.

We then created a multivariate model, which included constant terms and interactions with gestation for each predictor. We used backwards stepwise selection with a p-value threshold of 0.10 to identify terms to remain in the final model.

For Figures 1 and S1, we used our models to predict each woman's blood pressure at week 12, then used these to separate women into deciles. Statistical analyses were performed in *R* version 4.0.2, using packages *lspline, lme4* and *lmerTest*.

Results

We identified 31,077 women, with 185,178 BP measurements. After excluding women without a BP taken prior to 16 weeks' gestation (n=12,173 women) and clustered measurements (n=9,769 measurements), we included 18,915 women with 116,829 BP measurements. Women had a median 7 (interquartile range [IQR] 4-7) visits. The median gestation at first antenatal visit was 13.4 weeks (11.9 – 14.6). Baseline data is in Table 1.

Table 1. Baseline demographics of the study population (n=18,915)	
Age (years)	31.2 (5.0)
BMI (kg/m^2)	24.7 (22.0 – 28.8)
Nulliparous	7,541 (39.8%)
Smoker	1,765 (9.4%)
Region of birth	
Australia	7,155 (37.9%)
South and East Asia (incl. China)	6,895 (36.5%)
Middle East	1,698 (9.0%)
Africa	1,123 (5.9%)
Western Europe/North America	1,903 (10.1%)
South and Central America	103 (0.5%)
Other	132 (0.7%)
Comorbidities	
Obesity	3,909 (20.7%)
Hypertension	198 (1.1%)
Diabetes	264 (1.4%)

Data given as mean (standard deviation), median (interquartile range) or number (%).

Average blood pressure level and trajectory through pregnancy

Across the whole cohort, mean SBP and DBP decreased prior to 18 weeks gestation (SBP β = -0.05, 95% confidence interval (CI) [-0.09, -0.01]; DBP, β = -0.23 [-0.26, -0.20]). They both increased between 18-32 weeks (SBP β = 0.20 [0.19, 0.22] and DBP β = 0.13 [0.12, 0.14]), before accelerating between 32-36 weeks (β = 0.50 [0.45, 0.55], and β = 0.60 [0.56 – 0.64], respectively), and after 36 weeks gestation (β = 1.03 [0.96, 1.10] and β = 0.77 [0.72, 0.82], respectively) (Table 2, Figures 1 and 2).

Table 2. Univariate analysis results for the relationship between each predictor and average blood pressure				
Predictors	**Systolic**		**Diastolic**	
Gestation	β (95% CI)	P	β (95% CI)	P
<18 weeks	-0.05 (-0.09, -0.01)	0.01	-0.23 (-0.26, -0.20)	<0.001
18 – 32	0.20 (0.19, 0.22)	<0.001	0.13 (0.12, 0.14)	<0.001
32-36	0.50 (0.45, 0.55)	<0.001	0.60 (0.56, 0.64)	<0.001
36+ weeks	1.03 (0.96, 1.10)	<0.001	0.77 (0.71, 0.82)	<0.001
Baseline BP	0.55 (0.55, 0.56)	<0.001	0.47 (0.46, 0.48)	<0.001
BMI (kg/m^2)	0.69 (0.60, 0.78)	<0.001	0.49 (0.42, 0.57)	<0.001
Age (years)	0.34 (0.22, 0.45)	<0.001	0.24 (0.15, 0.34)	<0.001
Nulliparity	1.07 (0.13, -2.26)	0.08	-0.30 (0.66, -1.26)	0.54
Smoking	2.97 (0.64, 5.30)	0.01	0.85 (-1.03, 2.72)	0.38
Region of birth				
Australia	Ref	Ref	Ref	Ref
Africa	-5.83 (-6.35, - 5.30)	<0.001	-2.48 (-2.84, -2.11)	<0.001
South/East Asia	-5.70 (-5.98, -5.42)	<0.001	-2.39 (-2.59, -2.20)	<0.001
Middle East	-6.86 (-7.30, -6.42)	<0.001	-3.80 (-4.10, -3.49)	<0.001
South/ Central America	-2.73 (-3.93, -0.62)	0.007	-1.80 (-2.96, -0.64)	0.002
Europe/America	-2.10 (-2.52, -1.68)	<0.001	-0.88 (-1.18, -0.59)	<0.001
Other	-6.94 (-10.77,-3.12)	<0.001	-3.60 (-6.29, -0.91)	0.009

Data given as mean (standard deviation), median (interquartile range) or number (%). β indicates association with average blood pressure across pregnancy

Figure 1 Trajectory of systolic blood pressure through pregnancy (A), separated into deciles of predicted systolic blood pressure at week 12 (B).

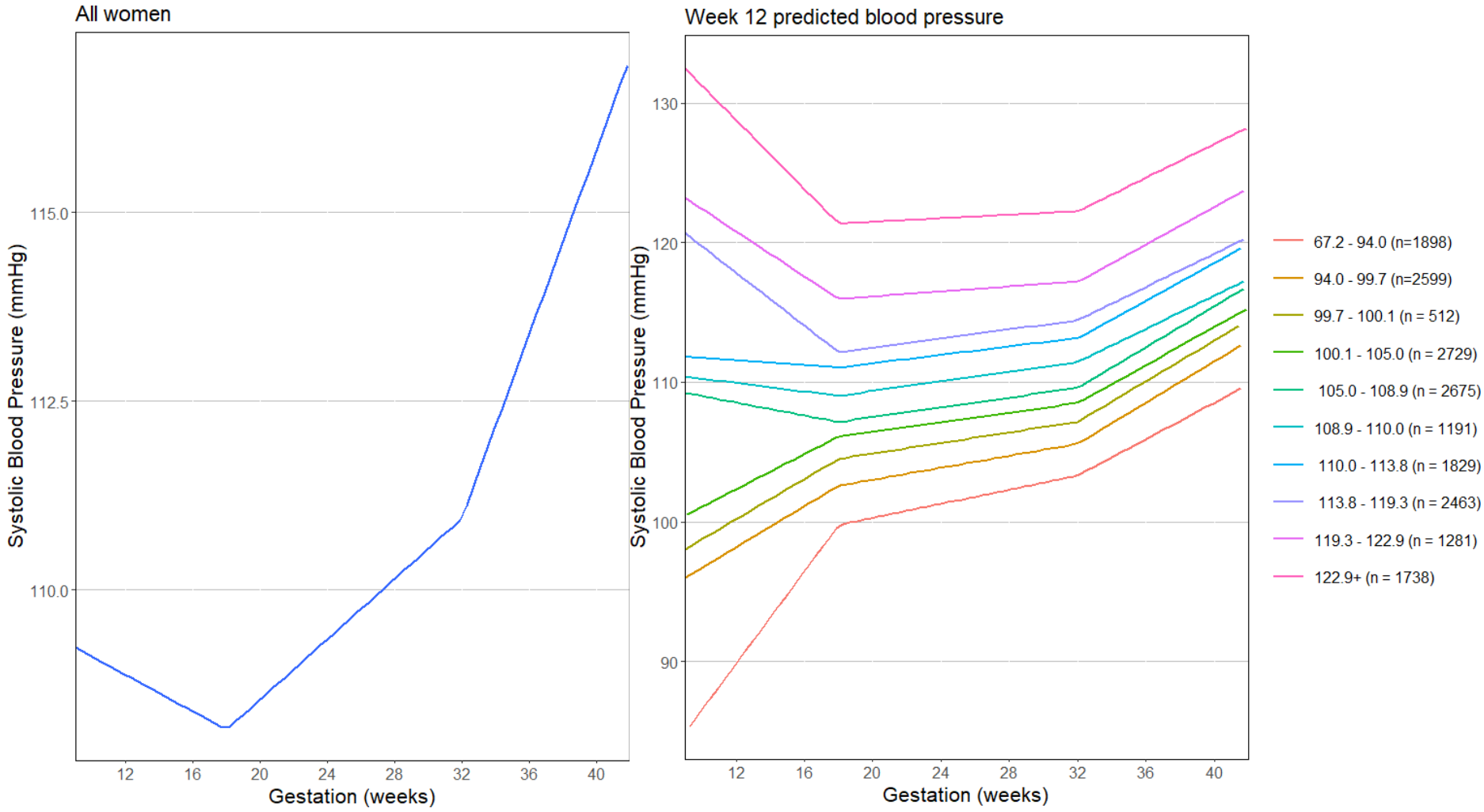
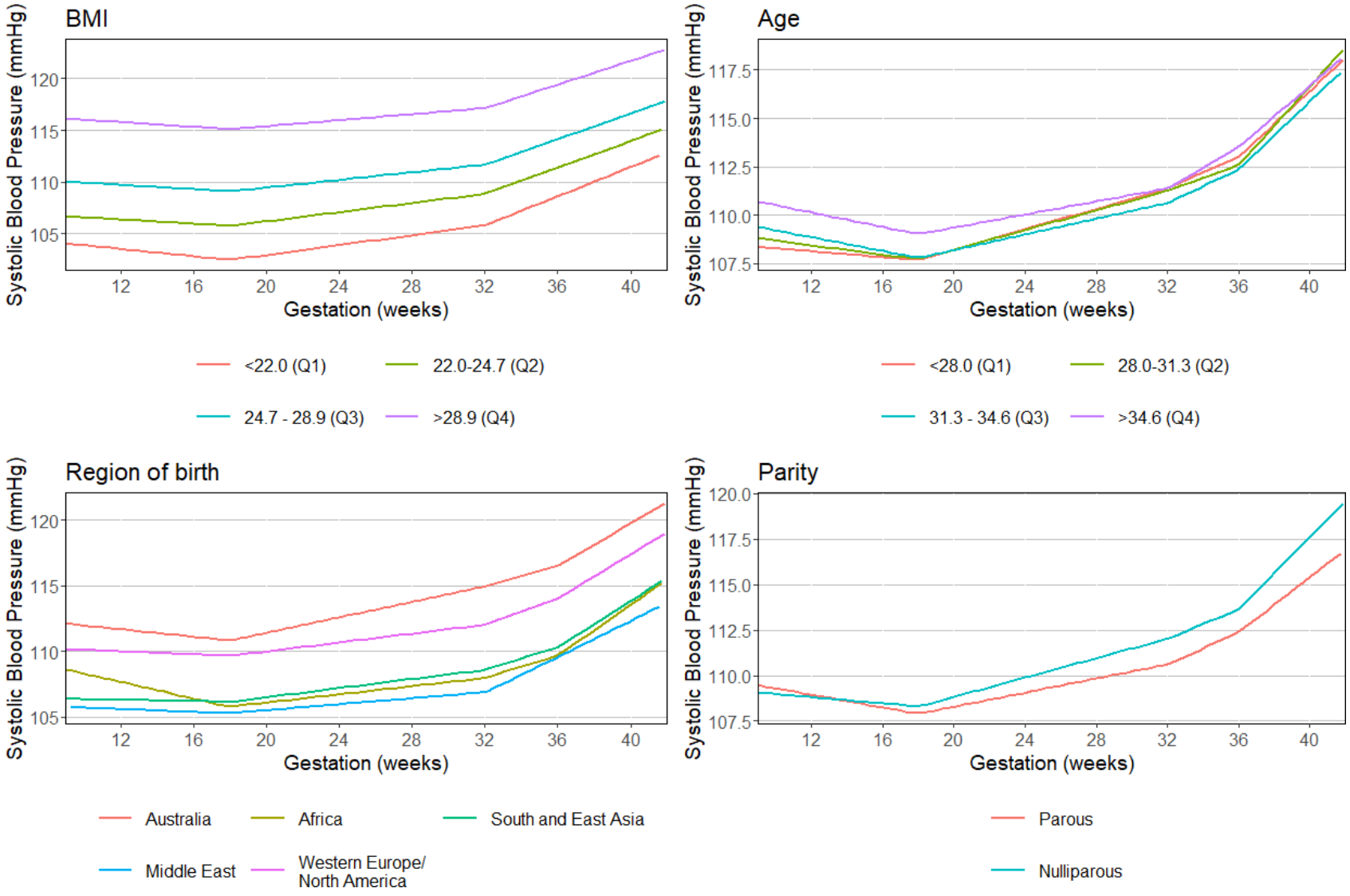


Figure 2. Systolic blood pressure trajectory based on quartile of BMI and age; region of birth; and parity.



Association of baseline blood pressure with blood pressure trajectory

Data for the association between bBP and blood pressure trajectory can be found in Tables 2 and 3 and Figure 1. bBP was positively associated with a higher mean SBP and DBP through pregnancy (β = 0.55, 95% CI [0.54, 0.56] and β = 0.47 [0.46, 0.48], respectively) (Table 2).

Prior to 18 weeks, a bBP was negatively associated with weekly change in both SBP and DBP (β = -0.083 [-0.086, -0.080] and β = -0.101 [-0.104, -0.097]). The mean change per week prior to 18 weeks for SBP was 10.13 – 0.093 x bBP, and for DBP was 7.30 – 0.11 x bBP (Table 3).

Where these equal zero – 109mmHg for SBP, 66mmHg for DBP – is the threshold, above which, prior to 18 weeks, blood pressure would on average fall, and below which blood pressure would on average rise (Figure1 & Figure 2).

bBP was negatively associated with weekly change in SBP and DBP between 18 and 32 weeks. Baseline SBP was also negatively associated with weekly change between 32-36 weeks, and positively associated again after 36 weeks gestation. (Table 3).

Association of maternal characteristics with blood pressure trajectory

Data for the association between maternal characteristics and blood pressure trajectory can be found in Tables 2and 3 and Figure 2.

A higher body mass index was associated with a higher SBP and DBP at 12 weeks gestation (β = 0.69, 95% CI [0.60, 0.78] and β = 0.49, [0.42, 0.57], respectively). A higher BMI was also associated with a higher weekly change in SBP prior to 18 weeks, and a lower weekly change in both SBP and DBP between 18 and 32 weeks.

Older age was associated with a higher SBP and DBP at 12 weeks (β = 0.34 [0.22 – 0.45] and β = 0.24 [0.15, 0.34]),respectively.

Age was also associated with a lower weekly SBP change prior to 18 weeks; a lower weekly change for SBP and DBP between 18 and 32 weeks; and a higher weekly SBP change after 36 weeks (Table 2). Australian-born women had, on average through pregnancy, the highest SBP and DBP. Women born in the Middle East had the lowest SBP and DBP. Region of birth had no association with BP trajectory.

Smoking was associated with a higher SBP at 12 weeks (β = 2.97, [0.64, 5.30]), as well as a lower weekly change between 18-32 weeks for both SBP and DBP.

Nulliparity was not associated with a SBP or DBP at 12 weeks. It was associated with a higher weekly change prior to 18 weeks for SBP, and between 18- 32 weeks for both SBP and DBP, and after 36 weeksfor SBP.

Multivariate analysis

Table 4 displays results of our multivariate analysis. For our final SBP model, there were constant terms for bBP, BMI, smoking and region of birth and interaction terms for baseline SBP, BMI, and nulliparity. A higher baseline BP was associated with a lower weekly change prior to 18 weeks and between 18 – 32 weeks. A higher BMI was associated with a lower SBP at 12 weeks, but a higher weekly change prior to 18weeks. Older age was associated with a higher weekly SBP change prior to 18 weeks gestation, but a lower weekly change between 18 – 32 and 32 – 36 weeks. Nulliparity was associated with a higher weekly SBP change prior to 18 weeks, between 18 – 32 weeks, and after 36 weeks' gestation. Smoking was associated with a higher SBP at 12

Table 3. Interaction of individual predictors with gestation					
Predictors		**Systolic**		**Diastolic**	
Baseline BP	Spline segment	β (95% CI)	P value	β (95% CI)	P value
Gestation	<18 weeks	9.07 (8.74, 9.41)	<0.001	6.49 (6.28, 6.74)	<0.001
	18 – 32 weeks	0.59 (0.46, 0.73)	<0.001	0.24 (0.15, 0.33)	<0.001
	32 – 36 weeks	-0.08 (-0.53, 0.38)	0.74	0.43 (0.13, 0.74)	<0.001
	36+ weeks	1.86 (1.21, 2.51)	<0.001	0.89 (0.46, 1.32)	0.005
Interaction	<18 weeks	-0.083 (-0.086, -0.080)	<0.001	-0.101 (-0.104, -0.097)	<0.001
	18 – 32 weeks	-0.004 (-0.005, -0.003)	<0.001	-0.002 (-0.003, -0.001)	0.007
	32 – 36 weeks	0.005 (0.001, 0.010)	0.01	0.003 (-0.002, 0.007)	0.23
	36+ weeks	-0.008 (-0.014, -0.002)	0.01	-0.002 (-0.009, 0.004)	0.49
BMI					
Gestation	<18 weeks	-0.22 (-0.49, -0.03)	0.02	-0.24 (-0.39, -0.09)	0.001
	18 – 32 weeks	0.42 (0.35, 0.49)	<0.001	0.26 (0.20, 0.31)	<0.001
	32 – 36 weeks	0.44 (0.21, 0.68)	<0.001	0.54 (0.36, 0.73)	<0.001
	36+ weeks	1.00 (0.67, 1.33)	<0.001	0.78 (0.51, 1.05)	<0.001
Interaction	<18 weeks	0.007 (0.001, 0.013)	0.018	0.002 (-0.003, 0.007)	0.53
	18 – 32 weeks	-0.009 (-0.011, -0.006)	<0.001	-0.005 (-0.007, -0.003)	<0.001
	32 – 36 weeks	0.003 (-0.006, 0.011)	0.53	0.003 (-0.04, 0.010)	0.47
	36+ weeks	0.001 (-0.012, 0.014)	0.88	-0.006 (-0.011, 0.010)	0.91
Age					
Gestation	<18 weeks	0.39 (0.13, 0.66)	0.004	-0.06 (-0.28, 0.15)	0.55
	18 – 32 weeks	0.43 (0.33, 0.52)	<0.001	0.30 (0.22, 0.38)	<0.001
	32 – 36 weeks	0.09 (-0.22, 0.41)	0.56	0.53 (0.27, 0.78)	<0.001
	36+ weeks	0.69 (0.24, 1.15)	0.003	0.82 (0.45, 1.18)	<0.001
Interaction	<18 weeks	-0.01 (-0.021, -0.006)	<0.001	-0.005 (-0.012, 0.001)	0.08
	18 – 32 weeks	-0.007 (-0.010, -0.004)	<0.001	-0.005 (-0.008, -0.003)	<0.001
	32 – 36 weeks	0.013 (0.003, 0.023)	0.01	0.002 (-0.006, 0.011)	0.57
	36+ weeks	0.01 (-0.004, 0.025)	0.14	-0.002 (-0.013, 0.010)	0.79
Nulliparity					
Gestation	<18 weeks	-0.07 (-0.004, 0.17)	0.013	-0.25 (-0.29, -0.21)	<0.001
	18 – 32 weeks	0.17 (0.05, 0.11)	<0.001	0.09 (0.08, 0.11)	<0.001
	32 – 36 weeks	0.52 (-0.12, 0.08)	<0.001	0.61 (0.56, 0.66)	<0.001
	36+ weeks	0.94 (0.04, 0.32)	<0.001	0.68 (0.60, 0.75)	<0.001
Interaction	<18 weeks	0.08 (0.002, 0.020)	0.04	0.01 (-0.05, 0.07)	0.77
	18 – 32 weeks	0.08 (0.05, 0.11)	<0.001	0.10 (0.08, 0.13)	<0.001
	32 – 36 weeks	-0.02 (-0.12, 0.08)	0.73	-0.01 (-0.09, 0.07)	0.78
	36+ weeks	0.18 (0.04, 0.32)	0.01	0.17 (0.06, 0.29)	0.003
Smoking					
Gestation	<18 weeks	0.05 (-0.02, 0.11)	0.16	-0.27 (-0.32, 0.22)	<0.001
	18 – 32 weeks	0.17 (0.15, 0.20)	<0.001	0.14 (0.12, 0.16)	<0.001
	32 – 36 weeks	0.53 (0.45, 0.60)	<0.001	0.61 (0.55, 0.67)	<0.001
	36+ weeks	1.01 (0.91, 1.11)	<0.001	0.75 (0.67, 0.83)	<0.001
Interaction	<18 weeks	-0.02 (-0.17, 0.13)	0.79	-0.02 (-0.14, 0.11)	0.81
	18 – 32 weeks	0.13 (0.07, 0.19)	<0.001	0.07 (0.02, 0.12)	0.01
	32 – 36 weeks	-0.18 (-0.38, 0.03)	0.09	-0.05 (-0.21, 0.12)	0.57
	36+ weeks	0.10 (-0.19, 0.38)	0.51	-0.04 (-0.27, 0.19)	0.76

Weekly change in blood pressure during each period of pregnancy equals the β for gestation plus the β for the predictor.

Table 4. Multivariate analysis results					
Predictors		**Systolic**		**Diastolic**	
Constant terms		β (95% CI)	P value	β (95% CI)	P
Gestation					
<18 weeks		9.47 (8.93, 10.02)	<0.001	6.49 (5.89, 6.43)	<0.001
18 – 32 weeks		0.73 (0.50, 0.96)	<0.001	0.20 (0.08, 0.32)	<0.001
32-36 weeks		-0.24 (-1.09, 0.62)	0.59	0.51 (0.06, 0.96)	0.03
36+ weeks		0.53 (-0.51, 1.57)	0.32	0.37 (-0.37, 1.11)	0.13
Baseline BP		1.04 (1.02, 1.06)	<0.001	1.06 (0.99, 1.02)	<0.001
BMI		-0.09 (-0.13, 0.68)	<0.001	-0.05 (-0.08, -0.02)	0.002
Smoking during pregnancy		0.35 (0.02, 0.68)	0.04	*	*
Region of birth					
Australia		Ref		Ref	
Africa		-2.51 (-3.06, -2.15)	<0.001	-1.12 (-1.38, -0.86)	<0.001
South and East Asias		-1.99 (-2.40, -1.87)	<0.001	-0.85 (-0.98, -0.70)	<0.001
Middle East		-2.73 (-3.35, -2.57)	<0.001	-1.66 (-1.88, -1.44)	<0.001
South and Central America		-1.31 (-2.54, 0.26)	0.07	-0.85 (-1.68, -0.03)	0.08
Europe/North America		-0.61 (-1.02, -0.20)	0.04	-0.42 (-0.63, -0.21)	0.31
Other		-0.54 (-4.91, 3.83)	0.66	-1.59 (-3.51, 0.34)	0.69
Interactions with gestation					
Baseline BP	*<18 weeks*	-0.12 (-0. 12, -0.11)	<0.001	-0.14 (-0.13, -0.13)	<0.001
	18 – 32 weeks	-0.003 (-0.005, -0.001)	0.008	0.001 (-0.001, 0.002)	0.83
	32 – 36 weeks	0.005 (-0.003, 0.012)	0.22	0.000 (-0.005, 0.006)	0.21
	36+ weeks	-0.008 (-0.067, 0.051)	0.79	-0.02 (-0.07, -0.21)	0.42
BMI	*<18 weeks*	0.11 (0.10, 0.12)	<0.001	0.06 (0.06, 0.06)	<0.001
	18 – 32 weeks	-0.004 (-0.009, 0.002)	0.06	0.000 (-0.006, 0.001)	0.002
	32 – 36 weeks	-0.007 (-0.023, 0.008)	0.34	0.000 (-0.008, 0.009)	0.93
	36+ weeks	0.073 (-0.005, 0.197)	0.24	0.018 (0.003, 0.032)	0.02
Age	*<18 weeks*	0.013 (0.005, 0.020)	<0.001	0.018 (0.014, 0.022)	<0.001
	18 – 32 weeks	-0.006 (-0.010, -0.002)	0.005	-0.003 (-0.005, -0.001)	0.019
	32 – 36 weeks	0.012 (-0.004, 0.027)	0.14	0.001 (-0.009, 0.009)	0.92
	36+ weeks	-0.21 (-0.34, -0.07)	0.002	-0.031 (-0.107, 0.004)	0.42
Nulliparity	*<18 weeks*	0.16 (0.08, 0.23)	<0.001	0.04 (-0.03, 0.10)	0.25
	18 – 32 weeks	0.07 (0.02, 0.11)	0.003	0.11 (0.06, 0.11)	<0.001
	32 – 36 weeks	0.02 (-0.14, 0.19)	0.78	0.02 (-0.08, 0.11)	0.76
	36+ weeks	0.22 (-1.58, 1.15)	0.02	0.18 (-0.60, 0.97)	0.02

β for constant term indicate association with week 12 blood pressure; coefficients for interactions indicate association with weekly change in blood pressure. * = not included in final model.

weeks. Australian-born women had the highest SBP at 12 weeks, and women born in the Middle-East the lowest.

For our final DBP model, there were constant terms for baseline DBP, BMI and region of birth, and interaction terms for baseline DBP, BMI, age and nulliparity. A higher baseline DBP was associated with a lower weekly change in DBP prior to 18 weeks' gestation. A higher BMI was associated with a lower DBP at week 12, but a higher weekly change prior to 18 weeks' gestation. Age was associated with a higher weekly change prior to 18 weeks. Nulliparity was associated with a higher weekly change between 18 – 32 weeks and after 36 weeks' gestation. Australian-born women had the highest DBP at 12 weeks, and women born in the Middle-East the lowest.

Discussion

Main Findings

Our data show an inverse relationship between bBP and the magnitude of blood pressure change in the first half of pregnancy; and relationships between maternal characteristics, particularly BMI, on blood pressure change throughout pregnancy.

The relationship between blood pressure early in pregnancy and its subsequent course has been observed, but the implications not discussed, in existing literature. The ALSPAC[11] and INTERGROWTH-21[12] projects were large, prospective studies that measured blood pressure longitudinally during pregnancy, with the aim of developing pregnancy-specific reference ranges. In sub- analyses, the former found that for every 10mmHg higher a woman's SBP was at 12 weeks, the average difference was only 4mmHg at 20 weeks and 3mmHg at 37 weeks' gestation.13 The latter observed that women with a bBP in the lowest quartile experienced increasing blood pressure throughout pregnancy, while the highest quartile had falls in blood pressure in the second trimester before increasing to pre-pregnancy levels at term.[7] These observations indicate the same inverse relationship as we have.

A limitation of both studies, and ours, was the lack of preconception blood pressure measurements. Haemodynamic adaptation begins in the early weeks of pregnancy, and women infrequently have pre-pregnancy blood pressure measurements available. However, Shen et al[14] measured blood pressure from pre-conception to post-birth in 1282 women, and found that the lower a woman's preconception blood pressure, the less it fell (or the more it rose) during the first half of pregnancy.

All three sets of data are in line with an inverse relationship between bBP and its trajectory in the first half of pregnancy. Reason and evidence give us a possible explanation.

Pregnancy is a stress-test on the maternal vascular system.[15] The expansion of plasma volume, a fall in SVR, and a compensatory rise in CO are key to ensuring adequate uteroplacental perfusion.[1] It is logical that the better a woman's vascular function prior to pregnancy, the more pronounced her adaptive haemodynamic response to the stress of pregnancy will be. Any system that has not been stressed will have a bigger response to a stimulus than a system that is already adapted to the same stress.

Prospective research agrees. Elevated blood pressure in younger people (e.g. pregnant women) is driven by a higher CO, with relatively normal SVR. This pattern reverses with age, as arteries stiffen and SVR becomes the driver of elevated blood pressure.[16,17]And there is a minimal difference in CO during pregnancy between women with and without

pre-existing hypertension.[18] Differences in blood pressure during pregnancy are predominantly due to a higher SVR for women with preexisting hypertension.[19] This suggests an inverse relationship between bBP and vasodilating capacity during pregnancy – which would manifest as an inverse relationship between bBP and the change in blood pressure across gestation.

This hypothesis also fits with the effect of BMI we have highlighted. Pregnancy-specific data on the relationship between BMI and haemodynamics in pregnancy remain sparse. However small prospective studies indicate that during pregnancy, when haemodynamics are indexed to a woman's body surface area, obesity is associated with lower CO index and higher SVR index.[20,21] But outside pregnancy, among people with the same blood pressure, those with obesity tend to have a higher CO but lower SVR; while among women with a similar BMI, hypertension is associated with lower CO and higher SVR.[22] And from our data, among women with the same blood pressure, those with a higher BMI had a more rapid increase in blood pressure in the first half of pregnancy, which would result from an attenuated fall in SVR. This would also result in a lower CO *index* and higher SVR *index* for women with obesity.

A possible alternative explanation is that women with a lower bBP have had their haemodynamic adaptation occur earlier in pregnancy. If this were true, then we would expect to see difference in the timing of the mid-pregnancy plateau and third-trimester inflection. But our data does not show this. And a recent meta-analysis suggests that only 54-56% of change in CO and SVR during pregnancy happens prior to 14 weeks gestation.[23] Haemodynamic adaptation may begin early in pregnancy, but it does not stop until the third trimester.

Strengths and limitations

That this was a retrospective study, with the limitations they inherently entail, should limit the conclusions drawn from it. However, our key results align with prospective research and are plausible.

It has been suggested that the diverging blood pressure patterns we observed simply reflect regression to the mean.[10] Individual measurements that are more extreme are likely to be followed by measurements that are closer to the mean, leading to all groups coalescing in a similar range. While this pattern must be present to some extent, it cannot fully explain our data. Interactions in our models between gestation and blood pressure indicate that the course of blood pressure throughout pregnancy is dependent on where it began. Further, using mixed-effects models accounts for the inherent correlation in a given woman's measurements.

We did not look at any outcomes that are in and of themselves of relevance to clinician or woman – stillbirth, or eclampsia, for example. For our results to be meaningful, we must be able to attribute to BMI or blood pressure a difference in adverse outcomes, such as complications from HDoP.

Implications

The internationally accepted threshold for diagnosing hypertension in pregnancy is 140/90mmHg.[24] But there is little compelling evidence that it is the ideal cut-off, nor that we should have a uniform threshold for all women. Its continued use has been justified by statistical limits,[25] expert opinion, or ease of application.[10]

HDoP are best thought of as the upper end of the spectrum of pregnancy-related changes in endothelial function and blood pressure. Dose-response relationships between HDoP and risk

factors such as blood pressure and BMI indicate a"continuum of risk"[26] that is not isolated to women with diagnosed chronic hypertension or obesity, for example. These risk factors also shift statistical limits – two standard deviations away from the mean will be very different for a woman with a BMI of 35kg/m^2 and a bBP 135/85mmHg, to woman with a BMI of 20kg/m^2 and a bBP of 100/60mmHg. For many years, a rise in blood pressure by ≥30mmHg systolic or 15mmHg diastolic was considered sufficient to diagnose HDoP. [27-29] This was abandoned in the late 1990s, when a number of studies demonstrated that such a rise in women who remained normotensive was not associated with a higher rate of adverse outcomes.[30,31] A rise of this magnitude was considered to fall "within the normal statistical range".[25] However, the INTERGROWTH-21 project observed that during pregnancy, fewer than 10% of women had a rise in SBP by 24mmHg or DBP by 18mmHg, and fewer than 3% had a rise of >34mmHg/26mmHg, at any time during pregnancy.[7] Perhaps abandoning relative blood pressure as a criterion was hasty?

Our data is insufficient to answer this. And our results are relevant only if what we have observed translates into different outcomes from HDoP. Preliminary work suggests that among women diagnosed with preeclampsia, those with risk factors such as chronic hypertension and obesity may suffer fewer complications.[32,33] This could reflect over-diagnosis. Further research is needed as to whether these differences in haemodynamics result in any meaningful difference in severe morbidity.

Conclusion

The course of blood pressure through pregnancy depends on baseline blood pressure, on BMI, and on other maternal characteristics. This likely indicates differences in the haemodynamic adaptation to pregnancy. This could influence which women are diagnosed with HDoP. If this results in any differences in clinical outcomes, that should prompt a rethink of how we diagnose HDoP.

References

1. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation*. 2014;130:1003-1008
2. Thilaganathan B. Pre-eclampsia and the cardiovascular–placental axis. *Ultrasound in Obstetrics & Gynecology*. 2018;51:714-717
3. Tranquilli AL. Mid-trimester blood pressure in pregnancy. Blood pressure fall or fall of a myth? *J Hypertens*. 2011;29:658-659
4. Page EW, Christianson R. The impact of mean arterial pressure in the middle trimester upon the outcome of pregnancy. *Am J Obstet Gynecol*. 1976;125:740-746
5. MacGillivray I, Rose GA, Rowe B. Blood pressure survey in pregnancy. *Clinical science*. 1969;37:395-407
6. Loerup L, Pullon RM, Birks J, Fleming S, Mackillop LH, Gerry S, et al. Trends of blood pressure and heart rate in normal pregnancies: A systematic review and meta-analysis. *BMC Med*. 2019;17:167
7. Green LJ, Kennedy SH, Mackillop L, Gerry S, Purwar M, Staines Urias E, et al. International gestational age-specific centiles for blood pressure in pregnancy from the intergrowth-21st project in 8 countries: A longitudinal cohort study. *PLOS Medicine*. 2021;18:e1003611
8. Cheung KL, Lafayette RA. Renal physiology of pregnancy. *Advances in chronic kidney disease*. 2013;20:209-214
9. Macdonald-Wallis C, Tilling K, Fraser A, Nelson SM, Lawlor DA. Associations of blood pressure change in pregnancy with fetal growth and gestational age at delivery: Findings from a prospective cohort. *Hypertension*. 2014;64:36-44
10. Tanner MS, Davey MA, Mol BW, Rolnik DL. The evolution of the diagnostic criteria of preeclampsia-eclampsia. *Am J Obstet Gynecol*. 2022;226:S835-s843
11. Golding J, Pembrey M, Jones R. Alspac--the avon longitudinal study of parents and children. I. Study methodology. *Paediatric and perinatal epidemiology*. 2001;15:74-87
12. Villar J, Altman D, Purwar M, Noble J, Knight H, Ruyan P, et al. The objectives, design and implementation of the intergrowth-21st project. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2013;120:9-26
13. Macdonald-Wallis C, Silverwood RJ, Fraser A, Nelson SM, Tilling K, Lawlor DA, et al. Gestational-age-specific reference ranges for blood pressure in pregnancy: Findings from a prospective cohort. *J Hypertens*. 2015;33:96-105
14. Shen M, Tan H, Zhou S, Smith GN, Walker MC, Wen SW. Trajectory of blood pressure change during pregnancy and the role of pre-gravid blood pressure: A functional data analysis approach. *Scientific Reports*. 2017;7:6227
15. Facca TA, Mastroianni-Kirsztajn G, Sabino ARP, Passos MT, Dos Santos LF, Famá EAB, et al. Pregnancy as an early stress test for cardiovascular and kidney disease diagnosis.

Pregnancy hypertension. 2018;12:169-173

16. Folkow B. The pathophysiology of hypertension. *Drugs*. 1993;46:3-7

17. Sun Z. Aging, arterial stiffness, and hypertension. *Hypertension*. 2015;65:252-256

18. Kalafat E, Perry H, Bowe S, Thilaganathan B, Khalil A. Prognostic value of maternal cardiovascular hemodynamics in women with gestational hypertension and chronic hypertension in pregnancy. *Hypertension*. 2020;76:506-513

19. Tihtonen K, Kööbi T, Huhtala H, Uotila J. Hemodynamic adaptation during pregnancy in chronic hypertension. *Hypertens Pregnancy*. 2007;26:315-328

20. Vonck S, Lanssens D, Staelens AS, Tomsin K, Oben J, Bruckers L, et al. Obesity in pregnancy causes a volume overload in third trimester. *European journal of clinical investigation*. 2019;49:e13173

21. Sarno L, Morlando M, Giudicepietro A, Carlea A, Sidhu S, Campanile M, et al. The impact of obesity on haemodynamic profiles of pregnant women beyond 34 weeks' gestation. *Pregnancy hypertension*. 2020;22:191-195

22. Schmieder RE, Messerli FH. Does obesity influence early target organ damage in hypertensive patients? *Circulation*. 1993;87:1482-1488

23. Mulder E, de Haas S, Mohseni Z, Schartmann N, Abo Hasson F, Alsadah F, et al. Cardiac output and peripheral vascular resistance during normotensive and hypertensive pregnancy – a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*.n/a

24. Sisti G, Williams B. Body of evidence in favor of adopting 130/80 mm hg as new blood pressure cut-off for all the hypertensive disorders of pregnancy. *Medicina (Kaunas)*. 2019;55:703

25. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. 1988;158:892-898

26. Macdonald-Wallis C, Tilling K, Fraser A, Nelson SM, Lawlor DA. Established preeclampsia risk factors are related to patterns of blood pressure change in normal term pregnancy: Findings from the avon longitudinal study of parents and children. *J Hypertens*. 2011;29:1703-1711

27. Dildy GA, Cotton DB. Management of severe preeclampsia and eclampsia. *Critical Care Clinics*. 1991;7:829-850

28. National high blood pressure education program working group report on high blood pressure in pregnancy. *Am J Obstet Gynecol*. 1990;163:1691-1712

29. Management of hypertension in pregnancy: Executive summary. *Medical Journal of Australia*. 1993;158:700-702

30. North RA, Taylor RS, Schellenberg J-C. Evaluation of a definition of pre-eclampsia. *BJOG: An International Journal of Obstetrics & Gynaecology*. 1999;106:767-773

31. Levine RJ, Ewell MG, Hauth JC, Curet LB, Catalano PM, Morris CD, et al. Should the definition of preeclampsia include a rise in diastolic blood pressure of >/=15 mm hg to a level

<90 mm hg in association with proteinuria? *Am J Obstet Gynecol*. 2000;183:787-792

32. Tanner MS, De Guingand D, Reddy M, Rowson S, Rolnik DL, Da Silva Costa F, et al. The effect of preexisting medical comorbidities on the preeclamptic phenotype: A retrospective cohort study. *Hypertens*. 2021;40:336-345

33. Tanner MS, Malhotra A, Davey M-A, Wallace EM, Mol BW, Palmer KR. Maternal and neonatal complications in women with medical comorbidities and preeclampsia. *Pregnancy hypertension*. 2022;27:62-68

Summary

Baseline blood pressure, body mass index, age and parity all influence the course of blood pressure through pregnancy. But I'm most interested in baseline blood pressure and BMI. First, because their association with subsequent blood pressure is the strongest; and second, because we have data tying both a high baseline blood pressure (i.e. essential hypertension) and a high BMI (i.e. obesity) to fewer complications from preeclampsia.

As we discussed, fewer complications indicates that either these characteristics imbue a protective effect on women with preeclampsia, or they contribute to a propensity for being diagnosed with preeclampsia. Our data from Chapter Four indicates a logical explanation for the latter. There are systematic differences in blood pressure throughout pregnancy depending on maternal characteristics. And this will lead to systematic differences in how likely women are to be diagnosed with preeclampsia. This leads to both under- and over-diagnosis.

Consider two women at 34 weeks' gestation, presenting with a blood pressure of 135/85mmHg and proteinuria. Should we be more concerned about the woman who has obesity and type 2 diabetes and began pregnancy with a blood pressure of 130/80mmHg; or the woman who had a baseline blood pressure at 90/60mmHg and has a low BMI? The latter case is likely to be more concerning. But if the first woman has an ever-so-slightly higher blood pressure, or sees a clinician who is concerned due to her obesity and diabetes, she may be diagnosed (unnecessarily) while the second woman, who is likely at far higher risk of complications, remains undiagnosed.

Furthermore, the associations we have seen between blood pressure and BMI are not restricted to only those women above a certain threshold. The relationship is direct. A woman does not need to have obesity or essential hypertension to expect to have her blood to be influenced by these characteristics. There is a difference between a woman with a BMI of 22 and a BMI of 27, just as there is between a woman with a BMI of 27 and a woman with a BMI of 32. If, on a continuous scale, we see differences in blood pressure associated with maternal characteristics, we will likely also see differences in the diagnosis of preeclampsia and in the likelihood of complications.

Thus in Chapter Five we circled back to Chapter Two and Three. But this time we looked at the direct relationship between baseline blood pressure and BMI and complications from preeclampsia looked at the direct relationship between complications from preeclampsia, and baseline blood pressure and BMI.

Chapter Five

"We look for medicine to be an orderly field of knowledge and procedure. But it is not. It is an imperfect science, an enterprise of constantly changing knowledge, uncertain information, fallible individuals, and at the same time lives on the line. There is science in what we do, yes, but also habit, intuition, and sometimes plain old guessing. The gap between what we know and what we aim for persists. And this gap complicates everything we do."

Atul Gawande, *Complications: A Surgeon's Notes on an Imperfect Science*

Introduction

We observed in Chapters Two and Three a significant association between the presence of comorbidities and the likelihood of complications from preeclampsia. We have suggested that this association could arise due to systematic differences in either the prognosis *or* the diagnosis of preeclampsia.

In Chapter Four we showed that there were direct, continuous relationships between baseline BMI and blood pressure and the trajectory of blood pressure subsequently in pregnancy. And so in Chapter Five we put these findings together. We look at the women diagnosed with preeclampsia in Chapter Four, and we assess the relationship between baseline blood pressure and BMI and complications from preeclampsia.

We hypothesised that given these differences in blood pressure trajectory, there would be differences in the likelihood of complications from preeclampsia; and that those women with a higher blood pressure and BMI at baseline would suffer fewer complications. Not because these features are protective, but because these women may have been diagnosed with preeclampsia unnecessarily.

Maternal characteristics influence the prognosis of preeclampsia

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Key points

Question: Do maternal body mass index and baseline blood pressure influence the likelihood of complications from preeclampsia?

Findings: Among women diagnosed with preeclampsia, a higher body mass index and a higher blood pressure in the first half of pregnancy were associated with a lower incidence of severe complications.

Meaning: Maternal characteristics are strongly associated with the likelihood of complications from preeclampsia. Using for all women the same threshold to diagnose preeclampsia risks mischaracterising the prognosis of the syndrome.

Abstract

Importance: Obesity and elevated blood pressure are risk factors for developing preeclampsia. However, evidence is sparse regarding their effect on the outcomes from preeclampsia.

Objective: To determine whether body mass index and blood pressure influence the outcomes of women diagnosed with preeclampsia.

Design: This retrospective cohort study involved women giving birth following a diagnosis of preeclampsia between 2016- 2019.

Setting: One tertiary and two secondary maternity hospitals.

Participants: Women diagnosed with preeclampsia (n = 671), identified via maternity records.

Exposure: Body mass index and blood pressure.

Main outcome and measures: A composite of maternal complications, stillbirth, or a birthweight below the third centile. Maternal complications included eclampsia, placental abruption, haemolysis, elevated liver enzymes low platelets syndrome, death, or intensive care unit admission. We evaluated the association between complications and body mass index and blood pressure, using them first as continuous predictors, then using them to divide the women into groups.

Results: Of the 671 women with preeclampsia we studied, 76 (11.3%) suffered a severe complication. Higher body mass index and baseline blood pressure were associated with fewer complications (risk ratio for an increase of 5kg/m^2 in body mass index 0.76, 95% confidence interval [0.61, 0.93]; risk ratio for 10mmHg increase in mean arterial pressure 0.73 [0.59, 0.89]). The lowest rate of complications was seen in women with obesity and a higher baseline blood pressure (6/149, 4.0%); the highest, women without obesity and with a lower baseline blood pressure (48/293, 16.4%, OR 4.69 [2.10 – 12.4]).

Conclusions and relevance: Heavier women with a higher blood pressure are suffer fewer complications following a diagnosis of preeclampsia. Some may be unnecessarily diagnosed. This should spark a review of how we diagnose preeclampsia. Maternal characteristics should form part of the equation.

Introduction

Preeclampsia, the onset of hypertension and organ dysfunction in pregnancy,[1] is associated with 10-15% of maternal[2,3] and 10% of perinatal mortality[4] globally. It develops when impaired remodelling of the uterine spiral arteries leads to a hypoxic placenta, which releases pro-inflammatory and anti-angiogenic proteins into the maternal circulation.[5] Widespread endothelial dysfunction develops, followed by organ damage.[6,7]

There remains no diagnostic test for preeclampsia. Clinicians rely on clinical diagnosis, which can be subjective. Two women may have both hypertension and proteinuria, the cardinal signs of preeclampsia; but the severity of their syndrome, and their prognosis, may be vastly different. A higher body mass index (BMI) is associated with a higher blood pressure[8] and more proteinuria[9] through pregnancy; and higher blood pressure is independently associated with proteinuria.[10,11] Proteinuria and hypertension may, for heavier women with higher blood pressures, reflect a physiological response to pregnancy. In contrast, a woman with a low BMI who rapidly develops hypertension and proteinuria in the early third trimester is likely to be at high risk of complications.

Despite their differences, these women are diagnosed and treated under the same framework. There is little research observing how their outcomes may differ. We thus evaluated how maternal BMI and blood pressure influence the likelihood of complications for women diagnosed with preeclampsia.

Methods

Monash Health Humans Research Ethics Committee approved the study (#73135). Data were retrieved from Birthing Outcomes System (BOS) database records. Clinicians record data throughout pregnancies on BOS, including maternal demographics, pregnancy care, and complications.

Women were included if they had delivered at our institution between 2016 and 2019, were diagnosed with preeclampsia, and had at least one BP measurement taken prior to 16 weeks gestation.

Systolic and diastolic blood pressure and BMI were taken from the first recorded visit. Mean arterial pressure (MAP) was calculated as 1/3 systolic plus 2/3 diastolic blood pressure. Preeclampsia and other complications were recorded as documented by treating staff. Our primary outcome was the frequency of a composite outcome of severe maternal complications, stillbirth, a birthweight below the third centile, or birth prior to 34 weeks gestation. Severe maternal complications included maternal death, intensive care unit (ICU) admission, placental abruption, or eclampsia. Other outcomes included a 5 minute APGAR score <7, neonatal ICU admission, birthweight and gestation at delivery.

We used Poisson regression to evaluate associations between baseline MAP and BMI as continuous variables and the likelihood of suffering a complication. We then identified the BMI and MAP cut-offs that had the highest area under receiver operating curve (AUC) for identifying women who did not develop complications. We used these two cut-offs to divide the cohort into four groups.

For each outcome, we calculated unadjusted odds ratios (OR) and 95% confidence intervals (CI). We compared the highest risk with the lowest-risk group; and the highest and lowest risk groups with the other three groups.

Results

There were 671 women in our study. The mean (standard deviation) age was 31.8 (5.6) years and BMI 28.7 (6.6) kg/m^2; 54% were nulliparous (Table 1); and 107 (15.9%) of women or their neonates suffered a complication (Table 1).

Table 1. Baseline demographics and outcomes	Study population (n = 671)
Age (years)	31.8 (5.6)
Body mass index (kg/m^2)	28.7 (6.6)
Parity	
0	358 (53.5%)
1-3	286 (42.6%)
4+	27 (4%)
Region of birth	
Australia	335 (49.9%)
East/South East Asia	199 (29.7%)
Middle East	37 (5.5%)
Europe/North America	67 (10.0%)
South/Central America	3 (0.4%)
Africa	30 (4.5%)
Smoked during pregnancy	52 (13.2%)
Any severe complication	107 (15.9%)
Maternal complication	17 (2.5%)
Placental Abruption	4 (0.6%)
Eclampsia	5 (0.7%)
ICU admission	8 (1.2%)
Stillbirth	4 (0.6%)
Birthweight <3rd centile	55 (8.2%)
Birth <34 weeks gestation	57 (8.5%)
Birth <37 weeks gestation	180 (26.8%)
NICU admission	57 (8.5%)
5 minute APGAR <7	22 (3.3%)

NICU, neonatal intensive care unit admission; Data given as number (%) or mean (standard deviation).

BMI and baseline blood pressure

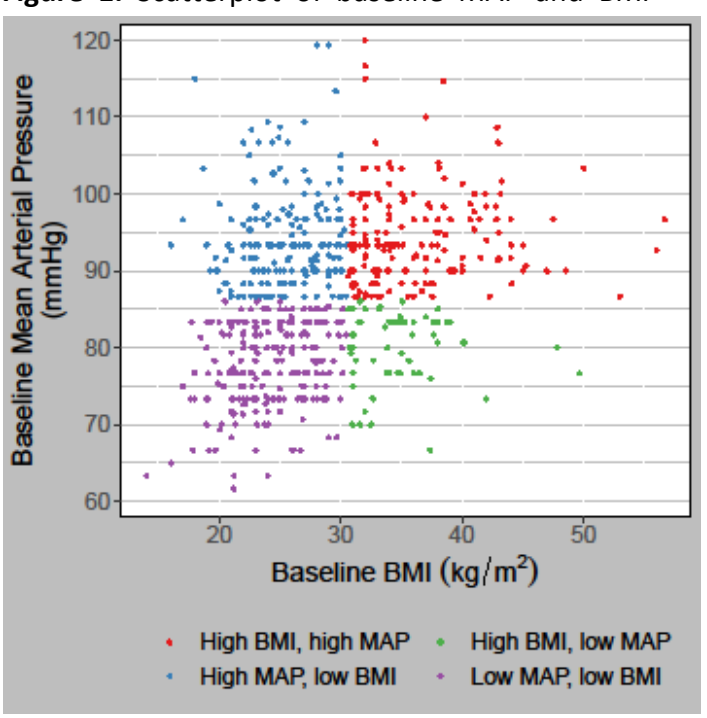
A higher baseline BMI was associated with a significant reduction in the odds of any severe complication (β = 0.95, 95% confidence interval [0.91, 0.99], p = 0.01) and a birthweight below the 3rd centile (β = 0.95 [0.91, 0.99], p = 0.04); a significantly higher birthweight (β = 20 [12-29], p < 0.001). Baseline BMI had no significant association with maternal complications or birth before 34 or 37 weeks gestation.

A higher baseline MAP was associated with a significant reduction in the odds of a severe complication, (β = 0.97 [0.95, 0.99], p < 0.001); a maternal complication (β = 0.95 [0.90, 0.99], p = 0.03); and a birthweight below the third centile (β = 0.97 [0.94, 0.99], p = 0.019). There was no significant association between baseline MAP and birth before 34- or 37- weeks gestation.

Group-wise analysis

A BMI cut-off of 30.5kg/m^2 and a MAP cutoff of 86mmHg (equal to 120/70mmHg) gave the highest AUC for identifying women who suffered complications. Thus we had four groups: Group 1 (n = 173) had a baseline MAP >86mmHg and BMI >30.5kg/m^2; Group 2 (n = 201), a baseline MAP >86mmHg and BMI ≤30.5kg/m^2; Group 3 (n = 59), a MAP ≤86mmHg & BMI >30.5kg/m^2; Group 4 (n = 238), a MAP ≤86mmHg, BMI ≤30.5kg/m^2. (Figure 1).

Figure 1. Scatterplot of baseline MAP and BMI



Red is Group 1 (High BMI, medium MAP); Blue, Group 2 (High MAP, medium BMI); Green, Group 3 (Low BMI, medium MP); Purple, Group 4 (Low MAP, medium BMI).

Table 2. Core maternal and neonatal outcomes, grouped by body mass index and mean arterial pressure.							
Group	**1**	**2**	**3**	**4**	**Risk Ratio/*β* (95% CI)**		
N	**172**	**202**	**58**	**239**	**4 versus 1**	**4 versus 1-3**	**2-4 versus 1**
Core Outcomes							
Any Severe complication	12 (7.0%)	30 (14.9%)	11 (19.0%)	54 (22.6%)	3.89 (2.08 – 7.86)‡	2.09 (1.37 – 3.17)‡	3.14 (1.74 – 6.16)‡
Any maternal complication	2 (1.2%)	2 (1.0%)	0 (0.0%)	13 (5.4%)	4.89 (1.33 – 31.54)*	6.15 (2.15 – 22.05)†	2.63 (0.73 – 16.83)
Abruption	1 (0.6%)	1 (0.5%)	0 (0%)	2 (0.8%)	–	–	–
Eclampsia	0 (0%)	1 (0.5%)	0 (0%)	4 (1.7%)	–	–	–
ICU Admission	1 (0.6%)	0 (0%)	0 (0%)	7 (2.9%)	–	–	–
Stillbirth	1 (0.6%)	1 (0.5%)	1 (1.7%)	1 (0.4%)	0.72 (0.03 – 18.20)	0.60 (0.03 – 4.71)	1.03 (0.13 – 20.90)
Birthweight <3rd centile	3 (1.7%)	17 (8.5%)	8 (13.6%)	27 (11.3%)	6.48 (2.29 – 27.12)‡	1.74 (1.02 – 2.96)*	5.97 (2.20 – 24.54)†
Birth <34 weeks gestation	8 (4.7%)	17 (8.4%)	8 (13.8%)	24 (10.0%)	2.29 (1.04 – 5.56)‡	1.35 (0.77 – 2.33)	2.23 (1.09 – 5.19)*
Other Outcomes							
Birth <37 weeks gestation	44 (25.6%)	61 (30.2%)	14 (24.1%)	61 (25.5%)	1.00 (0.64 – 1.57)	0.90 (0.63 – 1.29)	1.09 (0.74 – 1.63)
NICU admission	11 (6.4%)	20 (10.0%)	5 (8.5%)	21 (8.8%)	1.37 (0.68 – 2.96)	1.05 (0.61 – 1.79)	1.44 (0.78 – 2.93)
5 minute APGAR <7	4 (2.3%)	9 (4.5%)	2 (3.4%)	7 (2.9%)	1.26 (0.38 – 4.81	0.84 (0.32 – 2.00)	1.55 (0.58 – 5.37)
Birthweight (g)	3155 (666)	2862 (746)	2975 (931)	2851 (793)	-305 (-155, -454)‡	-140 (-261, -18)*	-289 (-421, -157)‡
Birth GA (weeks)	37.6 (36.9, 39.0)	37.4 (36.5, 38.4)	38.5 (37.1, 39.9)	37.9 (36.9, 39.1)	-0.2 (-0.7, 0.3)	0.04 (-0.4, 0.4)	-0.3 (-0.7, 0.2)

left half of the table gives number (%), mean (standard deviation) or median (interquartile range) of each outcome; the right half gives risk ratios ulated using Poisson regression or β coefficient calculated using linear regression and 95% confidence intervals. ICU, intensive care unit admission, centile, birthweight below the third centile. 3rd centile, birthweight below the third centile; NICU, neonatal intensive care unit; Birth GA, Gestational at birth. * denotes $p < 0.05$; †, $p < 0.01$; ‡, $p < 0.001$. Group 1 had a baseline MAP >86mmHg and BMI >30.5kg/m^2; Group 2 a baseline MAP >86mmHg BMI ≤30.5kg/m^2; Group 3, a MAP ≤86mmHg & BMI >30.5kg/m^2; Group 4, a MAP ≤86mmHg, BMI ≤30.5kg/m^2.

In Group 1, 12/172 women (7.0%) suffered a severe complication, lower than women in Group 2 (30/202, 14.9%); Group 3 (11/58, 19.0%). A complication was most common in Group 4 (54/238, 22.6%) (Table 2). Maternal complications were rarest in Groups 1 – 3 (0 – 1.2%) and most common in Group 4 (5.4%).

Group 1 also had the lowest (1.7%) rate of birthweights below the 3rd centile. Group 2's was not significantly different (8.5%), while Groups 3 and 4 were significantly higher (13.6% and 11.3%). The proportion of pregnancies resulting in delivery prior to 34 weeks gestation was similar in Groups 2 – 4 (8.4% - 13.8%), significantly higher than in Group 1 (4.7%). However, rates of birth before 37 weeks gestation were similar in all groups.

There were no significant differences in the rate of NICU admission or a low APGAR score, nor differences in the length of gestation, between the groups.

Discussion

In this retrospective cohort study of women diagnosed with preeclampsia, a higher BMI and blood pressure at baseline were strongly associated with higher birthweights and a lower likelihood of severe maternal complications or a birthweight below the third centile.

Key findings

These findings likely reflect differences in pathophysiology. There is a wealth of literature cataloguing the differences between early-onset preeclampsia, which arises before 34 weeks' gestation, and the late- onset subtype, which develops after 34 weeks. Early-onset preeclampsia is associated with placental insufficiency and angiogenic imbalance[12] and results in a severe syndrome.[13] Late-onset preeclampsia is linked to pre-existing maternal endothelial dysfunction, and is associated with fewer severe complications. The pathophysiology for these women is different, as is the management they receive. Based on our data, maternal characteristics may run parallel to gestation at diagnosis; that is, the differences between early-and late-onset preeclampsia are likely to be the same as the differences between women diagnosed with preeclampsia with and without vascular risk factors.

This work questions how we diagnose preeclampsia. The purpose of a diagnosis is to characterise, and identify ways to alter, the course of a pathological process.[14] The low rate of complications in women with a high BMI and blood pressure suggests these women may be unnecessarily diagnosed, as the label of preeclampsia is applied without these women being at a correspondingly increased risk of complications. The ideal management of preeclampsia may differ depending on maternal characteristics. Unnecessary diagnoses and interventions can lead to iatrogenic harm.

An alternative hypothesis is that women starting pregnancy with a low BMI and blood pressure are receiving inadequate monitoring, due to a perception that they are at low risk of complications. If this were to completely explain the variance in frequency of complications, we would expect to see the subgroups with the highest rate of complications to have the lowest rate of preterm birth, and vice-versa. However, our data indicates that Group 1, with the lowest risk of complications, also had the lowest risk of birth prior to 34 weeks' gestation. This indicates a difference in clinical severity, not merely surveillance practices. On the other hand, birth prior to 37 weeks was similarly common in all groups (24.1% - 30.2%). This suggests some role for the variable surveillance hypothesis.

Strengths and limitations

This study is limited by its small sample size. However, the large differences we observed should compel further research. Our work could also be criticised for its reliance on the accurate

coding of preeclampsia diagnoses. Clinicians may record a diagnosis of preeclampsia, even if a strict research definition is not met. This is selection bias. It means less-sick women are likely to be identified as having preeclampsia, and this is most likely to happen to women with higher BMI and BP.

However, this bias pervades every diagnosis of preeclampsia. As the diagnostic criteria has widened to place organ dysfunction alongside proteinuria,[15,16] the diagnosis of preeclampsia has become more subjective. Women are more likely to be diagnosed with preeclampsia if they are heavier, with a higher BP. They are more likely to be diagnosed, even if a strict research definition is not met. This bias towards over-diagnosis is what results in the vastly discrepant outcomes from preeclampsia.

If we look again at data from Groups 1 and 4 again, complications occurred in 12/173 (7.0%) and 54/238 (22.6%). For this difference to be purely due to selection bias, then the expected complication rate would be 22.6% in both groups. With 12 complications in Group 1, the number diagnosed would have to be 53 – leaving 120 (69%) of 173 women unnecessarily diagnosed. But if 69% of diagnoses are unnecessary, then of what value is the diagnosis?

Our data and conclusions are pragmatic. A diagnosis should be easily and universally applicable. A strict research definition may be creating the problem it is trying to solve – that is, ensuring all “like” cases are alike – by creating a divide between “clinical” and “research” preeclampsia. This reduces the generalisability of research findings. It is better to have a single definition that can be appropriately interpreted in both contexts.

Conclusions

Maternal characteristics significantly influence the likelihood of complications for women diagnosed with preeclampsia. Diagnostic criteria should account for this.

References

1. Brown M, Magee L, Kenny L, Karumanchi S, McCarthy F, Saito S, Hall D, Warren C, Adoyi G, Ishaku S. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy hypertension. 2018 05/01;13. doi:10.1016/j.preghy.2018.05.004.
2. Saleem S, McClure EM, Goudar SS, Patel A, Esamai F, Garces A, Chomba E, Althabe F, Moore J, Kodkany B, Pasha O, Belizan J, Mayansyan A, Derman RJ, Hibberd PL, Liechty EA, Krebs NF, Hambidge KM, Buekens P, Carlo WA, Wright LL, Koso-Thomas M, Jobe AH, Goldenberg RL, Global Network Maternal Newborn Health Registry Study I. A prospective study of maternal, fetal and neonatal deaths in low- and middle-income countries. Bulletin of the World Health Organization. 2014;92(8):605-612. eng. Epub 2014/06/05. doi:10.2471/BLT.13.127464. Cited in: Pubmed; PMID 25177075.
3. World Health Organisation. The World health report: 2005: make every mother and child count. Geneva: World Health Organization; 2019 2005. ISBN: 9241562900.
4. Vogel JP, Souza J, Mori R, Morisaki N, Lumbiganon P, Laopaiboon M, Ortiz-Panozo E, Hernandez B, Pérez-Cuevas R, Roy M. Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;121:76-88.
5. Redman CWG, Staff AC. Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity. Am J Obstet Gynecol. 2015 2015/10/01/;213(4, Supplement):S9.e1-S9.e4.
6. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol. 1999 Feb;180(2 Pt 1):499-506.
7. Roberts JM, Taylor RN, Goldfien A. Clinical and biochemical evidence of endothelial cell dysfunction in the pregnancy syndrome preeclampsia. American journal of hypertension. 1991 Aug;4(8):700-8.
8. Savitri AI, Zuithoff P, Browne JL, Amelia D, Baharuddin M, Grobbee DE, Uiterwaal CSPM. Does pre-pregnancy BMI determine blood pressure during pregnancy? A prospective cohort study. BMJ Open. 2016;6(8):e011626.
9. Macdonald-Wallis C, Lawlor DA, Heron J, Fraser A, Nelson SM, Tilling K. Relationships of Risk Factors for Pre-Eclampsia with Patterns of Occurrence of Isolated Gestational Proteinuria during Normal Term Pregnancy. PLOS ONE.
10. Peek M, Shennan A, Halligan A, Lambert PC, Taylor DJ, De Swiet M. Hypertension in pregnancy: Which method of blood pressure measurement is most predictive of outcome? Obstetrics & Gynecology. 1996 1996/12/01/;88(6):1030-1033.

11. Page EW, Christianson R. The impact of mean arterial pressure in the middle trimester upon the outcome of pregnancy. Am J Obstet Gynecol. 1976 Jul 15;125(6):740-6.
12. Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. Obstet Gynecol Surv. 2011 Aug;66(8):497-506
13. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal Morbidity Associated With Early-Onset and Late-Onset Preeclampsia. Obstetrics & Gynecology. 2014;124(4):771-781.
14. Tanner MS, Davey MA, Mol BW, Rolnik DL. The evolution of the diagnostic criteria of preeclampsia-eclampsia. *Am J Obstet Gynecol*. 2022;226:S835-s843
15. American College of Obstetricians and Gynaecologists. ACOG practice bulletin no. 202: Gestational hypertension and preeclampsia. *Obstetrics and Gynecology*. 2019;133:e1-e25
16. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension*. 2018;72:24-43

Summary

The results from Chapter Five are striking. Fewer than 3% of women in the lowest-risk group suffered complications – we may in fact be better off diagnosing not a single one of these women with preeclampsia! In contrast, nearly 1 in 5 women who developed preeclampsia with a low baseline blood pressure and BMI suffered complications.

This indicates that women with a high blood pressure and BMI are being diagnosed unnecessarily. There is no plausible explanation for why these comorbidities would genuinely offer a protective effect. But it is highly plausible, and in line with our prior expectations and findings throughout this thesis, that these characteristics are associated with an increased likelihood of being diagnosed with preeclampsia.

Above all else, this raises the question – for those women in the lowest risk group, should we even be diagnosing preeclampsia? I argue no. But even if the answer were yes, should we be treating these two groups of women – with risks of complications of 3% and 17% – the same? Surely not. If a diagnosis is to characterise the likelihood of complications and guide treatment accordingly, these two prognoses must be separated.

Chapter Five is my last analytical chapter. In Chapter Six, *The Evolution of the Diagnostic Criteria of Preeclampsia-Eclampsia*, we review and appraise the evidence that has underpinned the diagnostic criteria for preeclampsia through the past century, tying together our findings and putting them into context.

Chapter Six

"Writing laws is easy, but governing is difficult."
Leo Tolstoy, *War and Peace*

"There is room enough for an awful lot of people to be right about things and still not agree." Kurt Vonnegut, *The Sirens of Titan*

Introduction

While most theses begin with a literature review, this thesis ends with one. The executive summary of my thesis is that women with vascular risk factors are more likely to be diagnosed with preeclampsia, but many of these diagnoses are unnecessary. This demonstrates a flaw in how we diagnose preeclampsia. Different women with highly variable prognoses are considered the same – in diagnosis, in management and in research.

And so in Chapter Six we review the evidence that has guided the diagnostic criteria of preeclampsia as it evolved through the second half of the 20th and the early 21st century. How did we end up with this set of criteria? Is it the best we can do? And if not, what should we do differently in the future, both in clinical practice and research?

Chapter Six is my favourite chapter in this thesis, and it is the proudest I have been of a piece of work. I hope you enjoy reading it as much as I enjoyed writing it.

The evolution of the diagnostic criteria of preeclampsia-eclampsia

Michael S. Tanner, BMedSc (Hons); Mary-Ann Davey, DPH; Ben W. Mol, PhD; Daniel L. Rolnik, PhD

As the understanding of the pathophysiology of preeclampsia has improved, its diagnostic criteria have evolved. The classical triad of hypertension, edema, and proteinuria has become hypertension and organ dysfunction—renal, hepatic, neurologic, hematological, or uteroplacental. However, the most recent definitions have largely been based off consensus and expert opinion, not primary research. In this review, we explore how the criteria have evolved, particularly through the second half of the 20th and the beginning of the 21st century and offer a critical appraisal of the evidence that has led the criteria to where they stand today. Some key themes are the following: the debate between having a simple and convenient blood pressure cutoff vs a blood pressure cutoff that accounts for influencing factors such as age and weight, whether a uniform blood pressure threshold, a rise in blood pressure, or a combination is most discriminatory; whether existing evidence supports blood pressure and proteinuria thresholds in diagnosing preeclampsia, and whether using flow-charts and decision trees might be more appropriate than a single set of criteria. We also discuss the future of a preeclampsia diagnosis. We challenge the move toward a broad (vs restrictive) diagnosis, arguing instead for criteria that directly relate to the prognosis of preeclampsia and the response to treatments.

Key words: criteria, diagnosis, history, hypertensive disorders, management, preeclampsia

Introduction

Preeclampsia has a long history. It is a major cause of maternal and perinatal morbidity and mortality worldwide, preceding complications ranging from eclampsia and stroke to fetal growth restriction, prematurity, and stillbirth. As clinicians' understanding of the disease has evolved, so too have the criteria by which we diagnose the syndrome. The so-called classic triad of hypertension, proteinuria, and edema has been superseded with hypertension and organ dysfunction, be it renal, hepatic, hematological, neurologic, or placental, and it is now sufficient for a diagnosis. However, in recent guidelines, the diagnostic criteria for preeclampsia have commonly been updates of previous guidelines, often based on expert opinion and consensus. Ideally, diagnostic categories should be based on facts that help answer questions such as the following: which characteristics contribute to the patient's prognosis? And which therapeutics do we have to improve that prognosis? In this review, we explore the history of preeclampsia or eclampsia and critically appraise the evidence that brought us to the current diagnostic criteria. We discuss how preeclampsia might be diagnosed in the future and how ongoing and future research should be structured to best answer the 2 key questions of prognosis and treatment.

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Pre-20th Century

Hippocrates, who lived between 460 BC and 370 BC, said that headaches, drowsiness, and convulsions were of serious significance in pregnancy.[1] "Eclampsia" comes from the Greek "ἔκλαμψι2" which means a "light burst," and it is thought to have been first documented by the physician Johannes Varandeus in 1619.[2] In the 1700s, it was recognized that delivery was crucial for recovery, whereas eclampsia and epilepsy were distinguished by the middle of the century, with headaches identified as a prodromal symptom of the former.[3] By the end of the century, a link between edema and eclampsia was described, followed in the mid-1800s by the association of proteinuria and eclampsia.[3]

The Early 20th Century

In the late 19th and early 20th centuries, there was much speculation as to the etiology of preeclampsia. It was thought to be a renal disorder; compression of the uterus; epilepsy; or a bacterium coined as *Bacillus eclampsiae*, which turned out to be *Proteus vulgaris*.[4] Ahlfeld from Germany, in 1894, was perhaps the first to propose that preeclampsia was because of toxins produced in the placenta. The clinical presentation indicated as much, with Allbutt from Cambridge remarking in *The Lancet* in 1897 that the "vomiting, … nervous disturbance, … albuminuria, then enlargement of the heart" that are typical of preeclampsia would, if seen in a nonpregnant person, lead to the conclusion that "there is a circulating

toxin in the body."[5] As DeLee reflected in 1905, "…eclampsia is the disease of theories…only one point seems to be generally conceded, that eclampsia is because of the action of a toxin in the blood upon the nerve centres."[4]

By 1938, toxemia in pregnancy had been divided into mild preeclampsia, preeclampsia, and eclampsia, whereas nephritic toxemia remained a part of but separate to the rest of the spectrum.[6] Headache, vertigo, visual disturbances, retinal change, albuminuria, edema, and hypertension had been identified as manifestations, whereas convulsions indicated eclampsia and renal failure nephritic toxemia. The common feature was hypertension, defined "by convention" as a systolic blood pressure of 140 mm Hg and/or a diastolic pressure of ≥90 mm Hg.[6]

Because of the "lack of uniform terminology," the American Committee on Maternal Welfare (ACMW) in 1940 developed a classification for the toxemias of pregnancy.[7] The classification separated disorders not "peculiar" to pregnancy, which are, hypertensive and renal disease, from those "peculiar" to pregnancy, which are, preeclampsia and eclampsia. Preeclampsia was divided into mild and severe subtypes. Mild preeclampsia was characterized by hypertension ≥140/90 mm Hg, with slight or absent edema, and proteinuria of <6 g/L (equivalent to 2+). Two of hypertension, proteinuria, and edema were required. Two or more of moderate to severe edema, a blood pressure ≥160/100 mm Hg, or proteinuria greater than or equal to 6 g/L (3+ to 4+) constituted severe preeclampsia.

1950s

The Toxemias of Pregnancy by William J Dieckmann,[3] Professor at the University of Chicago, is a textbook published in 1952 that explores in detail the toxemias of pregnancy. Interestingly, Dieckmann[3] rejected the notion of a circulating toxin, stating that "the term toxemia is not well chosen because it suggests a circulating toxin which is probably not correct."

The textbook reproduces the "widely accepted" classification of the toxemias of pregnancy from the AC MW. The "general consensus" was that the blood pressure must be ≥140/90 mm Hg or more "for some time." The textbook offers no source for this. However, there is debate about whether a uniform cutoff is appropriate. Dieckmann[3] references a 1943 study from Master et al[8] from Mount Sinai Hospital, which found that both increasing age and weight were associated with higher blood pressure measurements. Master et al[8] proposed that there should not be a single blood pressure cutoff to define hypertension but that it should be a statistical definition: a reading of 2 standard deviations or more from the mean, given a certain age and weight.

Dieckmann[3] notes that this means that a uniform cutoff for hypertension in pregnancy will unnecessarily diagnose women, particularly older mothers, with preeclampsia or hypertensive disease. "Systolic and diastolic blood pressure level for classification of toxemia cannot be an arbitrary one, but must be adjusted to the patient's age and weight."[3]

He suggests that proteinuria of more than 0.3 g per 24 hours for 3 or more days is abnormal. It is unclear where this threshold originated. In a 1940 paper, he asserts that "usual qualitative tests reveal no protein in the urine of normal pregnancy patients, but a quantitative determination will yield 0 to 0.3 g per 24 hours." Edema was considered abnormal if it extended to the face and/or hands, or the ankles and/or tibia, despite being in bed.

Dieckmann[3] acknowledges that this set of criteria identifies women—those with only slight hypertension, or only a trace of proteinuria—as having preeclampsia, when they "should be classified as having pseudopreeclampsia." However, for simplicity's sake, he proposes that these women be included in the mild preeclampsia group.

Simplicity continued to be valued in the following years. Nelson, from Aberdeen Maternity Hospital, in a 1955 paper titled A Clinical Study of Pre-eclampsia,[9] proposed the following definition of preeclampsia that would still be in use 3 decades later: a rise in the diastolic blood pressure to 90 mm Hg or more on 2 separate occasions separated by at least a day. Neither proteinuria nor edema were required. The presence of proteinuria raised the classification to "severe." He defended the "extreme simplicity" of this schema, as "any investigation…which is almost entirely retrospective, must be kept to a simple set of rules which can be rigidly applied so that there is no temptation for the investigator to use their 'judgment'", which could cause "inconsistencies of diagnosis and grading."

Future research sought to evaluate the associations between blood pressure, proteinuria, and perinatal mortality. MacGillivray,[10] from the University of Aberdeen, in 1961, concluded that an increase in the diastolic blood pressure after 20 weeks' gestation of as little as 5 mm Hg was associated with increased perinatal mortality, and that the likelihood of developing proteinuria was associated with a diastolic blood pressure level of ≥90 mm Hg and not with a change in blood pressure. Women with a higher blood pressure early in pregnancy had a high likelihood of developing proteinuria. He thus supported Nelson's diastolic blood pressure cutoff of 90 mm Hg for diagnosing preeclampsia.

1970s

The American College of Obstetricians and Gynecologists (ACOG) published a comprehensive definition of preeclampsia in 1972. As reported by Chesley,[11] preeclampsia required the development of hypertension (≥140/90 mm Hg or a rise of ≥30/15 mm Hg) and significant proteinuria or edema after 20 weeks' gestation. However, the source of this threshold, *Obstetric-Gynecologic Terminology* by Edward Hughes,[12] does not offer any primary data in support. In the ensuing years, these criteria were only taken up intermittently.

Friedman and Neff,[13] in 1976, from Harvard Medical School, attempted to define the criteria for diagnosing hypertensive disorders of pregnancy that were based on "objective data" by developing thresholds that correlated with a risk of complications. In a cohort of 38,636 pregnancies, a maximum diastolic blood pressure of 75 to 84 mm Hg

during pregnancy correlated with the lowest rate of fetal mortality. Fetal mortality increased with a maximum diastolic blood pressure of 85 to 94 mm Hg, and above this level, there was a more marked increase. Fetal mortality was also increased with 2+ or more proteinuria, independent of blood pressure.

Increased blood pressure and proteinuria had a synergistic effect. A diastolic blood pressure of ≥95 mm Hg plus trace or less proteinuria, or a diastolic blood pressure of 84 mm Hg combined with 2+ or more proteinuria, were associated with an approximately 4-fold increased risk of fetal death. A diastolic blood pressure ≥85 mm Hg and proteinuria of at least 1+ was associated with a 7-fold increased risk of fetal mortality. The authors concluded that these findings "provide the basis for a proposed classification of hypertensive states in pregnant women." However, this did not lead to a widely accepted set of criteria.

A review by Davies[14] published in 1979 for the World Health Organization provided updated classifications from the ACMW. This classification differed from the existing ACOG criteria, chiefly because it "accepts hypertension *or* significant proteinuria *or* edema of the face and arms," whereas the ACOG guidelines required hypertension plus proteinuria or edema. Issues with this "babel of schemata," as Davies[14] described the conflicting criteria, were being noted, with a British Perinatal Mortality Survey, showing that 6.1% to 35.3% of women developed preeclampsia, depending on the criteria utilized.[14]

1980s

In 1986, the ACOG updated their 1972 criteria of Pregnancy-Induced Hypertension (PIH). As reported by Dildy and Cotton,[15] the diagnostic criteria were unchanged, including hypertension—either absolute or relative—and significant proteinuria or edema (Table 1). This guideline introduced the following criteria for severe PIH: involving significant hypertension (systolic ≥160 mm Hg or diastolic ≥110 mm Hg) or hypertension combined with organ dysfunction.

A 1987 World Health Organization guideline study group report[17] reiterated a diastolic blood pressure of 90 mm Hg as a "reasonable" cutoff for the diagnosis of hypertension in pregnancy. This was based off data from Friedmann and Neff,[13] as 90 mm Hg is halfway between 85 mm Hg (associated with perinatal mortality when seen with proteinuria) and 95 mm Hg (associated with perinatal mortality regardless of proteinuria) and off data from MacGillivray, as it is also associated with the later development of proteinuria.[10] However, if proteinuria is to remain part of the diagnostic criteria, why should a blood pressure threshold be chosen on the basis that is predicts proteinuria? It is more relevant to identify a blood pressure level that predicts adverse maternal and/or perinatal outcomes.

Conflicting proposals for the diagnosis of preeclampsia were published in April 1988. Davey and MacGillivray,[18] from the University of Cape Town, published theirs in the *American Journal of Obstetrics & Gynecology,* and Redman and Jefferies,[19] from John Radcliffe Hospital, Oxford, published in *The Lancet.*

Davey and MacGillivray's[18] guidelines had been approved by the International Society for the Study of Hypertension in Pregnancy (ISSHP) and by the International Committee of ISSHP in 1986 and also by the International Federation of Gynecology and Obstetrics in 1985. They considered the spectrum of hypertensive disorders to include gestational hypertension without proteinuria, gestational proteinuria without hypertension, and gestational proteinuric hypertension (preeclampsia).

They defined hypertension as a diastolic blood pressure ≥90 mm Hg on 2 consecutive readings, at least 4 hours apart, or a single reading ≥110 mm Hg. The use of a rise in blood pressure was abandoned, as "a rise of ~30 or 40 mm Hg may ~ fall within the normal statistical range," and "the absolute level of blood pressure provides the best guide to fetal and maternal prognosis and the development of proteinuria." The threshold of 90 mm Hg was given for 3 reasons. First, "simplicity, precision and convenience;" second, "it corresponds with defined statistical limits: 3 standard deviations above the mean in early pregnancy; 2 standard deviations above the mean between 34 and 38 weeks; and 1.5 standard deviations above the mean at term;" and third, "It corresponds to the point of inflection of the curve relating diastolic blood pressure to mortality."

There is some nuance to these conclusions. Firstly, as described by Master,[8] statistical limits are influenced by maternal characteristics such as age and body mass index. Secondly, the point of inflection of the curve relating diastolic blood pressure to mortality, according to Friedmann and Neff who the authors cite, is strictly speaking, between 75 and 84 mm Hg. Finally, this curve is heavily influenced by the development of proteinuria. In sum, the criteria are not firmly rooted in either the prognosis or the management of preeclampsia.

Davey and MacGillivray rejected suggestions that different cut-offs for hypertension should be used at different stages of pregnancy or different populations, as it would "confus(e) and vitiate (spoil or impair the quality of) comparison of results." They conclude that it is better to have 1 diagnosis with various interpretations in different populations, stages of pregnancy and clinical circumstances, as opposed to various diagnoses with one interpretation.[18]

In contrast, Redman and Jefferies[19] attempted to devise a classification that not only identified women at an elevated risk of adverse outcomes, but it also did so in such a way that accounted for the fact that preeclampsia is a disease predominantly, but not exclusively, seen in nulliparous women.

The authors proposed that a classification should focus on diastolic blood pressure, as nulliparous women tended to have a higher systolic, but not diastolic, blood pressure at booking than did multiparous women. In a cohort of 15,000 women, they found that when women had a large increase in diastolic blood pressure, those with a lower booking blood pressure were more likely to be nulliparous. Similarly, among

TABLE 1
Brief summary of the evolution of various diagnostic criteria for preeclampsia

Author	Year	Definition of preeclampsia	Hypertension criteria	Proteinuria/edema criteria
Dieckmann[3]	1952	One of edema, proteinuria, hypertension, symptoms	≥140 mm Hg systolic and/or ≥90 mm Hg diastolic	
Nelson[9]	1955	Gestational hypertension	≥90 mm Hg diastolic	
ACOG[12]	1972	Gestational hypertension plus proteinuria	Rise of 30 mm Hg Systolic or 15 mm Hg diastolic or ≥ 140/≥≥90	Proteinuria—0.3 g/L in 24-h urine collection
Davies[14]	1979	Gestational hypertension or significant proteinuria or edema of the face and arms, or any 2	+≥30/15 or ≥140/90	Edema: edema of the face and arms Proteinuria: 2+ on dipstick
ACOG[16]	1986	Gestational hypertension plus edema and/or proteinuria	+≥30/15 or ≥140/90	Edema: ≥1+ pitting edema after 12 h of bedrest; weight gain of ≥5 pounds in 1 week Proteinuria: ≥300 mg in a 24-h collection; urine protein concentration ≥1 g/L
WHO[17]	1987	Gestational hypertension plus proteinuria	≥140/90	Proteinuria: 300 mg in a clean-catch or midstream specimen or in a 24-h collection
Davey and MacGillivray[18]	1988	Gestational hypertension plus proteinuria	≥90 diastolic	Proteinuria: ≥ 300 mg per 24 h, or 2 dipstick x2
Redman and Jefferies[19]	1988	Gestational hypertension plus rise in blood pressure	+≥25 to ≥90 diastolic, from a booking <90	Nil
NHBPEWG[20]	1990	Gestational hypertension plus proteinuria	+≥30/15; if no reading from early in pregnancy available, ≥140/90	Proteinuria: 0.3 g or more in a 24-h specimen or 1+ dipstick in a random urine determination
ASSHP[21]	1993	Gestational hypertension; Severe preeclampsia = severe hypertension organ dysfunction	+≥25/15 or ≥140/90 Severe preeclampsia: ≥170/110	
CHSC[22]	1997	Gestational hypertension plus proteinuria	≥90 Diastolic	Proteinuria: ≥0.3 g in 24-h urine collection
NHBPEWG[23]	2000	Gestational hypertension plus proteinuria	≥140/90	Proteinuria: 1+ dipstick or 0.3 g in 24 h
ASSHP[24]	2000	Gestational hypertension plus organ dysfunction	≥140/90	Table 2
ISSHP[25]	2001	Research definition: Gestational hypertension plus proteinuria Clinical definition: Gestational hypertension plus organ dysfunction	≥140/90	Proteinuria: urinary excretion of 0.3 g protein or higher in a 24-h urine specimen
ACOG[26]	2002	Gestational hypertension plus proteinuria	≥140/90	Proteinuria: Urinary excretion of 0.3 g protein or higher in a 24-h urine specimen

Tanner. Evolution of the diagnosis of preeclampsia. Am J Obstet Gynecol 2022.

(continued)

TABLE 1
Brief summary of the evolution of various diagnostic criteria for preeclampsia *(continued)*

Author	Year	Definition of preeclampsia	Hypertension criteria	Proteinuria/edema criteria
ACOG[27]	2013	Gestational hypertension plus organ dysfunction	≥140/90	Proteinuria: Urinary excretion of 0.3 g protein or higher in a 24-h urine specimen, or 1+ dipstick
ISSHP[28]	2014	Gestational hypertension plus organ dysfunction	≥140/90	Table 2
ACOG[24]	2018	Gestational hypertension plus organ dysfunction	≥140/90	Table 2
ISSHP[29]	2018	Gestational hypertension plus organ dysfunction	≥140/90	Table 2

+ ≥30/15 means a rise in systolic blood pressure of 30 mm Hg systolic or diastolic of 15 mm Hg; ≥140/90 means an absolute systolic blood pressure of ≥140 mm Hg systolic or 90 mm Hg diastolic.

ACOG, American College of Obstetricians and Gynecologists; *ASSHP*, Australasian Society for the Study of Hypertension in Pregnancy; *CHSC*, Canadian Hypertension Society Conference; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *NHBPEWG*, National High Blood Pressure Education Working Group; *WHO*, World Health Organization.

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women who recorded a high maximum diastolic blood pressure, those with a greater increase were also more likely to be nulliparous. Nulliparity was thus associated with both a higher rise in *and* maximum diastolic blood pressure. Any subsequent classification of hypertensive disorders should thus involve both.

They found that perinatal mortality and the rate of proteinuria increased significantly among women, with a rise in the diastolic blood pressure of at least 30 mm Hg; and that birthweight, but not gestational age at delivery, was lower in those with a rise of >25 but <29 mm Hg. Thus, they suggested that a rise in the diastolic blood pressure of at least 25 mm Hg, from a booking diastolic blood pressure of <90 mm Hg to >90 mm Hg, should be diagnostic of preeclampsia. No proteinuria would be required.

The authors applied this to a second dataset of 15,000 women. Compared with Nelson's criterion, this criterion diagnosed preeclampsia in fewer women (11.5% vs 26.3%). The extra women diagnosed by Nelson's criteria were older, heavier, developed less proteinuria, and delivered at a later gestation; their babies had higher birthweights and lower mortality. Overall, the new criterion identified a more severe form of disease. However, the authors did not compare their criterion against the more specific 1972 ACOG classification. Nelson's criterion had already received criticism for offering too broad a definition.

The debate over the appropriate classification of preeclampsia prompted an editorial in The Lancet in 1989,[30] which challenged the idea that the hypertensive disorders of pregnancy required labeling and classification. "It is sufficient to know the risks and appropriate treatment of the various manifestations of hypertension in pregnancy," the editorial argues. It suggests that flow diagrams and decision analysis, with their use of data at the time of decision-making and their incorporation of the probability of adverse outcomes, are more pragmatic for management than strictly assigning women to having preeclampsia or not. Davey and MacGillivray[31] rejected the idea that a classification precludes the

use of flow diagrams, decision analysis, and further observations, arguing that classifying preeclampsia was "the first step ensuring that doctors and nurses mean the same things by the same words."

1990s

The 1990s saw consensus reports on hypertension in pregnancy from a range of groups, including the National High Blood Pressure Education Working Group (NHBPEWG) in 1990[20]; The Australasian Society for the Study of Hypertensive Disorders in Pregnancy (ASSHP) in 1993,[21] The American College of Obstetricians and Gynecologists (ACOG) in 1996[16]; and The Canadian Hypertension Society Conference (CHSC) in 1997.[22] Table 1 summarizes the similarities and differences.

The NHPEWG report defined hypertension as a rise in blood pressure of ≥30/15 mm Hg or an absolute blood pressure of ≥ 140/90 mm Hg. The ASSHP defined hypertension as a rise of ≥ 25/15 mm Hg, or an absolute level ≥ 140/90 mm Hg. The ACOG's 1996[1] guidelines used ≥140/90 mm Hg, and the CHSC only a diastolic ≥90 mm Hg. They also differed in the definition of preeclampsia. The NHPEWG and CHSC required gestational hypertension plus proteinuria; the ASSHP, only gestational hypertension, with organ dysfunction (including proteinuria) leading to a diagnosis of severe preeclampsia. The ACOG did not define preeclampsia but defined only PIH with organ dysfunction and/or severe hypertension, warranting a diagnosis of severe PIH.

2000s

New and updated guidelines from the NHBPEWG, the ASSHP, the ACOG, and the ISSHP followed in the early 2000s.

A few key changes were introduced to the NHBPEWG Report of 2000.[23] It abandoned the use of a rise in blood pressure as sufficient to diagnose hypertension. This followed work by North et al[32] in 1999, and Levine et al,[33] in 2000, who determined that women who experienced a rise in blood pressure of ≥ 30/15 mm Hg to a level <140/90 mm Hg, were not at a higher risk of complications than normotensive women without such a rise. Edema too was abandoned because of its high prevalence among healthy pregnant women.

The ASSHP consensus statement of 2000 was the first to offer a clinical diagnosis of preeclampsia, which included organ dysfunction beyond proteinuria (Table 1). Renal, hepatic, neurologic, hematological, and uteroplacental dysfunction were considered to be diagnostic of preeclampsia. This guideline maintained a 140/90 mm Hg cutoff for diagnosing hypertension in pregnancy, as it was "outside 2 standard deviations of the blood pressure mean in the normal pregnant population."

The ISSHP in 2001[25] concluded that further research comparing maternal and fetal outcomes between a "restrictive" definition of hypertension and proteinuria and an "inclusive" definition of hypertension and other organ dysfunction was warranted and that the criteria should remain restrictive. The ACOG's 2002 criteria[26] were based off the NHBPEPWG report from 2000, defining preeclampsia as elevated blood pressure plus significant proteinuria. Organ dysfunction was still considered a feature of "severe preeclampsia."

A decade later, there was a shift toward the "inclusive" definition of preeclampsia. The ACOG's 2013 guidelines abandoned the reliance on proteinuria for diagnosing preeclampsia, with other organ dysfunction now sufficient.[27] The ISSHP's updated recommendations in 2014[28] followed suit. An important distinction was that ISSHP considered uteroplacental dysfunction, such as fetal growth restriction, as diagnostic, whereas the ACOG did not. Conversely, pulmonary edema was included in the ACOG's but not the ISSHP's guidelines. Other differences were minor, such as cut-offs for platelet counts (<100,000/mL for ACOG, <150,000/mL for ISSHP) and liver enzymes (transaminases twice the upper limit of normal for ≥ ACOG, ≥ 40 IU/L for ISSHP). Table 2 summarizes the criteria for organ dysfunction. In 2018, both the groups published updated guidelines,[34,29] which remained largely unchanged.

Subtypes of Preeclampsia

Preeclampsia is commonly classified into an early-onset or a late-onset disease (arising before or after 34 weeks gestation). The 2 subtypes have been described as "qualitatively different."[35] Early-onset preeclampsia is associated with a high-resistance, low-output hemodynamic state, whereas late-onset disease demonstrates a low-resistance, high-output state.[36] They share some but not all risk factors, and the effect of each risk factor differs. Angiogenic biomarkers that have prognostic value are higher in early- than late-onset disease,[37] and maternal and perinatal outcomes are worse in early-onset disease.[38]

However, these differences exist on a spectrum. The earlier preeclampsia develops, the more severe the angiogenic imbalance and the worse the outcomes are. The ASpirin for evidence-based PREeclampsia prevention trial showed that aspirin reduces the incidence of preterm preeclampsia but has no influence on term disease.[39] However, it is not clear whether this reflects a protective effect, or whether aspirin delays the onset of preeclampsia, meaning women give birth before it develops.

No clear pathologic evidence differentiates early- and late-onset preeclampsia. There is an ongoing debate as to whether preeclampsia is a placental disorder that leads to disruption of the maternal endothelial system or if placental dysfunction is secondary to suboptimal maternal cardiovascular adaptation to pregnancy.[40] Both are likely true, and so it is the varying extent to which each process occurs that leads to disparate prognoses. Gestation at onset is a useful heuristic for judging the likely prognosis of preeclampsia, but it must be remembered that 34 weeks is not a hard cutoff.

Summary and Future Directions

The criteria defining preeclampsia have not changed significantly in recent years, but the evidence underpinning them has.

Blood Pressure

The evidence underpinning blood pressure thresholds in the most recent ACOG

and ISSHP criteria can be retraced through guidelines to the 2000[23] and 1990[20] NHBPEWG reports and to a 1988 report from the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure[41] that focused on the nonpregnant population. This report has been superseded by the 2017 American Heart Association/American Cardiology Society guidelines, which lowered the threshold for stage 1 hypertension to 130 mm Hg systolic and/or 80 mm Hg diastolic, instead of 140 and 90 mm Hg, respectively. Recent evidence for pregnant women, too, suggests that 130/80 mm Hg is the threshold above which the risk of perinatal complications begins to rise.[42,43] This raises the question whether 140/90 mm Hg is an outdated threshold.

Proteinuria

Despite occasional protestations to the contrary,[44] the prognostic significance of proteinuria in preeclampsia remains unclear. A 24-hour protein ≥300 mg is, as the ISSHP criteria from 2018 reflects, "more a time-honored value than one with scientific proof."[34] In justifying this threshold, the ACOG's 2018 guideline[28] cites the 2000 NHBPEP working group report (a consensus report)[23], a meta-analysis studying the relationship between significant proteinuria on spot urine protein-creatinine ratio (PCR) and 24 hour[45], and a cohort study that determined among pregnant women 95th and 99th centile cut-offs for proteinuria.[46] None is based on a relationship with the prognosis.

A 2009 meta-analysis concluded that proteinuria was "a poor predictor of either fetal or maternal complications in women with preeclampsia,"[47] and prospective research has shown that significant proteinuria is common without developing preeclampsia.[48] Although some studies suggest that proteinuria in preeclampsia is associated with more severe disease,[49] these should be interpreted carefully, as a higher blood pressure is associated with more proteinuria. Thus, any relationship between proteinuria and complications may be better explained by blood pressures (the collider bias[50]).

TABLE 2
Differences in the definitions of organ dysfunction in the diagnostic criteria for preeclampsia

Criterion or organ system	ASSHP,[24] 2000, Brown et al,[25] 2001	ACOG,[27] 2013; ACOG,[34] 2018	Tranquilli et al,[28] 2014; Brown et al,[29] 2018
Proteinuria	300 mg/24 h or spot urine PCR ≥30 mg/mmoB00 mg/24 h; urine PCR ≥ 0.3; dipstick 1+ [2013], 2+ [2018]	≥ 1+, 30 mg/dL; urine PCR ≥ 30 mg/mmol (0.3 mg/mg)	
Other renal	Creatinine ≥0.09 mmol/L [90 mmol/L] or oliguriaSerum creatinine >1.1 mg/dL; doubling of serum creatinine in absence of other renal disease	Creatinine ≥90 mmol/L (1 mg/dL)	
Hepatic	Raised serum transaminases and/or severe epigastric/right upper quadrant pain	Liver transaminases ≥ twice the normal concentration	Alanine aminotransferase or aspartate aminotransferase ≥40 IU/L
Neurologic	Convulsions; hyperreflexia with clonus; severe headaches with hyperreflexia; persistent visual disturbances	Cerebral or visual symptoms	Eclampsia; altered mental status; blindness; stroke; clonus; severe headaches; persistent visual scotomata
Hematological	Thrombocytopenia; disseminated intravascular coagulation; hemolysis	Platelets <100,000/mL	Platelets < 150,000/mL; disseminated intravascular coagulation, hemolysis
Other	Fetal growth restriction	Pulmonary edema	Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, stillbirth)

ACOG, American College of Obstetricians and Gynecologists; *ASSHP*, Australasian Society for the Study of Hypertension in Pregnancy; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *Urine PCR*, urine protein: creatinine ratio.
Tan et al. Evolution of the diagnosis of preeclampsia. Am J Obstet Gynecol 2022.

Finally, measuring proteinuria is challenging. A 24-h collection is considered as gold-standard but is "frequently inaccurate"[51]. Urine PCR is also imperfect. Two meta-analyses suggest that a cutoff of 0.26-0.30 has a sensitivity of 81% to 83% and specificity of 76% for detecting proteinuria >300 mg in a 24-hour collection.[45,52] However, even if these tests were perfect, sparse to nonexistent data ties proteinuria to outcomes from preeclampsia.

Other Organ Dysfunction

Research into links between organ dysfunction and complications is also limited. Reddy et al[53] showed that women meeting the ACOG's 2018 thresholds for low platelets and elevated liver enzymes had odds ratios (OR) for complications of 3.70 (95% confidence interval [CI], 1.98-6.89) and 2.32 (95% CI, 1.39-3.87), respectively. Women meeting the ISSHP's less restrictive thresholds had lower ORs, of 2.09 (95% CI, 1.34-3.24) and 1.66 (95% CI, 1.04-2.67). Symptoms such as headache were not associated with complications. Future research should take a follow a similar approach.

Future Criteria

The diagnostic criteria of preeclampsia are again becoming a "babel of schemata"[14], and once more, there is debate about what the goals of a preeclampsia diagnosis should be.

A recurring theme in prospective studies[54,55] is that compared with a narrow definition (ie, hypertension and proteinuria), a broad definition has a higher sensitivity for identifying women who suffer complications but a lower specificity. Authors have supported this, as "the purpose of classification is to identify groups of women who require specific care,"[55] such as closer monitoring.

This makes sense. However, it implies that if a woman does not meet the diagnostic criteria, they would not require closer monitoring. However, preeclampsia represents a spectrum of disease. Those who fall immediately on either side of the criteria's dividing line are similar. Clinical judgment should be applied, and the lack of a diagnosis should not exclude a woman from closer surveillance.

There are other implications to broadening the criteria. Evidence-based guidelines are only useful insofar as the population they are applied to reasonably mimics the population they were developed in. If women are diagnosed with preeclampsia without meeting a strict research definition, the guidelines will be less applicable. Varying definitions also make it difficult to compare the incidence, outcomes, and prognosis between studies. There are also economic implications—closer monitoring of women at a low risk of complications stretches the resources of hospitals and clinicians.

The diagnosis and classification of preeclampsia should instead be rooted in a relationship with prognosis and treatment. Prognostic studies and randomized controlled trials should be developed around the following 2 questions: what is the natural course of preeclampsia, and how can treatment alter it?

Angiogenic biomarkers are potentially valuable here.[56,57] However, much work has focused on a diagnosis of preeclampsia and not its complications as the outcome.[56,58] Ruling out a diagnosis of preeclampsia in the ensuing weeks may reduce unnecessary interventions and admissions but has limited bearing on prognosis. Knowing the likelihood of a woman suffering a serious complication in the coming weeks is far more important. This is where research should focus.

Research into treatments should focus on how women respond and why. The Control of Hypertension in Pregnancy Study trial[59] showed that in women with hypertension in pregnancy, tight blood pressure control was not associated with better outcomes than less-tight control. But as Lees and Ferrazzi remarked "Would it not have been instructive – to understand the underlying differences in womens' cardiovascular status and in this light the response to treatment?".[60]

This reflects a difference in how we think in the clinical and research settings. Clinicians make a diagnosis such as preeclampsia, then move to treatment, deciding (for example) whether induction of labor or expectant management is best. This leads to a descriptive criteria for preeclampsia, as we identify and record how the disease manifests. In contrast, research begins with the intervention, then identifies those who respond to it. Consider the HYPITAT trial, which found that induction at 37 weeks improves maternal outcomes for women with mild hypertensive disease.[61] Treatment first, then the population who benefit.

How we diagnose and manage preeclampsia will continue to evolve in the future, but it should always be guided by following the most important questions in medicine: what is the prognosis of this patient? What can we do about it? ■

REFERENCES

1. Chadwick J, Mann WN; Hippocrates. The medical works of Hippocrates. Oxford, England: Blackwell Scientific Publications; 1950.
2. Bell MJ. A historical overview of preeclampsia-eclampsia. J Obstet Gynecol Neonatal Nurs 2010;39:510–8.
3. Dieckmann WJ. The Toxemias of pregnancy. St. Louis, MO: Mosby; 1952.
4. Loudon I. Some historical aspects of toxaemia of pregnancy. A review. Br J Obstet Gynaecol 1991;98:853–8.
5. Allbutt TC. Albuminuria in pregnancy. Lancet 1897;149:579–82.
6. Wood JE Jr, Nix H. Hypertension in the late toxemias of pregnancy. JAMA 1938;110:332–7.
7. Mussey RD, Hunt AB. The toxemias of pregnancy and the management of parturition. JAMA 1941;117:1309–13.
8. Master AM, Dublin LI, Marks HH. The normal blood pressure range and its clinical implications. J Am Med Assoc 1950;143:1464–70.
9. Nelson TR. A clinical study of pre-eclampsia. I. J Obstet Gynaecol Br Emp 1955;62:48–57.
10. MacGillivray I. Hypertension in pregnancy and its consequences. J Obstet Gynaecol Br Commonw 1961;68:557–69.
11. Chesley LC. Hypertension in pregnancy: definitions, familial factor, and remote prognosis. Kidney Int 1980;18:234–40.
12. Hughes EC. Obstetric-gynecologic terminology. FA Davis, Philadelphia;1972: 422.
13. Friedman EA, Neff RK. Hypertension-hypotension in pregnancy. Correlation with fetal outcome. JAMA 1978;239:2249–51.
14. Davies AM. Epidemiology of the hypertensive disorders of pregnancy. Bull World Health Organ 1979;57:373–86.
15. Dildy GA 3rd, Cotton DB. Management of severe preeclampsia and eclampsia. Crit Care Clin 1991;7:829–50.
16. ACOG technical bulletin. Hypertension in pregnancy. Number 219–January 1996

(replaces no. 91, February 1986). Committee on Technical Bulletins of the American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 1996;53:175–83.
17. World Health Organisation Group. *The hypertensive disorders of pregnancy;* Technical Report Series No. 758. WHO: Geneva, 1987.
18. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. Am J Obstet Gynecol 1988;158:892–8.
19. Redman CWG, Jefferies M. Revised definition of pre-eclampsia. Lancet 1988;1:809–12.
20. National High Blood Pressure Education Program working group report on high blood pressure in pregnancy. Am J Obstet Gynecol 1990;163:1691–712.
21. Brown MA, Gallery EDM, Gatt SP, et al. Management of hypertension in pregnancy: executive summary. Med J Aust 1993;158:700–2.
22. Helewa ME, Burrows RF, Smith J, Williams K, Brain P, Rabkin SW. Report of the Canadian Hypertension Society consensus conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. CMAJ 1997;157:715–25.
23. Gifford RW, August PA, Cunningham G, et al. Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. Am J Obstet Gynecol 2000;183:S1–22.
24. Brown MA, Hague WM, Higgins J, et al. The detection, investigation and management of hypertension in pregnancy: full consensus statement. Aust N Z J Obstet Gynaecol 2000;40:139–55.
25. Brown MA, Lindheimer MD, de Swiet M, Assche AV, Moutquin J-M. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20:IX–XIV.
26. American College of Obstetricians and Gynecologists–Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol 2002;99:159–67.
27. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–31.
28. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. Pregnancy Hypertens 2014;4:97–104.
29. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension 2018;72:24–43.
30. Classification of hypertensive disorders of pregnancy. Lancet 1989;1:935–6.
31. Classification of hypertensive disorders of pregnancy. Lancet 1989;2:112–3.
32. North RA, Taylor RS, Schellenberg JC. Evaluation of a definition of pre-eclampsia. Br J Obstet Gynaecol 1999;106:767–73.
33. Levine RJ, Ewell MG, Hauth JC, et al. Should the definition of preeclampsia include a rise in diastolic blood pressure of >/= 15 mm Hg to a level <90 mm Hg in association with proteinuria? Am J Obstet Gynecol 2000;183:787–92.
34. American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia. ACOG Practice Bulletin no. 202. Obstet Gynecol 2019;133:e1–25.
35. von Dadelszen P, Magee LA, Roberts JM. Subclassification of preeclampsia. Hypertens Pregnancy 2003;22:143–8.
36. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension 2008;52:873–80.
37. Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. Obstet Gynecol Surv 2011;66:497–506.
38. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet Gynecol 2014;124:771–81.
39. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017;377:613–22.
40. Thilaganathan B. Pre-eclampsia and the cardiovascular-placental axis. Ultrasound Obstet Gynecol 2018;51:714–7.
41. The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1988;148:1023–38.
42. Sisti G, Williams B. Body of evidence in favor of adopting 130/80 mm Hg as new blood pressure cut-off for all the hypertensive disorders of pregnancy. Medicina (Kaunas) 2019;55:703.
43. Reddy M, Rolnik DL, Harris K, et al. Challenging the definition of hypertension in pregnancy: a retrospective cohort study. Am J Obstet Gynecol 2020;222:606.e1–21.
44. Dong X, Gou W, Li C, et al. Proteinuria in preeclampsia: not essential to diagnosis but related to disease severity and fetal outcomes. Pregnancy Hypertens 2017;8:60–4.
45. Morris RK, Riley RD, Doug M, Deeks JJ, Kilby MD. Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis. BMJ 2012;345:e4342.
46. Kuo VS, Koumantakis G, Gallery ED. Proteinuria and its assessment in normal and hypertensive pregnancy. Am J Obstet Gynecol 1992;167:723–8.
47. Thangaratinam S, Coomarasamy A, O'Mahony F, et al. Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. BMC Med 2009;7:10.
48. Phillips JK, McBride CA, Hale SA, Solomon RJ, Badger GJ, Bernstein IM. Examination of prepregnancy and pregnancy urinary protein levels in healthy nulliparous women. Reprod Sci 2017;24:407–12.
49. Bramham K, Poli-de-Figueiredo CE, Seed PT, et al. Association of proteinuria threshold in pre-eclampsia with maternal and perinatal outcomes: a nested case control cohort of high risk women. PLoS One 2013;8:e76083.
50. Whitcomb BW, Schisterman EF, Perkins NJ, Platt RW. Quantification of collider-stratification bias and the birthweight paradox. Paediatr Perinat Epidemiol 2009;23:394–402.
51. Côté AM, Firoz T, Mattman A, Lam EM, von Dadelszen P, Magee LA. The 24-hour urine collection: gold standard or historical practice? Am J Obstet Gynecol 2008;199:625.e1–6.
52. Papanna R, Mann LK, Kouides RW, Glantz JC. Protein/creatinine ratio in preeclampsia: a systematic review. Obstet Gynecol 2008;112:135–44.
53. Reddy M, Fenn S, Rolnik DL, et al. The impact of the definition of preeclampsia on disease diagnosis and outcomes: a retrospective cohort study. Am J Obstet Gynecol 2021;224:217.e1–11.
54. Lai J, Syngelaki A, Nicolaides KH, von Dadelszen P, Magee LA. Impact of new definitions of preeclampsia at term on identification of adverse maternal and perinatal outcomes. Am J Obstet Gynecol 2021;224:518.e1–11.
55. Magee LA, Singer J, Lee T, et al. The impact of pre-eclampsia definitions on the identification of adverse outcome risk in hypertensive pregnancy - analyses from the CHIPS trial (Control of hypertension in Pregnancy Study). BJOG 2021;128:1373–82.
56. Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med 2016;374:13–22.
57. Lim S, Li W, Kemper J, Nguyen A, Mol BW, Reddy M. Biomarkers and the prediction of adverse outcomes in preeclampsia: a systematic review and meta-analysis. Obstet Gynecol 2021;137:72–81.
58. Duhig KE, Myers J, Seed PT, et al. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. Lancet 2019;393:1807–18.
59. Magee LA, von Dadelszen P, Singer J, et al. The CHIPS randomized controlled trial (control of hypertension in pregnancy study): is severe hypertension just an elevated blood pressure? Hypertension 2016;68:1153–9.
60. Lees C, Ferrazzi E. Relevance of haemodynamics in treating pre-eclampsia. Curr Hypertens Rep 2017;19:76.
61. Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild preeclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 2009;374:979–88.

Summary

The core conclusion of Chapter Six is that how we diagnose preeclampsia has largely been based off expert consensus, simplicity or statistical limits. Sparse data links the diagnostic criteria to the likelihood of complications.

If we believe that a diagnosis should communicate a given likelihood of a certain outcome (i.e., the prognosis), then how we currently diagnose preeclampsia is flawed. How to improve it? We must focus, in research and in clinical practice, on two key questions: what is the prognosis of the syndrome? And what can we do to alter it?

Characteristics that predict complications should form the diagnostic criteria; and characteristics that indicate a certain response to treatment should form further classification. Contrast this with the approaches through the 20th and early 21st centuries.

Chapter Six wraps up the most important ideas of our thesis. It leads nicely to our discussion, where I explore, in a wider context, the ideas generated by this thesis, offering interpretations and recommendations for future research and clinical practice.

Discussion

"We want progress in medicine to be clear and unequivocal, but of course it rarely is. Every new treatment has gaping unknowns – for both patients and society – and it can be hard to decide what to do about them."

— Atul Gawande, *Complications: A Surgeon's Notes on an Imperfect Science*

Key findings

So, to summarise our key findings. Chapter One was inconclusive, but suggested that compared to women without comorbidities, women with comorbidities may require a lower sFLT-1: PlGF ratio preeclampsia to be diagnosed. Chapter Two found that women with comorbidities suffered fewer complications, and would be diagnosed with preeclampsia with a milder clinical picture. Chapter Three argued that women with comorbidities suffered fewer complication, and that earlier intervention by clinicians likely plays a role. It also showed that this earlier intervention led to higher rates of neonatal complications. Chapter Four showed that women would have differences in blood pressure trajectory depending on their baseline blood pressure and BMI; and Chapter Five suggested that these difference likely have a major effect on the rate of adverse outcomes. Finally, Chapter Six claims that the diagnostic criteria for preeclampsia have often not been based on data linking criteria to adverse outcomes.

From here, I will summarise and contextualise our findings from a biological perspective. I will then discuss in more detail how, from an epidemiology perspective, an improved prognosis is indistinguishable from an increased likelihood of diagnosis; why there is an increasing rate of unnecessary diagnosis; and the future implications of this pattern. I use this to make recommendations for future research and clinical practice. Finally, I discuss the overall strengths and limitations of my work.

Preeclampsia: one syndrome, two processes

In the final paragraphs of Chapter Six, I remarked that: "No clear pathological evidence differentiates early- and late-onset preeclampsia. There is ongoing debate as to whether preeclampsia is a placental disorder which leads to disruption of the maternal endothelial system, or if placental dysfunction is secondary to suboptimal maternal cardiovascular adaptation to pregnancy. Both are likely true, and so it is the varying extent to which each process occurs that leads to disparate prognoses."

Early- and late-onset preeclampsia are considered "qualitatively different", with variation in haemodynamics, angiogenic imbalance and the severity of disease.[33-36] However, these differences occur on a spectrum. What these labels represent more generally are the two processes that appear most responsible for causing preeclampsia: placental insufficiency secondary to impaired remodelling of spiral arteries, and suboptimal adaptation of the maternal cardiovascular system to the demands of pregnancy. These processes meet with systemic maternal endothelial dysfunction.

It has been hypothesised that the primary placental insult occurs after the failure to differentiate of the villous trophoblast, the cells that cover the chorionic villi and facilitate gas and nutrient exchange between fetus and mother. This leads to placental insufficiency and the release of anti-angiogenic and pro-inflammatory proteins and reactive oxygen species. However, even with adequate differentiation of the trophoblast, these troublesome proteins are released in some amounts. And, for maternal, or extrinsic reasons, such as a suboptimal adaptation to the demands of pregnancy, this can be enough to trigger preeclampsia. Both these processes lead to a positive feedback loop – worsening endothelial function, leading to worsening placental insufficiency, leading to worse endothelial function. But there is a distinct aetiological difference – whether the primary insult is intrinsic to the placenta, or extrinsic, related to the mother. This represents a marked difference in prognosis. The placental contribution to the syndrome is approximately represented by the severity of angiogenic imbalance, such as the sFLT-1: PlGF ratio, which itself correlates with the severity of preeclampsia and likelihood of complications.

The early- and late-onset subtypes thus represent preeclampsia dominated by intrinsic and extrinsic processes respectively. And the relationship between these processes and the severity of preeclampsia means the gestation at which preeclampsia is diagnosed is a useful heuristic for identifying women at high risk of complication and thus requiring specific, closer management.[74]

But while gestation at diagnosis is useful insofar as it indicates the severity of disease, it is clear from our work that adding maternal characteristics to its interpretation can offer a more fine-grained picture. When in Chapter Two we compared women diagnosed and induced at the same gestational age, the presence of vascular risk factors was associated with a milder phenotype. These maternal characteristics are thus likely to be informative about the extent to which the syndrome arises from intrinsic and extrinsic processes. For a woman without risk factors, it could be that preeclampsia should be considered “early-onset”, and thus severe, if diagnosed prior to 35 or even 36 weeks gestation; but for a woman at high risk, perhaps it would be best to consider it “late-onset” unless diagnosed before
32 or 33 weeks. Maternal characteristics have the potential to improve the value of gestation at diagnosis as a simple heuristic.

Compare a 25-year-old expectant mother without a normal BMI and blood pressure with a 40 year-old with hypertension, diabetes and obesity. If both women were diagnosed with preeclampsia at 33^{+6} weeks’ gestation, there is likely to be a significant difference in the intrinsic and extrinsic contributions, and thus a difference in the severity and prognosis of preeclampsia. Both women are considered to have “early-onset” preeclampsia, even though the underlying pathology and prognosis for the second woman are likely to be closer to that of “late-onset” preeclampsia. Similarly, if both women were diagnosed at 35 weeks’ gestation, woman one is likely to have a phenotype closer to “early-onset” disease, despite being diagnosed with late-onset preeclampsia. Gestation at diagnosis has proved useful to guide management of preeclampsia, and will become far more useful once interpreted in the context of maternal characteristics.

The use of a hard cut-off at 34 weeks’ gestation also obscures the fact that these subtypes occur on a spectrum. Preeclampsia

arising at 33 weeks' gestation ("early-onset") is more similar in nature to preeclampsia arising at 35 weeks than it is to that arising at 24 weeks, even though the latter but not the former is also considered "early-onset" preeclampsia.

Imagine that a diagnosis of preeclampsia was solely dependent on the degree of placental insufficiency and angiogenic imbalance a woman developed. A small proportion of women will develop sufficient angiogenic imbalance to trigger the onset of preeclampsia, regardless of their pre-pregnancy endothelial function, with minimal contribution from extrinsic or maternal factors Another group of women will develop a milder degree of angiogenic imbalance; a degree that will, for women with adequate endothelial function, be insufficient to trigger preeclampsia.

Vascular risk factors essentially shift the cutoff for diagnosing preeclampsia. A degree of angiogenic imbalance that would not lead to diagnosis of preeclampsia now does. But given the connection between angiogenic imbalance and the severity of disease, the overall prognosis will have changed minimally. These *extra* women are at no higher risk of complications than those who go undiagnosed.

Improved prognosis and overdiagnosis: one and the same?

We can explain the relationship between unnecessary diagnoses and improved prognosis more generally. In the summary of Chapter Four, I wrote: "But now to the other side of the same coin. Studying how any factor interacts with complications or prognosis must be complemented with studying how that factor interacts with diagnosis. The effect of improving prognosis must be separated from the effect of increasing the apparent prevalence of a disease, such as preeclampsia, without having a bearing on outcomes. We discuss this in more detail in the discussion." This idea warrants further attention.

If a factor is associated with a lower or higher risk of a complication from a disease, then it either 1) affects prognosis without affecting diagnosis; 2) affects diagnosis without affecting prognosis; or 3) affects both prognosis and diagnosis, with effects adding or cancelling out each other. If a factor improves the prognosis of a disease or syndrome, but has no influence on whether someone is diagnosed with the disease, then it is associated with a better prognosis (i.e. a lower risk of complications). But if a factor has *no* influence on the prognosis of a disease/syndrome, but is associated with a higher likelihood of a person being *diagnosed* with the disease, then the factor will *also* be associated with a better prognosis. We can calculate the sensitivity and specificity of a diagnosis, with the "gold standard" being a complication from preeclampsia – i.e. we only want to diagnose women who are truly going to suffer a complication.

Now consider a population of 1000 women. Some 100 are diagnosed with preeclampsia; 899 are not; 10 develop complications from preeclampsia; and one woman suffers eclampsia without a prior diagnosis of preeclampsia. Now consider a second population of 1000 women. In this population, women are twice as likely to be diagnosed with preeclampsia. But the same 11 women develop eclampsia. A diagnosis will have a lower specificity and a lower positive predictive value. A lower specificity means a greater number of false positives, i.e. women diagnosed who do not suffer eclampsia. This is

the same effect as a factor that reduces the likelihood of complications following diagnosis - more false positives, fewer true positives.

A diagnosis based on clinical criteria is indistinguishable from a diagnostic test. It reflects a given certainty about the prognosis of a person. A diagnosis of preeclampsia suggests that there is a certain likelihood a woman will develop eclampsia, or fetal growth restriction, or other organ failure. But the more women a criterion identifies unnecessarily, the poorer these test characteristics.

There are two explanations for why vascular risk factors would be associated with fewer complications for preeclampsia. First, they could genuinely have some protective role against preeclampsia. However, there is no clear biological reason why this should be the case, which means our *a priori* probability is relatively low. And such an effect would not be associated with the incidence of preeclampsia for women with vascular risk factors that we see[48-53].

The second explanation is that these comorbidities increase the likelihood of being *diagnosed with*, but not *suffering complications from*, preeclampsia. This has a strong basis in both biology and epidemiology, and is the most likely explanation.

This interplay between diagnosis and prognosis can be extrapolated to all medicine. Research into factors that affect the prognosis of a condition must always consider how that factor influences diagnosis. We have seen this with the mistaken conclusion that obesity is protective against death from heart disease, for example.[75] Our data thus only tells us about what happens *after* a diagnosis of preeclampsia. Women with vascular risk factors are more likely to be diagnosed with preeclampsia, but the ramifications of a diagnosis are less serious.

Better safe than sorry (but not always)

The magnitude of the difference in risk for different groups of women indicates that this overdiagnosis is a big deal. Separating women on the basis of their baseline characteristics led to rates of complications ranging from 3% to 17%. This has consequences. It leads to iatrogenic harm; it can make research less generalisable; and it has socioeconomic costs, for both women and hospitals.

The potential for iatrogenic harm is clear. As we showed in Chapter Three, when diagnosed with preeclampsia, women with comorbidities tended to receive intervention at an earlier gestation than their counterparts without comorbidities. And in in Chapter Five, there was no significant difference in gestation at delivery between women in the lowest-risk (high BMI, high BP) and highest-risk (low BMI, low BP) groups, despite significant differences in the likelihood of complications. This suggests delaying intervention may be leading to complications for women without vascular risk factors, and/or that early intervention is leading to fewer maternal but more neonatal complications for women with comorbidities. Either way there is harm that has the potential to be averted, through a diagnostic criteria that is better linked to outcomes.

More systemic issues arise as a result of unnecessary diagnoses of preeclampsia. Broader diagnostic criteria make research less generalisable. This increases the demands and necessity of clinical judgement. Guidelines and research findings are useful insofar as the population they are applied to mimics the population in which they were developed. If a

study suggests a given course of management is beneficial for a given cohort of women, this is only relevant to the woman in front of the clinician if she is similar to the women included in the study.

But research diverges from reality. Never will a patient perfectly reproduce the characteristics of a study population. And even then, statistics tell us about a population, not a person. So clinical judgement, as I define it, is the process of bridging this knowledge gap. A woman in front of a clinician; if she perfectly represents the cohort from which evidence-based guidelines have been derived, then the optimal path forward is exactly what the guidelines suggest. If there is no research pertaining to a certain woman's situation, then the clinician must use their judgement alone. In practice, most situations occur somewhere between these two.

The limitations of clinical judgement

Clinical judgement is a key part of medicine, but is subject to a host of cognitive biases.[76] When the consequences of a mistake are particularly high, we should endeavour to minimise the necessity for a clinician to grope in the dark, without research-backed guidelines. When diagnostic criteria are broad, they are more sensitive but less specific for identifying those who will suffer complications. In contrast, a strict, restrictive definition is less sensitive but more specific. Fewer unnecessary diagnoses, but more complications in women not diagnosed.

This dichotomy has been used to argue that it is most important to not miss any women, and thus a broad diagnostic criteria is preferred.[77] But as we argued in Chapter Six, compared to a restrictive criteria, a broad diagnosis results in women who are diagnosed being less similar to other women diagnosed.

With restrictive criteria, fewer women will be diagnosed with a disease. But a clinician can be sure of the management of those who do meet the criteria: they will be most similar to the underlying population. With broad criteria, clinicians can easily make a diagnosis, but subsequent management is more challenging. With restrictive criteria, the hard part is determining which women should be diagnosed, but subsequent management is easier, as the evidence is closer to the women in practice. Should we be forcing clinicians to rely on clinical judgement when deciding whether or not to induce a woman at 34 weeks' gestation, or when deciding whether or not to make a diagnosis of preeclampsia in the first place? I argue for the latter. The stakes are lower. Ensuring women in clinical practice are as similar to women in research will improve outcomes.

The costs of overdiagnosis

Beyond iatrogenic harm and less generalisable research, there are socioeconomic implications from overdiagnosis. Hospital and clinician resources are finite. More women diagnosed with preeclampsia means more women receiving surveillance and early inductions, with less flexibility in when to give birth and fewer resources for those women who genuinely need a higher level of care. Managing preeclampsia is costly, largely due to resources required for infants. Costs for the infant fall dramatically the longer pregnancy can continue.[78]

And just as hospital resources are finite, so, too, are the resources of pregnant women: patience, money, time, and the many other stressors of pregnancy. These considerations are

rarely factored into decision making. Being diagnosed with preeclampsia means a host of extra burdens – blood pressure measurements, blood tests, fetal monitoring – plus the stress and worry of complications from a syndrome about which women often know little! Pregnancy is stressful enough. Many women diagnosed with preeclampsia in one pregnancy do not become pregnant again.[79] This is likely due to some extent to the unpleasantness of being unwell, with headaches, oedema, nausea and vomiting through pregnancy. But what role is played by the many months of invasive, uncomfortable and frustrating and persistent medical care, scans and blood tests? It is important to ensure a safe and healthy pregnancy. But these psychosocial costs must be considered. The harms of overdiagnosis come in many forms.

Rethinking preeclampsia (1): diagnosis

Let us now discuss in more detail how to better approach research into preeclampsia. Diagnosing and classifying preeclampsia (and anything else in medicine) should be based on factors that predict prognosis and response to treatment, a point we have made ad infinitum.

Preeclampsia is often treated as an *outcome* in research. It should not be. Preeclampsia does not *cause* placental abruption or fetal growth restriction in the same way that infection with *Neisseria Meningitis* causes meningitis. It is more accurate to say that placental insufficiency (among other factors) causes placental abruption. It is the initial insult, in the same way that entrance of *N. Meningitidis* entering cerebrospinal fluid is the cause of meningitis. Preeclampsia is a label that identifies indicators that this process is ongoing, and that a placental abruption and organ dysfunction is more likely. And so we identify the indicators, such as hypertension, proteinuria, and so forth. Thus we should not be trying to *predict* preeclampsia, but rather its complications. We should be trying to predict placental abruption, and eclampsia, and HELLP syndrome, and fetal growth restriction, and stillbirth. But not preeclampsia itself.

And as some have begun to argue, a diagnosis should be thought of as a screening test, not an endpoint in and of itself.[80] It indicates an increased risk of a complication; it itself is not necessarily a complication. Were preeclampsia to be defined more narrowly, it may function as a better proxy for complications, and predicting its development would be worthwhile. But even then – if you can perfectly predict preeclampsia but not predict its complications, nor do anything to avert them – how much does that actually help? A diagnosis of preeclampsia, in and of itself, is not nearly as informative as an outcome.

When we see that preeclampsia is a label suggesting that a given process is occurring, it becomes clearer why we must focus on prognosis and response to treatment. If we are trying to identify which women are going through a process that leads to complications, clinical features are only worthy of note if they give some information about the likelihood of complications. But if what we are looking for tells us nothing about what is going to happen, then we should look elsewhere.

Rethinking preeclampsia (2): prognosis

A key piece of the puzzle is developing a core outcome set for preeclampsia – both maternal and neonatal. This might include maternal death; eclampsia; placental abruption; acute pulmonary oedema; acute kidney injury; HELLP syndrome; ICU admission; fetal growth

restriction; and stillbirth. This process has begun,[81] but is as yet not widely generalised (I concede I too have not used a fixed set of core outcomes, a symptom of variable quality and availability of data). This, too, is limited by the significant heterogeneity of preeclampsia; but the fullPIERS outcome set[82] is starting to gain traction. It is likely to be useful primarily in prospective research; many of the more uncommon outcomes are unlikely to be captured in routinely collected data.

We should identify common characteristics that precede these complications, as well as characteristics that are present in those women who do *not* suffer a complication. If women who suffer complications commonly have a low blood pressure at baseline, low platelets, high blood pressure in the third trimester and a high sFLT-1: PlGF ratio, then these features should be included in how we diagnose preeclampsia. Women who develop adverse outcomes may have a lower blood pressure in the third trimester if their BMI at baseline is higher, and vice versa. Women with a high-resistance, low-output haemodynamic state may suffer more complications.

We can use these features to identify clusters of women, which would indicate a certain subtype of preeclampsia and a certain prognosis. Once we have identified these characteristics and their subsequent groups, we can compare different treatments among each. An ACE inhibitor may be more appropriate than a calcium channel blocker for preventing a hypertensive crisis in one group of women, but the reverse may be true in another. Metformin may be effective at prolonging pregnancy for some women,[83] but research should look for other agents for other women for whom metformin does not work. And we know aspirin reduces the likelihood of women being diagnosed with early-onset preeclampsia, but not for women with preexisting essential hypertension.[27,84] But we should go further, and ask if it prevents *complications*, and from there, in *which women* it prevents complications.

What is crucial is that this entire process should occur across all pregnant women, not solely among women diagnosed with preeclampsia, nor women deemed at "high-risk" of preeclampsia. Selecting for women diagnosed with preeclampsia introduces a form of selection bias. There are systemic differences in those diagnosed with preeclampsia, which influences outcomes. But a future diagnosis, driven only by features that predict prognosis, will mean a set of criteria that allow for the accurate characterisation of prognosis and subsequently more optimal management.

Angiogenic biomarkers – particularly the sFLT-1: PlGF ratio – are of particular interest here. All complications from preeclampsia in some studies have occurred in women with a significantly elevated sFLT-1: PlGF ratio.[37,38] This ratio should probably play a major role in future criteria. And if clinical diagnosis conflicts with angiogenic imbalance, which should take priority in assigning a given risk to a woman? Whichever characteristic better predicts a risk of complications. And if that is the sFLT-1: PlGF ratio, clinicians should not hesitate to give that precedence, even if a woman does not meet traditional diagnostic criteria.

This is particularly relevant for women with vascular risk factors. Women without vascular risk factors may *not* be diagnosed clinically, despite having an elevated ratio; in contrast, women *with* vascular risk factors may be diagnosed clinically, in the absence of an elevated ratio. This offers an exciting opportunity. The sFLT-1: PlGF ratio is currently our strongest prognostic indicator. It will be

valuable to study women who have a conflict between a clinical and biochemical diagnosis of preeclampsia – those who either meet the clinical criteria but without angiogenic imbalance, or those who do not meet the clinical criteria but have angiogenic imbalance. This is likely to identify the group of women who are unnecessarily diagnosed (the former), and who have a missed diagnosis (the latter). And women with vascular risk factors – the women most likely to be diagnosed unnecessarily – are those most likely to have a conflict between angiogenic imbalance and a clinical diagnosis. Thus this is an excellent starting point for further incorporating the sFLT-1: PlGF ratio into decision- making.

Here and now

Smaller, concrete steps should be tackled in the near future. If we are to continue using the current framework to diagnose preeclampsia, we should at least rethink specific thresholds. Some have argued recently that 130/80mmHg should be the threshold at which we diagnose preeclampsia, as this is the level above which the risk of perinatal complications begins to rise.[85,86] However, secondary analysis of a randomized control trial undertaken in a low-resource setting found that it was only above 140/90mmHg that complications began to rise.[87] Wherever the benchmark eventually falls, both arguments link thresholds to outcomes. This should be the new norm.

We can build on it by considering baseline BMI and blood pressure when interpreting a given threshold. The cut-off for diagnosing hypertension in pregnancy might be 130/80mmHg for women with a low BMI and blood pressure; 140/90mmHg for those with low BMI and high blood pressure or high BMI and low blood pressure; and 150/100mmHg for those with a high BMI and high blood pressure.

Further work into how we manage preeclampsia is pivotal. Recent work has suggested that metformin prolongs pregnancy for women with early-onset preeclampsia.[83] Not only should such studies be replicated, but they should be looked at in greater detail to identify *which* women respond to treatment. Similarly, the choice of antihypertensive agent for managing hypertension should be studied in the context of a woman's underlying haemodynamics. What is best for one may not be best for all. Finally, of interest is apheresis, or removal, of sFLT-1.[88] If preeclampsia is caused by a "toxin" in the blood, then removing that toxin should be an effective means of treating the disease. Should this be a fruitful area of exploration, it too will be made ever more valuable by identifying for *which* women there will be a positive therapeutic response.

This thesis is predominantly hypothesis-generating, but elements of our results can be incorporated into clinical practice. During pregnancy, clinicians should begin to interpret a woman's blood pressure in the context of her blood pressure and BMI at booking visits. They should steer away from being trigger-happy in labelling a woman with preeclampsia, and move towards diagnosing preeclampsia only when the diagnosis is clear.

On a systemic level, hospitals could introduce a "balance" measure that penalises unnecessary intervention resulting in early delivery. This has been investigated in the management of fetal growth restriction. Selvaratnam et al showed that reporting on missed cases of fetal growth restriction – i.e., reporting the false negative rate – was associated with a reduced incidence of severe fetal growth restriction and a subsequent

decrease in the stillbirth rate.[89] However, this came at the cost of a higher false positive rate, with more appropriately grown babies induced prior to term. The authors subsequently proposed this latter rate as a balance measure.[90] This means both false negatives (growth-restricted fetuses not detected) and false positives (appropriately grown fetuses induced early) are considered when evaluating hospital-level outcomes. A similar approach could be considered for preeclampsia. The challenge is determining the right indicators. A hospital-level measure, such as number of women induced for suspected preeclampsia whose fetuses require NICU admission, balances the costs and benefits across both individuals and the institution.

However, in the cases of both growth restriction and preeclampsia, these are a Band-Aid over a major knowledge gap – our relative inability to accurately detect complications. Measuring and evaluating how we care for women is of interest; but once the diagnosis and prognosis are characterised on a granular level, we will not need them. A balancemeasure is a blunt weapon, which implies that the cost of one missed cases is the same as one unnecessary diagnosis – an evaluation we can make only once we better understand the prognosis of a given woman and her fetus.

Before I sign off this thesis, I will briefly discuss the limitations and strengths of my research.

Limitations

The key limitation of this thesis is the reliance on retrospective data. This means we cannot ascribe causal relationships to my data, only associative. Perinatal epidemiological is fraught with sampling and survivorship biases[91] – consider that among low-birthweight babies, smoking has been shown to be associated with a lower mortality. Why? Because those neonates with a low birthweight whose mothers *did not* smoke are likely to have, for example, a congenital malformation as their cause of low birthweight, with worse outcomes than low birthweight due to smoking.[92]

I have used more advanced statistical techniques – causal mediation, mixed-effects models – to mitigate these challenges and limitations inherent in perinatal epidemiology. However, as much as in any field and perhaps more than most, prospective research is crucial to validate any observations made in retrospect.

Whether to define preeclampsia by a strict research definition or by how it is recorded by the treating clinician is an ongoing issue. Which should be preferred? That this is even a question highlights the issues of research generalisability I have discussed.

In some studies I have used a strict research definition; in others, I used diagnoses as recorded by the clinician. That these can be significantly different is problematic. A strict research criteria would likely result in smaller effect sizes than we have demonstrated. But how we diagnose preeclampsia should not be so different between research and clinical practice. It is more relevant and better practice to have a strict, but easily and widely applicable definition, which can be used for both. There is too much of a discrepancy between how preeclampsia is diagnosed in the literature and how it is seen in clinical practice.

Finally, there are my personal limitations. I am a medical student and a PhD candidate, not an obstetrician with years of experience at the coalface, making difficult management

decisions. And so my arguments are by and large made from a theoretical, not practical, perspective. Some of my proposals may be absurd. But at all times I have tried to make good-faith interpretations, balancing equally reason, data, and speculation. I may look back on these observations in one, five or 10 years and think them all wrong. But I am confident there is at least something of value, a new perspective, a new research direction, in these papers.

Strengths

After all, there are significant strengths to my work. There are three interacting qualities – large sample sizes, a narrow scope of research, and focused outcomes – that I have leveraged to make this the best research I can.

Small datasets have hampered research into preeclampsia. The large databases have offered the opportunity to do some of the larger studies into preeclampsia and its outcomes. Furthermore, the scope of my research has been narrow. It can be boiled down to two key questions: how do maternal characteristics influence 1) the diagnosis and 2) the prognosis of preeclampsia?

Finally, I have focused on outcomes that are directly tied to either diagnosis (sFLT-1: PlGF ratio, blood pressure during pregnancy, phenotype of preeclampsia) or prognosis (maternal or neonatal complications). While the outcomes I have studied varied through this thesis, they were, in every study, true to my overarching theme. Focused outcomes within a narrow scope of research using large datasets are a powerful trinity in research.

Conclusion

"Literature not only illuminated another's experience, it provided, I believed, the richest material for moral reflection."

— Paul Kalanithi, *When Breath Becomes Air*

Maternal characteristics significantly influence the diagnosis of preeclampsia. This highlights a major limitation in how we diagnose preeclampsia: the criteria we use are not linked to prognosis, or response to treatment.

We should diagnose preeclampsia based on the answers to two key questions: what is this woman's prognosis? And how will she respond to treatment? This will ensure preeclampsia is a well-defined condition that offers an established framework for management. The harms of unnecessarily diagnosing preeclampsia are perennially underestimated. We must not forget this.

References

1. Australian Bureau of Statistics Australian Historical Population Statistics. Canberra; Australian Bureau of Statistics., 2006. Accessed 15 February 2022. Available at: *[https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3105.0.65.0012006].*
2. World Health Organisation. Trends in maternal mortality 2000 to 2017: Estimates by WHO, UNICFER, UNFPA, World Bank Group and the United Nations Population Division. Geneva: World Health Organization; 2019. Accessed 15 February 2022.
3. World Health Organisation Newborn mortality. Geneva: World Health Organization; 2019. Accessed 15 February 2022.
4. Brown MA, Lindheimer MD, de Swiet M, Assche AV, Moutquin J-M. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the international society for the study of hypertension in pregnancy (isshp). *Hypertens*. 2001;20:ix-xiv
5. Duley L. The global impact of pre-eclampsia and eclampsia. *Seminars in Perinatology*. 2009;33:130-137
6. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the united states. *Obstet Gynecol*. 2009;113:1299-1306
7. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *The Lancet*. 2016;387:999-1011
8. Tanner MS, Davey MA, Mol BW, Rolnik DL. The evolution of the diagnostic criteria of preeclampsia-eclampsia. *Am J Obstet Gynecol*. 2022;226:S835-s843
9. Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: Pathophysiology and clinical implications. *BMJ*. 2019;366:l2381
10. Menkhorst E, Winship A, Van Sinderen M, Dimitriadis E. Human extravillous trophoblast invasion: Intrinsic and extrinsic regulation. *Reproduction, Fertility and Development*. 2016;28:406-415
11. Pijnenborg R, Dixon G, Robertson WB, Brosens I. Trophoblastic invasion of human decidua from 8 to 18 weeks of pregnancy. *Placenta*. 1980;1:3-19
12. Fukui A, Yokota M, Funamizu A, Nakamua R, Fukuhara R, Yamada K, et al. Changes of nk cells in preeclampsia. *Am J Reprod Immunol*. 2012;67:278-286
13. VanWijk MJ, Kublickiene K, Boer K, VanBavel E. Vascular function in preeclampsia. *Cardiovascular Research*. 2000;47:38-48
14. Palmer KR, Tong S, Kaitu'u-Lino TJ. Placental-specific sflt-1: Role in pre-eclamptic pathophysiology and its translational possibilities for clinical prediction and diagnosis. *Molecular Human Reproduction*. 2016;23:69-78
15. Ishihara N, Matsuo H, Murakoshi H, Laoag-Fernandez JB, Samoto T, Maruo T. Increased apoptosis in the syncytiotrophoblast in human term placentas complicated by either preeclampsia or intrauterine growth retardation. *Am J Obstet Gynecol*.

2002;186:158-166
16. Agarwal I, Karumanchi SA. Preeclampsia and the anti-angiogenic state. *Pregnancy Hypertension*. 2011;1:17-21
17. Shibuya M. Vascular endothelial growth factor (VEEGF) and its receptor (VEGFR) signaling in angiogenesis: A crucial target for anti- and pro-angiogenic therapies. *Genes & cancer*. 2011;2:1097-1105
18. Maynard SE, Min J-Y, Merchan J, Lim K-H, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sflt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *The Journal of Clinical Investigation*. 2003;111:649-658
19. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive value of the sflt-1:Plgf ratio in women with suspected preeclampsia. *New England Journal of Medicine*. 2016;374:13-22
20. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Zeisler H, Calda P, et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. *Hypertension*. 2014;63:346-352
21. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi J-M. Pre-eclampsia: Pathophysiology, diagnosis, and management. *Vasc Health Risk Manag*. 2011;7:467-474
22. Sánchez-Aranguren LC, Prada CE, Riaño-Medina CE, Lopez M. Endothelial dysfunction and preeclampsia: Role of oxidative stress. *Frontiers in Physiology*. 2014;5
23. Konukoglu D, Uzun H. Endothelial dysfunction and hypertension. *Advances in Experimental Medicine and Biology*. 2017;956:511-540
24. Noris M, Perico N, Remuzzi G. Mechanisms of disease: Pre-eclampsia. *Nature Clinical Practice. Nephrology*. 2005;1:98-114; quiz 120
25. Thilaganathan B. Pre-eclampsia and the cardiovascular–placental axis. *Ultrasound in Obstetrics & Gynecology*. 2018;51:714-717
26. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy: Isshp classification, diagnosis, and management recommendations for international practice. *Hypertension*. 2018;72:24-43
27. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *New England Journal of Medicine*. 2017;377:613-622
28. Lim S, Li W, Kemper J, Nguyen A, Mol BW, Reddy M. Biomarkers and the prediction of adverse outcomes in preeclampsia: A systematic review and meta-analysis. *Obstetrics & Gynecology*. 2021;137:72-81
29. von Dadelszen P, Payne B, Li J, Ansermino JM, Pipkin FB, Côté A-M, et al. Prediction of adverse maternal outcomes in pre-eclampsia: Development and validation of the fullpiers model. *The Lancet*. 2011;377:219-227

30. Stepan H, Herraiz I, Schlembach D, Verlohren S, Brennecke S, Chantraine F, et al. Implementation of the sflt-1/plgf ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: Implications for clinical practice. *Ultrasound in Obstetrics & Gynecology*. 2015;45:241-246
31. National Institute for Health and Care Excellence. PlGF-based testing to help diagnose suspected pre-eclampsia (NICE Diagnostic Guideline 23). (2016). Available at: https://www.nice.org.uk/guidance/dg23. [Accessed 8 March 2021].
32. American College of Obstetricians and Gynecologists.. ACOG practice bulletin no. 202: Gestational hypertension and preeclampsia. *Obstetrics and Gynecology*. 2019;133:e1-e25
33. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. *Obstetrics & Gynecology*. 2014;124:771-781
34. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: Two different maternal hemodynamic states in the latent phase of the disease. *Hypertension*. 2008;52:873-880
35. Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. *Obstet Gynecol Surv*. 2011;66:497-506
36. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia. *Hypertension*. 2008;52:873-880
37. Chaiworapongsa T, Romero R, Savasan ZA, Kusanovic JP, Ogge G, Soto E, et al. Maternal plasma concentrations of angiogenic/anti-angiogenic factors are of prognostic value in patients presenting to the obstetrical triage area with the suspicion of preeclampsia. *J Matern Fetal Neonatal Med*. 2011;24:1187-1207
38. Rana S, Schnettler WT, Powe C, Wenger J, Salahuddin S, Cerdeira AS, et al. Clinical characterization and outcomes of preeclampsia with normal angiogenic profile. *Hypertens*. 2013;32:189-201
39. Abbas AM, Fikry EM, Mostafa TS, Shaltout AS, El-Baz MAH. Prognostic value of serum soluble fms-like tyrosine kinase (sflt-1) levels in pre-eclampsia and eclampsia; a prospective cohort study. *Hypertens Pregnancy*. 2018;37:137-143
40. Chaiworapongsa T, Romero R, Korzeniewski SJ, Kusanovic JP, Soto E, Lam J, et al. Maternal plasma concentrations of angiogenic/antiangiogenic factors in the third trimester of pregnancy to identify the patient at risk for stillbirth at or near term and severe late preeclampsia. *Am J Obstet Gynecol*. 2013;208:287.e281-287.e215
41. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, et al. The sflt-1/plgf ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol*. 2012;206:58.e51-58.e58
42. Pinheiro CC, Rayol P, Gozzani L, Reis LM, Zampieri G, Dias CB, et al. The relationship of angiogenic factors to maternal and neonatal manifestations of early-onset

and late-onset preeclampsia. *Prenat Diagn*. 2014;34:1084-1092
43. Doherty A, Carvalho JC, Drewlo S, El-Khuffash A, Downey K, Dodds M, et al. Altered hemodynamics and hyperuricemia accompany an elevated sFlt-1/PlGF ratio before the onset of early severe preeclampsia. *J Obstet Gynaecol Can*. 2014;36:692-700
44. Morgan JL, Nelson DB, Roberts SW, Wells CE, McIntire DD, Cunningham FG. Association of baseline proteinuria and adverse outcomes in pregnant women with treated chronic hypertension. *Obstetrics and Gynecology*. 2016;128:270-276
45. Powe CE, Thadhani R. Diabetes and the kidney in pregnancy. *Seminars i n Nephrology*. 2011;31:59-69
46. Macdonald-Wallis C, Lawlor DA, Heron J, Fraser A, Nelson SM, Tilling K. Relationships of risk factors for pre-eclampsia with patterns of occurrence of isolated gestational proteinuria during normal term pregnancy. *PloS One*. 2011;6:e22115-e22115
47. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ (Clinical research ed.)*. 2008;336:211-215
48. Lecarpentier E, Tsatsaris V, Goffinet F, Cabrol D, Sibai B, Haddad B. Risk factors of superimposed preeclampsia in women with essential chronic hypertension treated before pregnancy. *PloS One*. 2013;8:e62140-e62140
49. Weissgerber TL, Mudd LM. Preeclampsia and diabetes. *Current Diabetes Reports*. 2015;15:9-9
50. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies. *BMJ (Clinical research ed.)*. 2005;330:565-565
51. Seely EW, Ecker J. Chronic hypertension in pregnancy. *Circulation*. 2014;129:1254-1261
52. Piccoli GB, Cabiddu G, Attini R, Vigotti FN, Maxia S, Lepori N, et al. Risk of adverse pregnancy outcomes in women with CKD. *Journal of the American Society of Nephrology*. 2015;26:2011-2022
53. Schneider S, Freerksen N, Röhrig S, Hoeft B, Maul H. Gestational diabetes and preeclampsia – similar risk factor profiles? *Early Human Development*. 2012;88:179-184
54. Bleakley C, Hamilton PK, Pumb R, Harbinson M, McVeigh GE. Endothelial function in hypertension: Victim or culprit? *The Journal of Clinical Hypertension*. 2015;17:651-654
55. Bolad I, Delafontaine P. Endothelial dysfunction: Its role in hypertensive coronary disease. *Curr Opin Cardiol*. 2005;20:270-274
56. Tabit CE, Chung WB, Hamburg NM, Vita JA. Endothelial dysfunction in diabetes mellitus: Molecular mechanisms and clinical implications. *Rev Endocr Metab Disord*. 2010;11:61-74
57. Lobato NS, Filgueira FP, Akamine EH, Tostes RC, Carvalho MHC, Fortes ZB. Mechanisms of endothelial dysfunction in obesity-associated hypertension. *Braz J Med Biol Res*. 2012;45:392-400
58. Malyszko J. Mechanism of endothelial dysfunction in chronic kidney disease.

International journal of clinical chemistry. 2010;411:1412-1420
59. Levine RJ, Maynard SE, Qian C, Lim K-H, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. *New England Journal of Medicine*. 2004;350:672-683
60. Levine RJ, Qian C, Maynard SE, Yu KF, Epstein FH, Karumanchi SA. Serum sflt1 concentration during preeclampsia and mid trimester blood pressure in healthy nulliparous women. *Am J Obstet Gynecol*. 2006;194:1034-1041
61. Australian Institute of Health and Welfare. Incidence of gestational diabetes in Australia [Internet]. Canberra: Australian Institute of Health and Welfare, 2019 [cited 2022 Feb. 25]. Available from: https://www.aihw.gov.au/reports/diabetes/incidence-of-gestational-diabetes-in-australia
62. Ananth CV, Duzyj CM, Yadava S, Schwebel M, Tita ATN, Joseph KS. Changes in the prevalence of chronic hypertension in pregnancy, united states, 1970 to 2010. *Hypertension*. 2019;74:1089-1095
63. Australian Institute of Health and Welfare.Australia's mothers and babies. 2021
64. Fitzpatrick A, Mohammadi F, Jesudason S. Managing pregnancy in chronic kidney disease: Improving outcomes for mother and baby. *Int J Womens Health*. 2016;8:273-285
65. Gilbert W, Young A, Danielsen B. Pregnancy outcomes in women with chronic hypertension: A population-based study. *The Journal of Reproductive Medicine*. 2007;52:1046-1051
66. Murphy HR, Bell R, Cartwright C, Curnow P, Maresh M, Morgan M, et al. Improved pregnancy outcomes in women with type 1 and type 2 diabetes but substantial clinic-to-clinic variations: A prospective nationwide study. *Diabetologia*. 2017;60:1668-1677
67. Yu L, Zeng X-L, Cheng M-L, Yang G-Z, Wang B, Xiao Z-W, et al. Quantitative assessment of the effect of pre-gestational diabetes and risk of adverse maternal, perinatal and neonatal outcomes. *Oncotarget*. 2017;8:61048-61056
68. Odibo A, Nelson D, Stamilio D, Sehdev H, Macones G. Advanced maternal age is an independent risk factor for intrauterine growth restriction. *American Journal of Perinatology*. 2006;23:325-328
69. Xiong X, Saunders LD, Wang FL, Demianczuk NN. Gestational diabetes mellitus: Prevalence, risk factors, maternal and infant outcomes. *International Journal of Gynecology & Obstetrics*. 2001;75:221-228
70. Stubert J, Reister F, Hartmann S, Janni W. The risks associated with obesity in pregnancy. *Dtsch Arztebl Int*. 2018;115:276-283
71. Fink JC, Schwartz SM, Benedetti TJ, Stehman-Breen CO. Increased risk of adverse maternal and infant outcomes among women with renal disease. *Paediatric and Perinatal Epidemiology*. 1998;12:277-287

72. Kendrick J, Sharma S, Holmen J, Palit S, Nuccio E, Chonchol M. Kidney disease and maternal and fetal outcomes in pregnancy. *Am J Kidney Dis*. 2015;66:55-59
73. Loudon I. Some historical aspects of toxaemia of pregnancy. A review. *BJOG: An International Journal of Obstetrics & Gynaecology*. 1991;98:853-858
74. Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM. The definition of severe and early-onset preeclampsia. Statements from the international society for the study of hypertension in pregnancy (ISSHP). *Pregnancy Hypertension*. 2013;3:44-47
75. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: A systematic review of cohort studies. *The Lancet*. 2006;368:666-678
76. Whelehan DF, Conlon KC, Ridgway PF. Medicine and heuristics: Cognitive biases and medical decision-making. *Irish Journal of Medical Science (1971 -)*. 2020;189:1477-1484
77. Magee L, Singer J, Lee T, Rey E, Asztalos E, Hutton E, et al. The impact of preeclampsia definitions on the identification of adverse outcome risk in hypertensive pregnancy – analyses from the chips trial (control of hypertension in pregnancy study). *BJOG*. 2021;128:1373-1382
78. Hao J, Hassen D, Hao Q, Graham J, Paglia MJ, Brown J, et al. Maternal and infant health care costs related to preeclampsia. *Obstetrics and Gynecology*. 2019;134:1227-1233
79. Van Pampus MG, Aarnoudse JG. Long-term outcomes after preeclampsia. *Clinical Obstetrics and Gynecology*. 2005;48:489-494
80. Vidaeff AC, Saade GR, Sibai BM. Preeclampsia: The need for a biological definition and diagnosis. *American Journal of Perinatology*. 2021;38:976-982
81. Duffy J, Cairns A, Richards-Doran D, van 't Hooft J, Gale C, Brown M, et al. A core outcome set for pre-eclampsia research: An international consensus development study. *BJOG*. 2020;127:1516-1526
82. Von Dadelszen P, Payne B, Li J, Ansermino JM, Pipkin FB, Côté AM, et al. Prediction of adverse maternal outcomes in pre-eclampsia: Development and validation of the fullpiers model. *The Lancet*. 2011;377:219-227
83. Cluver CA, Hiscock R, Decloedt EH, Hall DR, Schell S, Mol BW, et al. Use of metformin to prolong gestation in preterm pre-eclampsia: Randomised, double blind, placebo controlled trial. *BMJ*. 2021;374:n2103
84. Poon LC, Wright D, Rolnik DL, Syngelaki A, Delgado JL, Tsokaki T, et al. Aspirin for evidence-based preeclampsia prevention trial: Effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history. *Am J Obstet Gynecol*. 2017;217:585.e581-585.e585
85. Reddy M, Rolnik DL, Harris K, Li W, Mol BW, Da Silva Costa F, et al. Challenging

the definition of hypertension in pregnancy: A retrospective cohort study. *Am J Obstet Gynecol*. 2020;222:606.e601-606.e621

86. Sisti G, Williams B. Body of evidence in favor of adopting 130/80 mm hg as new blood pressure cut-off for all the hypertensive disorders of pregnancy. *Medicina (Kaunas)*. 2019;55:703

87. Bone JN, Magee LA, Singer J, Nathan H, Qureshi RN, Sacoor C, et al. Blood pressure thresholds in pregnancy for identifying maternal and infant risk: A secondary analysis of community-level interventions for pre-eclampsia (clip) trial data. *The Lancet Global Health*. 2021;9:e1119-e1128

88. Thadhani R, Hagmann H, Schaarschmidt W, Roth B, Cingoez T, Karumanchi SA, et al. Removal of soluble fms-like tyrosine kinase-1 by dextran sulfate apheresis in preeclampsia. *J Am Soc Nephrol*. 2016;27:903-913

89. Selvaratnam R, Davey MA, Anil S, McDonald S, Farrell T, Wallace E. Does public reporting of the detection of fetal growth restriction improve clinical outcomes: A retrospective cohort study. *BJOG.*2020;127:581-589

90. Selvaratnam RJ, Wallace EM, Hunt RW, Davey MA. Preventing harm: A balance measure for improving the detection of fetal growth restriction. *ANZJOG*. 2021;61:715-721

91. Snowden JM, Bovbjerg ML, Dissanayake M, Basso O. The curse of the perinatal epidemiologist: Inferring causation amidst selection. *Curr Epidemiol Rep*. 2018;5:379-387

92. Hernández-Díaz S, Schisterman EF, Hernán MA. The birth weight "paradox" uncovered? *Am J Epidemiol*. 2006;164:1115-1120

Appendix 1

2020 was a unique year.

Due to the COVID-19 pandemic, a decision was made in the Obstetrics and Gynaecology department of Monash Health to move much of the antenatal care program to telehealth.

This was a momentous task, and the speed and efficiency with which it happened is testament to the skill and experience of the staff at Monash Health. But as with any health care intervention, safety is paramount. It is of little benefit saving a woman hours waiting in the clinic and hundreds of dollars in parking fees if you increase her risk of fetal growth restriction, or her preeclampsia goes undetected.

Minimising the risk to these women was of utmost importance. Beyond minimising the risk of complications from COVID-19, the transition to telehealth had the potential to be transformative for women who are at high risk of, and go on to develop, preeclampsia. Women with preeclampsia are typically subjected to an arduous battery of monitoring, investigations, and frequent appointments.

I played a major role in the evaluation of the telehealth program, particularly the data analysis. This culminated in a paper that was published in *The Lancet* in July 2021. Given the importance of this research and my significant time investment during my PhD candidature, I am including it as an appendix.

Widespread implementation of a low-cost telehealth service in the delivery of antenatal care during the COVID-19 pandemic: an interrupted time-series analysis

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Summary

Background **Little evidence is available on the use of telehealth for antenatal care. In response to the COVID-19 pandemic, we developed and implemented a new antenatal care schedule integrating telehealth across all models of pregnancy care. To inform this clinical initiative, we aimed to assess the effectiveness and safety of telehealth in antenatal care.**

Methods **We analysed routinely collected health data on all women giving birth at Monash Health, a large health service in Victoria (Australia), using an interrupted time-series design. We assessed the impact of telehealth integration into antenatal care from March 23, 2020, across low-risk and high-risk care models. Allowing a 1-month implementation period from March 23, 2020, we compared the first 3 months of telehealth integrated care delivered between April 20 and July 26, 2020, with conventional care delivered between Jan 1, 2018, and March 22, 2020. The primary outcomes were detection and outcomes of fetal growth restriction, pre-eclampsia, and gestational diabetes. Secondary outcomes were stillbirth, neonatal intensive care unit admission, and preterm birth (birth before 37 weeks' gestation).**

Findings **Between Jan 1, 2018, and March 22, 2020, 20 031 women gave birth at Monash Health during the conventional care period and 2292 women gave birth during the telehealth integrated care period. Of 20 154 antenatal consultations provided in the integrated care period, 10 731 (53%) were delivered via telehealth. Overall, compared with the conventional care period, no significant differences were identified in the integrated care period with regard to the number of babies with fetal growth restriction (birthweight below the 3rd percentile; 2% in the integrated care period *vs* 2% in the conventional care period, p=0·72, for low-risk care models; 5% in the integrated care period *vs* 5% in the conventional care period, p=0·50 for high-risk care models), number of stillbirths (1% *vs* 1%, p=0·79; 2% *vs* 2%, p=0·70), or pregnancies complicated by pre-eclampsia (3% *vs* 3%, p=0·70; 9% *vs* 7%, p=0·15), or gestational diabetes (22% *vs* 22%, p=0·89; 30% *vs* 26%, p=0·06). Interrupted time-series analysis showed a significant reduction in preterm birth among women in high-risk models (–0·68% change in incidence per week [95% CI –1·37 to –0·002]; p=0·049), but no significant differences were identified in other outcome measures for low-risk or high-risk care models after telehealth integration compared with conventional care.**

Interpretation **Telehealth integrated antenatal care enabled the reduction of in-person consultations by 50% without compromising pregnancy outcomes. This care model can help to minimise in-person interactions during the COVID-19 pandemic, but should also be considered in post-pandemic health-care models.**

Funding **None.**

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Introduction

In March, 2020, health-care systems around the world had to rapidly adjust to cope in response to the COVID-19 pandemic. Services for many subacute aspects of health care were cancelled or completely shifted to telehealth for care delivery; however, maternity care presented a unique challenge, since it cannot be cancelled nor converted to a completely digital format. In Australia, the antenatal care schedule has remained largely unchanged since introduction by the UK Government in 1929,[1] with the majority of antenatal appointments occurring within the hospital environment, where up to 9G% of women in Australia give birth.[2] In response to concerns that hospitals would be overwhelmed by COVID-19 cases, antenatal care delivery had to be adapted to protect pregnant women and staff from unnecessary exposure to SARS-CoV-2.

On March 13, 2020, the Australian Government announced a temporary change in public health funding through the Medicare Benefits Schedule to support telehealth use in health-care delivery. Telehealth models have previously been implemented in high-cost settings that have extensive technological infrastructure and support systems in place, or in specific patient groups who live remote to specialist care.[3,4]

Little evidence is available on telehealth use in antenatal care delivery;[3,5] thus, in response to the COVID-19

Research in context

Evidence before this study

Telehealth has been implemented for the provision of pregnancy care in high-income, low-income and, middle-income countries. We searched PubMed and Ovid databases from database inception to March, 2020, for articles published in English, using the search terms "telehealth" OR "telemedicine" AND "pregnancy" OR "antenatal care" OR "obstetrics" OR "maternity". Studies or reviews that focused specifically on the use of telehealth or telemedicine for the delivery of routine antenatal care were identified from abstract review. A 2020 systematic review found that targeted telehealth interventions have been associated with improved pregnancy outcomes, such as smoking cessation and higher breastfeeding rates. The use of telehealth interventions has also been associated with a reduced number of unplanned in-person visits in high-risk pregnancies, while maintaining similar pregnancy outcomes. This review identified 19 studies done in low-risk pregnancies (n=6827) and 13 studies in high-risk pregnancies (n=1514); however, the majority of included studies focused on targeted use of telehealth, such as for smoking cessation, health and wellbeing in pregnancy, influenza vaccinations, or diabetes management. Three studies were done in high-risk pregnancies alone (n=353) that assessed the use of telehealth to minimise in-person antenatal attendances. All three studies engaged considerable infrastructure comprised of web-based support tools for the management of blood sugar levels in gestational diabetes, or remote monitoring devices, such as blood glucose meters, blood pressure monitors, and pulse oximetry monitors. The use of these tools across the three studies was associated with a reduction in the number of unscheduled visits. None of the included studies specifically assessed the virtual delivery of routine antenatal care using telehealth. However, virtual obstetric services have been developed, predominately within the USA. Although evidence from these programmes indicate that women provided with virtual care had similar pregnancy outcomes to those given conventional care and patient satisfaction with virtual care is good, these models often incorporated additional technological infrastructure to support home monitoring and were used in small patient populations.

Added value of this study

The widespread integration of telehealth into the delivery of antenatal care for both low-risk and high-risk pregnancy care models is achievable. To our knowledge, this is the first low-cost model of telehealth integrated antenatal care. We found that telehealth integrated antenatal care was achievable in a publicly funded health-care system. Rapid replacement of around 50% of in-person antenatal consultations with virtual telehealth visits was not associated with a change in adverse pregnancy outcomes or complications when compared with conventional antenatal care. Although the motivation for this change in care was driven by the COVID-19 pandemic, pregnancy outcomes were not influenced directly by COVID-19 in pregnancy since no COVID-19 cases were reported in our study population during the study period.

Implications of all the available evidence

Telehealth can be incorporated into antenatal care delivery for both low-risk and high-risk pregnancies, not only for targeted strategies such as diabetes management and smoking cessation, but also for routine antenatal care visits. Our findings indicate that antenatal care delivered using telehealth is likely to result in the same or improved outcomes when compared with conventionally delivered care; thus, future research is needed to ensure these findings are maintained over a longer period and after the COVID-19 pandemic. Existing literature indicates that telehealth applications are associated with a high level of patient satisfaction. Although this model of care will assist with the development of resilient, personalised health systems, the cost-effectiveness of telehealth in antenatal care remains to be determined.

pandemic, in the Australian state of Victoria a large health-care network developed a new integrated antenatal care schedule incorporating telehealth for consultation delivery via voice calls or video calls across all models of pregnancy care. On March 23, 2020, this integrated antenatal care schedule was implemented across three maternity hospitals within the Victorian health-care system, with the aim of reducing in-person consultations by up to GG%, while maintaining a high standard of antenatal care.

Little evidence was available to inform this clinical initiative; thus, we aimed to assess the uptake and safety of telehealth integrated antenatal care for low-risk and high-risk pregnancies. Since physical examination is not possible during telehealth consultations, we hypothesised whether the use of telehealth integrated antenatal care might adversely impact on the ability to detect common complications of pregnancy, particularly those contingent on physical examination, such as pre-eclampsia and fetal growth restriction.

Although this new antenatal care schedule is crucial during the current COVID-19 pandemic, evaluation of the telehealth integrated care model might assist other health services considering such a programme, particularly with the observed resurgence in COVID-19 cases in many countries. Additionally, this evaluation might guide the future use of telehealth integrated antenatal care as part of building resilient health systems better placed to withstand epidemics while providing more individualised patient care.

Methods

Study design

We used an interrupted time-series analysis to compare telehealth integrated antenatal care with conventionally delivered care on pregnancy outcomes across a large

health service in Victoria, Australia. Monash Health is the largest publicly funded maternity service in Melbourne (VIC, Australia), consisting of two secondary and one tertiary referral hospitals. Monash Health provides care for approximately 10 000 births with around 100 000 antenatal consultations done annually. This research was approved by Monash Health Human Research Ethics Committee (RES-20-0000300Q–G4284); the requirement for individual participant consent was waived due to the use of de-identified data. The findings of this study were reported in accordance with the RECORD guidelines.[6]

Data sources

Births that occurred at or after 20 weeks' gestation or with a birthweight of 400 g or higher, if gestation was uncertain, between Jan 1, 2018, and July 2G, 2020, were included in the analysis. Data were extracted from the Birthing Outcomes System (Melbourne Clinical and Translational Sciences, Melbourne, VIC, Australia) raw database. The Birthing Outcomes System is an electronic database used to document maternal clinical information; antenatal, intrapartum and post-partum details; and pregnancy outcomes. The routinely collected health outcome data had minimal missing data, with missing data for the following variables: birthweight (n=1 [<1%]), neonatal intensive care unit (NICU) admission (n=302 [1%]), and body-mass index (BMI; n=1499 [7%]). The missing data were excluded from their respective analyses. Data on antenatal appointments and types were obtained from the Monash Health business intelligence portal. Low-risk care models included midwifery-led, shared care (with hospital and general practitioner appointments) and collaborative care (with obstetrician and midwifery appointments) models. Obstetric specialist-led care was defined as a high-risk care model.

Procedures

A multidisciplinary team of obstetric, midwifery, and general practice providers developed a telehealth integrated antenatal care schedule (figure 1). Telehealth consultations were delivered by video call (Healthdirect Australia, Haymarket, NSW, Australia) or via telephone, on the basis of patient preference and a decision support tool (appendix). Telehealth consultations were supplemented with a suite of patient and staff information sheets, and systems to support remote blood pressure checks and fetal growth assessments. Blood pressure was self-checked on purchased automated blood pressure monitors, with local health providers, or at the time of hospital ultrasound assessments. Remote monitoring of fetal growth involved the introduction of self-measured symphyseal-fundal heights weekly from 24 weeks' gestation plotted on provided fetal growth charts supported by educational material, and ultrasound assessment of fetal growth was done in hospital according to national clinical care recommendations.[7,8] Women were screened regularly for gestational diabetes via an oral glucose tolerance test and if positive monitored blood glucose levels during the conventional care period; endocrinology consultations were delivered via telehealth. We collected information on pregnancy outcomes following telehealth implementation between April 20 and July 2G, 2020. Data were extracted from the Birthing Outcomes System raw database by the health information team, who cleaned and validated data, which was provided to investigators as an Excel spreadsheet for all births within the requested time period for all variables requested, including baseline maternal demographics, maternal age, BMI, parity, and smoking status. We also collected data on the number and type of antenatal consultations done each week. Telehealth appointments were defined as those done via telephone or videoconferencing. The number of appointments missed for in-person and telehealth appointments was also recorded.

Conventional antenatal care at Monash Health was provided in accordance with the National Health and Medical Research Council guidelines on antenatal care in uncomplicated pregnancies,[8] which involves ten antenatal consultations delivered in person across pregnancy. Women with pregnancy complications could

See Online for appendix

Low-risk care models

	First trimester		Second trimester		Third trimester					
Telehealth	Midwifery assessment clinic	16 weeks' gestation	22 weeks' gestation–first consultation with doctor			31 weeks' gestation	34 weeks' gestation		38 weeks' gestation	
In person					28 weeks' gestation			36 weeks' gestation		≥40 weeks' gestation

High-risk care models

	First trimester		Second trimester		Third trimester					
Telehealth	Midwifery assessment clinic	First consultation with doctor		22 weeks' gestation		31 weeks' gestation	34 weeks' gestation			
In person			16–18 weeks' gestation		28 weeks' gestation			36 weeks' gestation	38 weeks' gestation	≥40 weeks' gestation

Figure 1: **Telehealth integrated antenatal care schedule for low-risk and high-risk models of care**

have more consultations depending on clinical need. We collected information for all women who gave birth at Monash Health between Jan 1, 2018, and March 22, 2020, which was defined as the conventional care period. Integrated care incorporating telehealth was implemented on March 23, 2020. The period March 23–April 19, 2020, was defined as the implementation period. The period April 20–July 2G, 2020, was defined as the integrated care period.

Outcomes

The primary outcome was the safety of telehealth integrated care compared with conventional care for the detection and management of pre-eclampsia, fetal growth restriction, and gestational diabetes.

For fetal growth restriction, singleton birthweight percentiles (<3rd and <10th percentiles) were determined using local population charts.[9] A health service performance indicator for undiagnosed fetal growth restriction was used, defined as the proportion of babies with a birthweight below the 3rd percentile born at or after 40 weeks' gestation divided by the number of babies with a birthweight below the 3rd percentile born at or after 32 weeks' gestation.[10] Additionally, we determined the number of singleton pregnancies induced for suspected fetal growth restriction. To ensure any improvements in rates of fetal growth restriction were not the result of an increase in early-term births, we assessed the proportion of women who were induced for suspected fetal growth restriction before 39 weeks' gestation who delivered a baby with a birthweight above the 10th percentile.

For pre-eclampsia detection and management, we assessed the proportion of women diagnosed with pre-eclampsia; gestation at birth; and the incidence of severe pre-eclamptic complications, defined as a composite of eclampsia, placental abruption, haemolysis, elevated liver enzymes, Haemolysis, Elevated Liver enzymes and Low Platelets syndrome, acute pulmonary oedema, admission to an intensive care unit, acute kidney injury requiring dialysis, and stillbirth. Pre-eclampsia was defined in accordance with the International Society for the Study of Hypertension in Pregnancy's guideline.[11]

To assess gestational diabetes detection and management, we analysed the proportion of women with gestational diabetes who required insulin, and the incidence of macrosomia, defined as a birthweight above the 97th percentile. Gestational diabetes was diagnosed in accordance with the Australasian Diabetes in Pregnancy Society guidelines.[12]

Secondary outcomes were: stillbirth; NICU admission; and preterm birth (birth before 37 weeks' gestation). Stillbirth was defined as the death of a baby from 20 weeks' gestation, or with a birthweight of 400 g or more if gestational age was unknown.

Statistical analysis

Due to the rapid implementation of this programme during the COVID-19 pandemic, we did no power calculations, but the outcomes for all women over this time period were reported.

Continuous outcomes were presented as mean (SD) for normally distributed variables and median (IQR) for skewed data. Baseline characteristics were described for the conventional, implementation, and integrated care periods. The incidence of pre-eclampsia, fetal growth restriction, and gestational diabetes in the three time periods were described, and we compared differences between the conventional and integrated care periods using a χ^2 test. We calculated weekly incidence of dichotomous outcomes (singletons with birthweight <10th percentile, singletons with birthweight <3rd percentile, singletons with birthweight <3rd percentile born at or after 40 weeks' gestation, singletons induced for suspected fetal growth restriction, singletons induced at <39 weeks for suspected fetal growth restriction with birthweight >10th percentile, women diagnosed with pre-eclampsia, women diagnosed with gestational diabetes [all who required insulin and women with a baby with macrosomia (birthweight >97th percentile)], stillbirth, NICU admission, and preterm birth [<37 weeks' gestation]) stratified by model of care (low risk or high risk) and did an interrupted time-series analysis using a Prais–Winsten generalised

	Conventional care (n=20 031)	Implementation period (n=685)	Integrated care (n=2292)	p value
Age, years	31·29 (5·19)	31·36 (5·04)	31·61 (5·31)	0·03
Body-mass index, kg/m²	25 (22–29)	25 (22–30)	25 (22–29)	0·08
Smoking in pregnancy	1253 (6%)	46 (7%)	147 (6%)	0·86
Nulliparous	7983 (40%)	271 (40%)	894 (39%)	0·73
Multiple pregnancy	375 (2%)	11 (2%)	51 (2%)	0·43
Maternal region of birth				
Australia	8363 (42%)	292 (43%)	1012 (44%)	0·06
Africa	813 (4%)	23 (3%)	109 (5%)	..
Southern Asia	5961 (30%)	209 (31%)	642 (28%)	..
Southeast and eastern Asia	3158 (16%)	109 (16%)	363 (16%)	..
Central and western Asia	266 (1%)	7 (1%)	30 (1%)	..
Europe	907 (5%)	32 (5%)	72 (3%)	..
Other	563 (3%)	13 (2%)	64 (3%)	..
Antenatal visits				
In person	165 256/165 263 (99·9%)	3667/5443 (68%)	9423/20 154 (47%)	<0·0001
Telehealth	107/165 263 (0·06%)	1776/5443 (33%)	10 731/20 154 (53%)	..
Appointments not attended	8538/165 263 (5%)	500/5443 (9%)	1589/20 154 (8%)	<0·0001
In person*	8537/165 256 (5%)	358/3667 (10%)	682/9423 (7%)	<0·0001
Telehealth*	1/107 (1%)	142/1776 (8%)	907/10 731 (8%)	0·02

Data are mean (SD), median (IQR), n (%), or n/N (%). *Denominators reflect the total number of appointments of that type offered during the period.

Table 1: **Maternal and antenatal care characteristics in the conventional and telehealth integrated care periods**

least-squares regression-based approach, accounting for autocorrelation of the residuals and added robust SEs to determine any changes in each of the outcomes after telehealth implementation.[13] We did not correct for seasonality. We also assessed the Durbin–Watson statistic as an indicator of how well the model corrected for autocorrelation with a value of 2 indicating no autocorrelation within the model; all models met this assessment of accounting for autocorrelation. The coefficients reported were the pre-trend slope (rate of change in incidence of respective outcomes per week in the conventional care period [Jan 1, 2018—March 22, 2020]), the intervention slope (difference in rate of change in incidence of respective outcomes between April 20 and July 2G, 2020, relative to the conventional care period), and the post-trend slope (rate of change in incidence of respective outcomes per week in the integration period [April 20—July 2G, 2020]).

To minimise selection and misclassification bias, all women who attended antenatal care at Monash Health were assessed after giving birth. We used routinely collected health outcome data, to minimise the risk of missing data. In allowing an implementation period, misclassification bias was minimised, since women identified with pre-eclampsia and fetal growth restriction in the conventional care period would have given birth during the implementation period.

Two-tailed p values of less than 0·05 were considered to indicate statistical significance. All statistical analyses were done using Stata IC (version 12.0).

Role of the funding source

There was no funding source for this study.

Results

Between Jan 1, 2018, and March 22, 2020, 20 031 women gave birth at Monash Health with conventional care. Telehealth was integrated into antenatal care delivery across Monash Health on March 23, 2020; thus we assessed comparative outcomes for 2292 women who gave birth between April 20 and July 2G, 2020. Thus, the total observational study period assessed outcomes from 23 008 births, comparing all women who gave birth during the 3-month telehealth integrated care with those who gave birth in the 2G months before telehealth implementation.

Women who gave birth during the telehealth integrated care period were slightly older (31·G1 *vs* 31·29 years; p=0·03) than those who gave birth during the conventional care period. No other significant differences between the groups were observed for BMI, smoking, parity, or region of birth (table 1).

During the study period, the mean number of antenatal consultations done remained stable at approximately 1400 per week. However, the proportion of consultations delivered via telehealth increased rapidly during the implementation period, with a mean of 7GG telehealth consultations done per week (7GG [53%] of 1400 consultations via telehealth *vs* 0·9G [0·0G%] consultations during the conventional care period; table 1, figure 2A). Most of these consultations were by video call with 5% done via telephone (data not shown). In low-risk care models women received a mean of five (5G%) of nine visits by telehealth, whereas women in high-risk models received four (40%) of ten visits via telehealth (figure 2B).

The total number of appointments that women did not attend was significantly higher in the integrated care period than the conventional care period (1589 [8%] of 20 154 consultations *vs* 8538 [5%] of 1G5 2G3 consultations; p<0·0001; table 1). However, during the integrated care period, the overall number of appointments that were not attended was similar for both telehealth and in-person consultations (figure 3). A higher number of in-person consultations were missed than telehealth consultations in high-risk care models (figure 3A), whereas the number of telehealth consultations missed was higher than in-person consultations in low-risk care models (figure 3B).

Regarding fetal growth restriction, no significant differences were identified in the proportion of babies born with a birthweight below the 3rd percentile in the integrated care period when compared with the

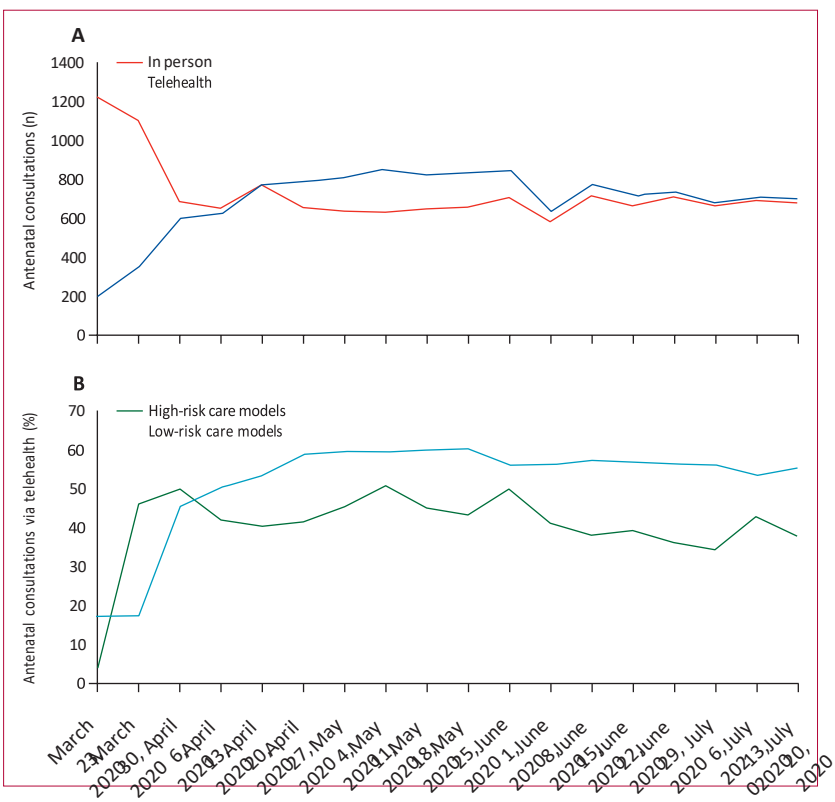

Figure 2: **Number of in-person and telehealth consultations delivered per week after telehealth implementation on March 23, 2020**

Absolute number of in-person and telehealth consultations (A) and the percentage of antenatal consultations delivered by telehealth for low-risk and high-risk care models (B) between March 23 and July 20, 2020. The implementation period was defined as March 23–April 19, 2020, and the integrated care period was defined as the period April 20–July 26, 2020.

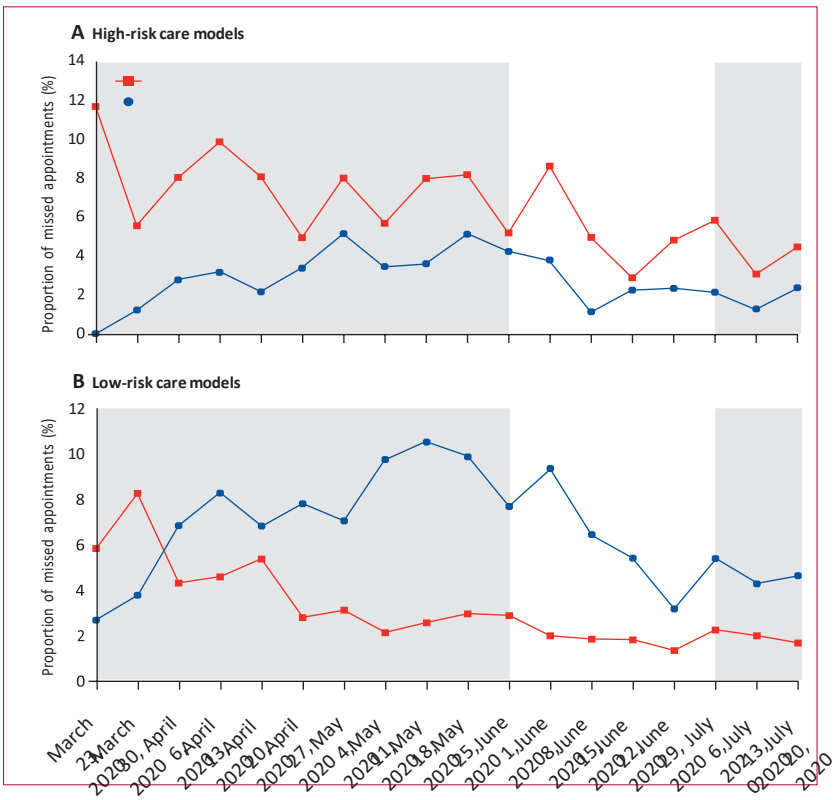

Figure 3: **Proportion of consultations not attended per week following telehealth implementation**
Proportion of missed appointments for in-person and telehealth consultations for high-risk care models (A) and low-risk care models (B). Shaded areas indicate the periods of community lockdown in Melbourne (VIC, Australia) during the COVID-19 pandemic.

conventional care period for low-risk care models (39 [2%] of 17G7 singleton births in the integrated care period *vs* 322 [2%] of 15 470 singleton births in the conventional care period; p=0·72) or high-risk models (25 [5%] of 474 singleton births *vs* 192 [5%] of 418G singleton births; p=0·50). No significant differences were identified in the proportion of babies born with a birthweight below the 10th percentile in the integrated care period when compared with the conventional care period for low-risk care models (1G7 [10%] of 17G7 singleton births in the integrated care period *vs* 150G [10%] of 15 470 singleton births in the conventional care period; p=0·71) or high-risk care models (G1 [13%] of 474 singleton births *vs* 580 [14%] of 418G singleton births; p=0·55; table 2). In interrupted time-series analysis, no significant differences were identified in the rate of change per week in the number of babies born with a birthweight below the 3rd percentile after the introduction of telehealth compared with the conventional care period in low-risk care models (0·0G% change per week [95% CI −0·07 to 0·20]; p=0·37) or high-risk care models (−0·14% change per week [−0·41 to 0·13]; p=0·31; table 3). Similarly, no significant differences were identified in the number of babies born with a birthweight below the 3rd percentile born at or after 40 weeks' gestation for the conventional care period and integrated care period (tables 2, 3). Compared with the conventional care period, no differences in the number of women who were induced for suspected fetal growth restriction per week were identified during the telehealth integrated care period for low-risk care models (−0·19 [95% CI −0·40 to 0·03]) or high-risk care models (−0·008 [−0·37 to 0·3G]), or for the number of women who were induced before 39 weeks resulting in a baby with a birthweight above the 10th percentile (table 3).

Additionally, no significant differences were identified in the incidence of stillbirth overall between the integrated and conventional care periods (1% in the integrated care period *vs* 1% in the conventional care period, p=0·79 for the low-risk care models; 2% *vs* 2%, p=0·70 for high-risk care models), or when crude rates were assessed for either care model (table 2). A 0·22% reduction in the number of stillbirths per week was observed after the integration of telehealth in high-risk care models when compared with conventional care (95% CI −0·47 to 0·03; p=0·09), but this difference was not statistically significant (table 3).

Compared with the conventional care period, in the implementation period, an initial decline was observed in the number of women diagnosed with pre-eclampsia in both low-risk care models (six [1%] of 53G women in the implementation period *vs* 455 [3%] of 15 493 women in the conventional care period) and high-risk care models (six [4%] of 149 women *vs* 328 [7%] of 4538 women; table 2). However, the number of pre-eclampsia diagnoses during the integrated care period was similar to that in the conventional care period (49 [3%] of 17G8 women in low-risk care models and 47 [9%] of 524 women in high-risk care models; table 2). For pregnancies complicated by pre-eclampsia, no significant difference in the median gestation at birth was identified after telehealth integration when compared with conventional care for women in low-risk care models (38·4 weeks [IQR 37·3–39·3) *vs* 38·2 weeks [37·2–39·3]; p=0·27) or women in high-risk care models (37·1 weeks [32·G–38·1] *vs* 3G·8 weeks [34·2–38·0]; p=0·99; table 2). The number of women with pre-eclampsia who had severe complications in the integrated care period was too low to make any conclusive inferences, but was similar to that for the conventional care period for the low-risk care model (two [4%] of 49 women in the integrated care period *vs* 20 [4%] of 455 women in the conventional care period; p=0·94) and high-risk care models (two [4%] of 47 women *vs* 23 [7%] of 328 women; p=0·48; table 2). No significant differences in the number of pre-eclampsia diagnoses per week were identified after the implementation of telehealth in low-risk care models (0·15% change per week [95% CI −0·03 to 0·34]; p=0·10) or high-risk care models (0·20% [−0·31 to 0·70]; p=0·44) when compared with the pre-trend slope for the conventional care period (table 3).

	Conventional care period	Implementation period	Integrated care period	p value*
Low-risk care models				
Fetal growth restriction				
Singletons with birthweight <10th percentile	1506/15 470 (10%)	58/535 (11%)	167/1767 (10%)	0·71
Singletons with birthweight <3rd percentile	322/15 470 (2%)	12/535 (2%)	39/1767 (2%)	0·72
Singletons with birthweight <3rd percentile born at or after 40 weeks' gestation†	74/306 (24%)	1/11 (9%)	8/34 (24%)	0·93
Singletons induced for suspected fetal growth restriction	665/15 470 (4%)	32/535 (6%)	82/1767 (5%)	0·50
Singletons induced at <39 weeks for suspected fetal growth restriction with birthweight >10th percentile‡	213/13 705 (2%)	5/471 (1%)	28/ 1579 (2%)	0·51
Pre-eclampsia				
Women diagnosed with pre-eclampsia	455/15 493 (3%)	6/536 (1%)	49/1768 (3%)	0·70
Gestation at delivery, weeks	38·2 (37·2–39·3)	38·3 (37·6–39·1)	38·4 (37·3–39·3)	0·27
Women with pre-eclampsia with severe complication§	20/455 (4%)	0	2/49 (4%)	0·94
Gestational diabetes				
Women diagnosed with gestational diabetes	3405/15 493 (22%)	113/536 (21%)	386/1768 (22%)	0·89
Requiring insulin	1242/3405 (36%)	43/113 (38%)	127/386 (33%)	0·12
Baby with macrosomia at birth (birthweight >97th percentile)	384/3405 (11%)	13/113 (12%)	33/386 (9%)	0·10
Perinatal morbidity or mortality¶				
Stillbirth	105/15 516 (1%)	1/537 (<1%)	11/1768 (1%)	0·79
NICU admission	237/15 516 (2%)	10/537 (2%)	29/1768 (2%)	0·60
Preterm birth (<37 weeks' gestation)	869/15 516 (6%)	30/537 (6%)	82/1768 (4%)	0·10
High-risk care models				
Fetal growth restriction				
Singletons with birthweight <10th percentile	580/4186 (14%)	30/139 (22%)	61/474 (13%)	0·55
Singletons with birthweight <3rd percentile	192/4186 (5%)	14/139 (10%)	25/474 (5%)	0·50
Singletons with birthweight <3rd percentile born at or after 40 weeks' gestation†	17/161 (11%)	1/11 (9%)	1/19 (5%)	0·47
Singletons induced for suspected fetal growth restriction	207/4186 (5%)	7/139 (5%)	30/474 (6%)	0·19
Singletons induced at <39 weeks for suspected fetal growth restriction with birthweight >10th percentile‡	56/3217 (2%)	1/98 (1%)	5/368 (1%)	0·55
Pre-eclampsia				
Women diagnosed with pre-eclampsia	328/4538 (7%)	6/149 (4%)	47/524 (9%)	0·15
Gestation at delivery, weeks	36·8 (34·2–38·0)	37 (35·4–38·4)	37·1 (32·6–38·1)	0·99
Women with pre-eclampsia with severe complication§	23/328 (7%)	0	2/47 (4%)	0·48
Gestational diabetes				
Women diagnosed with gestational diabetes	1178/4538 (26%)	41/149 (28%)	156/524 (30%)	0·06
Requiring insulin	584/1178 (50%)	22/41 (54%)	78/156 (50%)	0·92
Baby with macrosomia at birth (birthweight >97th percentile)	194/1178 (16%)	7/41 (17%)	27/156(17%)	0·79
Perinatal morbidity or mortality¶				
Stillbirth	99/4897 (2%)	2/159 (1%)	13/574 (2%)	0·70
NICU admission	723/4897 (15%)	23/159 (14%)	101/574 (18%)	0·01
Preterm birth (<37 weeks' gestation)	1307/4897 (27%)	42/159 (26%)	164/574 (29%)	0·34

Data are n/N (%) or median (IQR). The conventional care period was defined as Jan 1, 2018, to March 22, 2020, the implementation period as March 23 to April 19, 2020, and the integrated care period as April 20 to July 26, 2020. NICU=neonatal intensive care unit. *Conventional care period versus integrated care period. †Calculated as number of singleton babies born with a birthweight below the 3rd percentile at or after 40 weeks' gestation divided by number of babies born with a birthweight below the 3rd percentile after 32 weeks' gestation. ‡Calculated as number of babies induced before 39 weeks' gestation for suspected fetal growth restriction with birthweight above the 10th percentile divided by the number of babies born after 35 weeks' gestation with a birthweight above the 10th percentile. §Severe complication from pre-eclampsia defined as a composite of haemolysis, elevated liver enzymes and low platelets syndrome, eclampsia, placental abruption, pulmonary oedema, and stillbirth. ¶Denominator is all babies.

Table 2: **Maternal and neonatal complications in low-risk and high-risk care models**

An increase in the incidence of gestational diabetes diagnosed in high-risk care models was observed after telehealth implementation, but this difference was not significant (15G [30%] of 524 women in the integrated care period *vs* 1178 [2G%] of 4538 women in the conventional care period; p=0·0G), and no increase was

	Pre-trend slope*	p value	Intervention†	p value	Post-trend slope‡	p value
Low-risk care models						
Fetal growth restriction						
Singletons with birthweight <10th percentile	−0·006% (−0·21 to 0·008)	0·42	−0·002% (−0·37 to 0·36)	0·99	−0·083% (−0·38 to−0·35)	0·96
Singletons with birthweight <3rd percentile	−0·003% (−0·009 to 0·003)	0·26	0·06% (−0·07 to 0·20)	0·37	0·06% (−0·08 to 0·19)	0·39
Singletons with birthweight <3rd percentile born at or after 40 weeks' gestation	−0·04% (−0·18 to 0·09)	0·57	−0·58% (−3·48 to 2·33)	0·70	−0·61 (−3·51 to 2·28)	0·68
Singletons induced for suspected fetal growth restriction	−0·009% (−0·02 to 0·001)	0·08	−0·19% (−0·40 to 0·03)	0·09	−0·19% (−0·41 to 0·02)	0·08
Singletons induced at <39 weeks for suspected fetal growth restriction with birthweight >10th percentile	−0·02% (−0·36 to −0·04)	0·013	−0·25% (−3·51 to 3·02)	0·88	−0·45% (−3·70 to 2·80)	0·78
Pre-eclampsia						
Women diagnosed with pre-eclampsia	−0·001% (−0·001 to 0·009)	0·83	0·15% (−0·03 to 0·34)	0·10	0·15% (−0·03 to 0·32)	0·10
Gestational diabetes						
Women diagnosed with gestational diabetes	0·04% (0·016 to 0·054)	<0·001	−0·02% (−0·52 to 0·47)	0·93	0·01% (−0·48 to 0·50)	0·95
Requiring insulin	−0·04% (−0·09 to 0·02)	0·18	0·72% (−0·42 to 1·85)	0·21	0·68% (−0·44 to 1·81)	0·23
Baby with macrosomia at birth (birthweight >97th percentile)	−0·05% (−0·09 to −0·21)	0·001	0·55% (−0·26 to 1·36)	0·18	0·49% (−0·31 to 1·30)	0·22
Perinatal morbidity or mortality						
Stillbirth	0·001% (−0·002 to 0·005)	0·48	0·02% (−0·04 to 0·09)	0·52	0·02% (−0·04 to 0·08)	0·50
NICU admission	0·006% (−0·0003 to 0·01)	0·06	0·03% (−0·10 to 0·15)	0·69	0·03% (−0·09 to 0·15)	0·62
Preterm birth (<37 weeks' gestation)	0·003% (−0·008 to 0·01)	0·62	0·12% (−0·10 to 0·35)	0·29	0·12% (−0·09 to 0·35)	0·27
High-risk care models						
Fetal growth restriction						
Singletons with birthweight <10th percentile	0·0005% (−0·03 to 0·03)	0·98	−0·14% (−0·91 to 0·63)	0·73	−0·14 % (−0·90 to 0·63)	0·73
Singletons with birthweight <3rd percentile	0·01% (−0·003 to 0·03)	0·10	−0·14% (−0·41 to 0·13)	0·31	−0·12% (−0·39 to 0·14)	0·36
Singletons with birthweight <3rd percentile born at or after 40 weeks' gestation	−0·03% (−0·19 to 0·12)	0·66	0·55% (−0·48 to 1·57)	0·30	0·51% (−0·51 to 1·53)	0·32
Singletons induced for suspected fetal growth restriction	0·002% (−0·15 to 0·02)	0·76	−0·008% (−0·37 to 0·36)	0·97	−0·01% (−0·37 to 0·36)	0·98
Singletons induced <39 weeks for suspected fetal growth restriction with birthweight >10th percentile	0·03% (−0·19 to 0·25)	0·80	−0·70% (−6·47 to 5·08)	0·81	−0·67% (−6·44 to 5·10)	0·82
Pre-eclampsia						
Women diagnosed with pre-eclampsia	−0·003% (−0·03 to 0·02)	0·79	0·20% (−0·31 to 0·70)	0·44	0·19% (−0·31 to 0·71)	0·44
Gestational diabetes						
Women diagnosed with gestational diabetes	0·04% (−0·001 to 0·74)	0·06	0·38% (−0·51 to 1·27)	0·40	0·42% (−0·47 to 1·31)	0·34
Requiring insulin	0·13% (0·02 to 0·25)	0·03	−0·51% (3·49 to 2·46)	0·73	−0·38% (−3·35 to 2·59)	0·80
Baby with macrosomia at birth (birthweight >97th percentile)	−0·03% (−0·12 to 0·06)	0·47	−0·72% (−2·85 to 1·41)	0·51	−0·75% (−2·88 to 1·38)	0·49
Perinatal morbidity or mortality						
Stillbirth	0·002% (−0·008 to 0·01)	0·70	−0·22% (−0·47 to 0·03)	0·09	−0·22% (−0·47 to 0·03)	0·09
NICU admission	−0·0003% (−0·03 to 0·03)	0·98	−0·44% (−1·04 to 0·16)	0·15	−0·43% (−1·04 to 0·16)	0·15
Preterm birth (<37 weeks' gestation)	−0·03% (−0·07 to 0·006)	0·10	−0·68% (−1·37 to −0·002)	0·049	−0·71% (−1·40 to −0·03)	0·04

Data are percentage change per week (95% CI). NICU=neonatal intensive care unit. *Change in rate of respective outcomes per week during the conventional care period. †Change in incidence of respective outcomes per week during the telehealth integration period compared with the conventional care period. ‡Change in rate of respective outcomes per week during the integrated care period.

Table 3: **Interrupted time-series analysis for maternal and neonatal outcomes in conventional and integrated care periods for low-risk and high-risk care models**

observed among women in low-risk care models (38G [22%] of 17G8 women *vs* 3405 [22%] of 15 493; p=0·89; table 2). No changes were observed in the proportion of women with gestational diabetes requiring insulin or giving birth to a baby with a birthweight above the 97th percentile in the low-risk or high-risk care models (table 2). Across the conventional care period, a small increase in the number of women diagnosed with gestational diabetes per week was observed in low-risk care models (0·04% increase [95% CI 0·02–0·05]; p<0·001), with no significant change observed following the introduction of telehealth (p=0·93; table 3). Similarly, in high-risk care models, the number of women with gestational diabetes requiring insulin increased by 0·13% per week (95% CI 0·02–0·25; p=0·03) in the conventional care period, but this increase was not significantly altered with telehealth integration (p=0·73; table 3).

No significant differences were identified in the proportion of babies requiring NICU admission born to women in the low-risk models of care (29 [2%] of 17G8 babies in the integrated care period *vs* 237 [2%] of 15 51G babies in the conventional care period; p=0·G0; table 2), or the weekly change in rate of NICU admission in the conventional or intergrated care periods. Among women in high-risk care models, a significantly higher proportion of babies were admitted to NICU in the integrated care period than in the conventional period (101 [18%] of 574 babies *vs* 723 [15%] of 4897 babies; p=0·01; table 2); however, in interrupted time-series analysis no significant differences in the rate of weekly NICU admission were identified after telehealth integration compared with conventional care (–0·44% change per week [95% CI –1·04 to 0·1G]; p=0·15; table 3).

The proportion of babies born preterm was similar for all time periods for both low-risk care models (82 [4%] of 17G8 babies in the integrated care period *vs* 8G9 [G%] of 15 51G babies in the conventional care period; p=0·10) and high-risk care models (1G4 [29%] of 574 babies *vs* 1307 [27%] of 4897 babies; p=0·34; table 2). However, for women in high-risk care models, the number of preterm births reduced by 0·G8% per week (95% CI –1·37 to –0·002; p=0·049) after telehealth integration compared with the conventional care period (table 3).

Discussion

We found that our telehealth programme delivered around 50% of antenatal consultations via telehealth without affecting the detection and management of common pregnancy complications, including pre-eclampsia, fetal growth restriction, and gestational diabetes, when compared with conventionally delivered antenatal care.

The COVID-19 pandemic has been the catalyst for change in antenatal care delivery, prompting reduced in-person interactions, but also stimulating funding for telehealth services by the Australian Government.[14] Investment in telehealth integration into health care has been suggested not only to enhance preparedness for disasters,[15] particularly when infrastructure remains intact, as observed in the current pandemic,[1G] but also to improve the delivery of patient-centred care.[17] Evidence in many areas of medicine shows that care delivered via telehealth results in similar health outcomes to traditional in-person consultations.[18] In this study, we showed that pregnancy outcomes following the implementation of telehealth in antenatal care seem to be similar to those with conventional in-person care.

Although telehealth has been increasingly used in the 21st century, particularly to access specialist care for individuals who live in rural or remote areas, and has been shown to result in similar or improved clinical outcomes to in-person delivered care,[18] telehealth has seldom been used in antenatal care.[5,18,19] The available literature has mainly focused on the use of telemonitoring or mobile health applications for targeted approaches, such as smoking cessation, influenza vaccination, blood pressure monitoring, blood sugar level monitoring, and wellness checks.[4,19–2G] In developing our programme, regular antenatal consultations were maintained because fewer consultations have been associated with increased incidence of adverse pregnancy outcomes, patient anxiety, and dissatisfaction with care.[27,28] Therefore, telehealth was integrated into this schedule to maintain regular consultations, but to reduce the need for in-person attendance. We were able to leverage a telehealth system already in use at our health service for the delivery of paediatric telehealth consultations and modify the system for antenatal care. We recognised that a key limitation of telehealth is the inability to do physical examinations, which are essential in antenatal care for detecting hypertensive disorders of pregnancy and aberrant fetal growth; thus we also implemented low-cost measures to support these assessments in settings remote from hospital.

Home blood pressure monitoring has the potential to reduce iatrogenic intervention. A 2020 systematic review found that home blood pressure monitoring was associated with reduced incidence of antenatal admission, pre-eclampsia diagnosis, and induction of labour.[24] We observed an initial decrease in the number of pregnancies diagnosed with pre-eclampsia during population lockdown between March 1G and March 31, 2020, in Melbourne, when reductions in hospital attendances to pregnancy assessment units and emergency departments were observed. After lockdown was ended in the state of Victoria on May 31, 2020, a return to baseline was observed for women in low-risk models of care and an increased incidence of pre-eclampsia in women in high-risk models of care initially. Since the data presented was obtained for women who gave birth at hospital during this time, true diagnoses of pre-eclampsia would not have been missed. Furthermore, although the incidence of pre-eclampsia does not inform the timing of diagnosis and whether this was delayed through the use of telehealth, the gestation at

birth remained similar to the conventional care period. Considering the reduction in the incidence of preterm births during the initial stages of the COVID-19 pandemic,[29] it would be interesting to further assess whether this similar reduction in pre-eclampsia incidence was also more widely observed.

Detection of fetal growth restriction is challenging. Our health system predominately uses symphyseal-fundal height measurements for tracking fetal growth across pregnancy, in accordance with current recommended practice for low-risk pregnancies.[8] Insufficient evidence exists regarding the ability of symphyseal-fundal height measurements to detect fetal growth restriction, with this approach detecting 12–15% of babies with growth restriction in low-risk pregnancies.[30] Similar symphyseal-fundal heights results are obtained regardless of whether measurements are done by a health-care professional or self-measured.[31] No increases in undetected fetal growth restriction pregnancies or a change in the incidence of stillbirths—for which undetected fetal growth restriction is a major risk factor—were observed.[32] This has also not been achieved at the cost of increased iatrogenic intervention, with the balance measure of birth of appropriately grown babies before 39 weeks' gestation remaining stable for women in both low-risk and high-risk models of pregnancy care. Universal third trimester growth surveillance is more accurate for the identification of fetal growth restriction in the low-risk population than symphyseal-fundal heights; thus implementation of such an approach might further assist in reducing poor outcomes associated with fetal growth restriction.[33] There have been concerns that this approach might increase iatrogenic intervention; however, the use of universal third trimester growth surveillance in combination with telehealth has not been assessed previously.

Gestational diabetes was assessed as a surrogate marker of clinical care since diabetic management in pregnancy seems to be unaffected by the mode of care delivery,[2G] which was supported by the finding that the incidence of insulin-requiring gestational diabetes and macrosomia in the population remained stable across all time periods.

A similar number of missed appointments were observed for both in-person and telehealth consultations; however, the influencing factors for this might differ. In-person consultations might have been impacted by concerns of COVID-19 exposure and challenges with attending during lockdown, whereas challenges with technology, communication of appointments, and issues regarding access might have influenced attendance at telehealth consultations.[34] To better understand factors that might have influenced missed appointments and identify population groups for whom telehealth might not be suitable, an in-depth review of consumer characteristics is needed. The number of missed appointments in the telehealth integrated period in the last 4 weeks of the study period were lower than that in the conventional care period.

The strengths of this study are the uniformity of implementation of telehealth integrated care across a large health service, with large numbers of births assessed in both the conventional and integrated care periods, which strengthened the findings with minimal missing data. The large sample size is likely to have reduced the impact of bias, since all women assessed would have had telehealth integrated in their pregnancy care, with the exception of women who declined telehealth or could not be contacted for a telehealth consultation, or who had not had antenatal care, but attended the hospital for birth. Furthermore, the outcomes assessed were routinely collected data from all women who gave birth at the health service, enabling reliable assessment across time to review the effect of health-care changes on pregnancy outcomes. We are confident about the safety of this approach for the delivery of antenatal care, since there were no recorded COVID-19 cases in pregnancy in Victoria during the telehealth integrated care period. As such, any potential influence that COVID-19 in pregnancy might have had on these outcomes did not further bias or influence the results. We believe our findings are widely generalisable for implementation or adaption to other health services, since the population included were highly heterogeneous and video call technology is now widely and cheaply available.

Limitations of this study relate to its retrospective nature; however, the major risk of selection bias was minimised since all consecutive pregnancies were included in the analysis. Since the study period consisted of the first 3 months following implementation of integrated antenatal care, there is the possibility that further differences in outcomes might continue to change and become more apparent over time, particularly for endpoints, such as stillbirth, which were likely to be underpowered. Furthermore, the possible influence of concomitant measures associated with the COVID-19 pandemic and population lockdown on the findings of the interrupted time-series analysis cannot be excluded. Important variables yet to be assessed, such as detection of family violence, might have been affected by the pandemic and rate of detection via telehealth, and this warrants ongoing evaluation. Furthermore, since more than 95% of telehealth consultations were done by video call, these findings might not be generalisable to systems that solely use voice calls.

Considering these encouraging initial findings, this method of antenatal care delivery will continue, thereby enabling future evaluation to provide greater certainty as to the safety of this approach. Many changes have occurred during the pandemic, such that although the number of COVID-19 cases in Melbourne were low during the evaluation period, the impact of lockdown, physical distancing, and heightened anxiety might also influence changes observed. Consumer evaluation of both staff and patient satisfaction with this programme,

including its acceptance by diverse multicultural and socioeconomic groups, and cost-effectiveness will be crucial to inform its ongoing use. Assessment of telehealth programmes in antenatal care delivery for women in rural or remote regions of the USA indicate that the programmes have been well received by patients and health-care practitioners.[35] Additionally, although cost-effectiveness data in antenatal care are scarce,[3] the potential to reduce economic disruption of conventional antenatal care for patients exists, through minimising travel time and costs, and reducing potential loss of income due to non-attendance at work.

In conclusion, we successfully integrated telehealth into antenatal care delivery at a large publicly funded health-care network, utilising many low-cost interventions, making our findings widely applicable to a range of health-care settings. Although telehealth was implemented during a global health crisis, which facilitated the rapid development and uptake of telehealth, this programme might provide many benefits for the future delivery of antenatal care and minimise risk in future epidemics. We have shown that such an approach seems to be safe for continuing to achieve a high standard of pregnancy care.

Contributors

KRP, AR, KP, MLG, KB, HD, RF, AES, and RJH designed the intervention. KRP, AR, KP, KB, HD, RF, AES, AS, and RJH were involved in implementation of telehealth integrated care. KRP, BWM, and RJH designed the study. MT collected primary data. KRP, MT, and MD-T did data analysis. KRP and MD-T verified the data. KRP, DLR, EMW, BWM, and RJH interpreted the findings. KRP wrote the primary manuscript and all authors contributed to the final submitted manuscript.

Declaration of interests

BWM is a consultant for Guerbet, and has received research grants from Guerbet and Merck. KRP has received consultancy fees from Janssen. All other authors declare no competing interests.

Data sharing

De-identified individual participant data is available on request from Monash Health Human Research Ethics Committee (research@monashhealth.org.au).

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References

1 Ministry of Health. Maternal mortality in childbirth. Ante-natal clinics: their conduct and scope. London: Her Majesty's Stationery Office, 1929.

2 Australian Institute of Health and Welfare. Australia's mothers and babies data visualisations. https://www.aihw.gov.au/reports/mothers-babies/australias-mothers-babies-data-visualisations/contents/labour-and-birth/place-of-birth (accessed July 24, 2020).

3 Greiner AL. Telemedicine applications in obstetrics and gynecology. *Clin Obstet Gynecol* 2017; **60:** 853–GG.

4 de Mooij MJM, Hodny RL, O'Neil DA, et al. OB Nest: reimagining low-risk prenatal care. *Mayo Clin Proc* 2018; **93:** 458–GG.

5 Magann EF, McKelvey SS, Hitt WC, Smith MV, Azam GA, Lowery CL. The use of telemedicine in obstetrics: a review of the literature. *Obstet Gynecol Surv* 2011; **66:** 170–78.

G Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015; **12:** e1001885.

7 Papageorghiou AT, Ohuma EO, Gravett MG, et al. International standards for symphysis-fundal height based on serial measurements from the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project: prospective cohort study in eight countries. *BMJ* 201G; **355:** i5GG2.

8 Australian Government Department of Health. Clinical practice guidelines. Pregnancy care. Canberra, ACT: Australian Government Department of Health, 2018.

9 Dobbins TA, Sullivan EA, Roberts CL, Simpson JM. Australian national birthweight percentiles by sex and gestational age, 1998–2007. *Med J Aust* 2012; **197:** 291–94.

10 Hunt RW, Davey M, Ryan-Atwood T, Hudson R, Wallace EM, Anil S. Victorian perinatal services performance indicators 2017–18. 2019. https://www.bettersafercare.vic.gov.au/sites/default/files/2019-02/Vic%20perinatal%20services%20performance%20indicators%202017-18.pdf (accessed May 25, 2021).

11 Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens* 2018; **13:** 291–310.

12 Nankervis A, McIntyre H, Moses R, et al. ADIPS consensus guidelines for the testing and diagnosis of gestational diabetes mellitus in Australia. 2014. http://www.adips.org/downloads/ADIPSConsensusGuidelinesGDM-03.05.13Version ACCEPTEDFINAL.pdf (accessed May 25, 2021).

13 Linden A. Conducting interrupted time-series analysis for single- and multiple-group comparisons. *Stata J* 2015; **15:** 480–500.

14 Australian Government Department of Health. COVID-19 national health plan–primary care package–MBS telehealth services and increased practice incentive payments. https://www.health.gov.au/resources/publications/covid-19-national-health-plan-primary-care-package-mbs-telehealth-services-and-increased-practice-incentive-payments (accessed July 25, 2020).

15 Lurie N, Carr BG. The role of telehealth in the medical response to disasters. *JAMA Intern Med* 2018; **178:** 745–4G.

1G Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. *N Engl J Med* 2020; **382:** 1G79–81.

17 Duffy S, Lee TH. In-person health care as option B. *N Engl J Med* 2018; **378:** 104–0G.

18 Flodgren G, Rachas A, Farmer AJ, Inzitari M, Shepperd S. Interactive telemedicine: effects on professional practice and health care outcomes. *Cochrane Libr* 2015; **2015:** CD002098.

19 DeNicola N, Grossman D, Marko K, et al. Telehealth interventions to improve obstetric and gynecologic health outcomes: a systematic review. *Obstet Gynecol* 2020; **135:** 371–82.

20 Khalil A, Perry H, Lanssens D, Gyselaers W. Telemonitoring for hypertensive disease in pregnancy. *Expert Rev Med Devices* 2019; **16:** G53–G1.

21 Gyselaers W, Lanssens D, Perry H, Khalil A. Mobile health applications for prenatal assessment and monitoring. *Curr Pharm Des* 2019; **25:** G15–23.

22 van den Heuvel JFM, Kariman SS, van Solinge WW, Franx A, Lely AT, Bekker MN. SAFE@HOME - feasibility study of a telemonitoring platform combining blood pressure and preeclampsia symptoms in pregnancy care. *Eur J Obstet Gynecol Reprod Biol* 2019; **240:** 22G–31.

23 Alves DS, Times VC, da Silva ÉMA, Melo PSA, Novaes MA. Advances in obstetric telemonitoring: a systematic review. *Int J Med Inform* 2020; **134:** 104004.

24 Kalafat E, Benlioglu C, Thilaganathan B, Khalil A. Home blood pressure monitoring in the antenatal and postpartum period: a systematic review meta-analysis. *Pregnancy Hypertens* 2020; **19:** 44–51.

25 Feroz A, Perveen S, Aftab W. Role of mHealth applications for improving antenatal and postnatal care in low and middle income countries: a systematic review. *BMC Health Serv Res* 2017; **17:** 704.

2G Ming WK, Mackillop LH, Farmer AJ, et al. Telemedicine technologies for diabetes in pregnancy: a systematic review and meta-analysis. *J Med Internet Res* 201G; **18:** e290.

27 WHO. WHO recommendations on antenatal care for a positive pregnancy experience: summary. Geneva, Switzerland: World Health Organization, 2018. http://apps.who.int/iris/bitstream/handle/10GG5/259947/WHO-RHR-18.02-eng.pdf;jsessionid=81133G5FD531FG2F7E18F3585CC01880?sequence=1 (accessed June 14, 2021).

28 Dowswell T, Carroli G, Duley L, et al. Alternative versus standard packages of antenatal care for low-risk pregnancy. *Cochrane Libr* 2015; **2015:** CD000934.

29 Philip RK, Purtill H, Reidy E, et al. Reduction in preterm births during the COVID-19 lockdown in Ireland: a natural experiment allowing analysis of data from the prior two decades. *medRxiv* 2020; published June 5. https://doi.org/10.1101/2020.0G.03.20121442 (preprint).

30 Robert Peter J, Ho JJ, Valliapan J, Sivasangari S. Symphysial fundal height (SFH) measurement in pregnancy for detecting abnormal fetal growth. *Cochrane Libr* 2015; **2015:** CD00813G.

31 Bergman E, Kieler H, Petzold M, Sonesson C, Axelsson O. Self-administered measurement of symphysis-fundus heights. *Acta Obstet Gynecol Scand* 2007; **86:** G71–77.

32 Selvaratnam RJ, Davey MA, Anil S, McDonald SJ, Farrell T, Wallace EM. Does public reporting of the detection of fetal growth restriction improve clinical outcomes: a retrospective cohort study. *BJOG* 2020; **127:** 581–89.

33 Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet* 2015; **386:** 2089–97.

34 Scott Kruse C, Karem P, Shifflett K, Vegi L, Ravi K, Brooks M. Evaluating barriers to adopting telemedicine worldwide: a systematic review. *J Telemed Telecare* 2018; **24:** 4–12.

35 Bhandari NR, Payakachat N, Fletcher DA, et al. Validation of newly developed surveys to evaluate patients' and providers' satisfaction with telehealth obstetric services. *Telemed e-Health* 2019; **26**: 879–88.