Investigating incidence and prevalence of preeclampsia globally and within Aotearoa/New Zealand: An integrative review

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE DEGREE OF MASTER OF PROFESSIONAL PRACTICE
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ABSTRACT

Introduction: Preeclampsia is a complex hypertensive disorder diagnosed during pregnancy, ≥ 20 weeks' gestation. Collectively, preeclampsia and eclampsia account for one-third of severe maternal morbidities and are responsible for 10–15% of maternal mortality rates, predominantly in low to middle-income countries. While the pathogenesis of preeclampsia remains unclear, multiple studies suggest aetiology may stem from a combination of several complex, multifactorial interactions, including genetic and environmental causes. Few studies report on the global incidence or prevalence of preeclampsia, nor examine specific risk factors within individual nations, including Aotearoa/New Zealand. Moreover, due to reliance on now outdated diagnostic criteria, under-reporting of rates of preeclampsia is likely.

Aim: This research aims to 1) describe the incidence and prevalence of preeclampsia both globally and nationally, and 2) identify any environmental, geographical, cultural and socio-economic factors that may be associated with preeclampsia incidence and prevalence in Aotearoa/New Zealand. All primary research studies and other relevant published literature informing the topic between January 2010 and August 2020 will be critiqued and evaluated; in particular, those meeting with cross-sectional, cohort or systematic review criteria.

Method: The quantitative method of an integrative review was selected as the most suitable for an extensive critique and analysis of international and national literature available over the past decade which commented on the mapping of the global incidence and prevalence of preeclampsia, while identifying emergent themes of interest. Key word searches will be undertaken within the Wintec 'OneSearch' library access of major data bases, including (but not limited to) *CINAHL Complete, Clinical Trials, Directory of Open Access Journals, Gale Academic One File, PLOS/ONE* and *Science Direct.* Articles not relating specifically to preeclampsia incidence and/or prevalence will be excluded along with any duplicates, articles not available in English, and those involving animal rather than human participants. By assessing many forms of research, the existing body of knowledge can be evaluated and future areas for interest and research potential ascertained.

Results: Following analysis of six multi-database keyword searches identifying 2833 potential articles for review, the search was limited to include academic journals only and studies undertaken between January 2015 and August 2020, in order to attempt to exclude those drawing on pre-2014 diagnostic criteria for preeclampsia requiring manifestation of proteinuria. Once duplicates were excluded, abstracts were then analysed for potential inclusion. Keyword search six was abandoned due to a significant number of identified duplicates. Those making no specific reference to incidence or prevalence of preeclampsia were also excluded. In total, 64 studies from around the globe were included in the final review analysis and examined in full-text PDF format. Many studies published beyond 2015 continued to apply outdated diagnostic criteria for preeclampsia or failed to report their countries overall incidence and/or prevalence of preeclampsia. Other studies that later re-evaluated their findings in line with the revised 2014 International Society for the Study of Hypertension in Pregnancy Guidelines noted higher incidence of preeclampsia once new criteria were applied. Many studies attributed the incidence of preeclampsia to poverty, delayed and/or inaccurate diagnosis, limited health resources, or inequitable access to those that were available; however, this aspect needs further and more in-depth exploration. There were no studies originating from Aotearoa/New Zealand that met with inclusion criteria, meaning scope for future research within this context is warranted.

Conclusion: Globally and within Aotearoa/New Zealand, incidence and prevalence of preeclampsia cannot be determined in exact measures, due largely to limitations in reporting, and the potential for missed diagnosis due to use of conflicting diagnostic criteria. Additionally, further examination and assessment of factors such as environmental, geographical, cultural, and social considerations which may influence and/or impact on the incidence and prevalence of preeclampsia, both globally and within an Aotearoa/New Zealand framework, should be comprehensively explored and evaluated.

Key Words: preeclampsia, geographic location, altitude, international, worldwide, global, distribution, spread, occurrence, incidence

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"Titiro whakamuri, kokiri whakamua"

Look back and reflect in order to move forward …

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Arohanui wāhine ma

CONSIDERATION OF ETHICS

The commitment to engage with the research process is a legal prerequisite for all New Zealand registered midwives (New Zealand College of Midwives [NZCOM], 2015). Furthermore, knowledge of research methodology provides deeper insight and appreciation for research processes whilst simultaneously encouraging health practitioners to become well-informed research consumers (Whitehead & Maude, 2016).

There exists no predisposed right to conduct or undertake research. Ethical and culturally appropriate research methods, by definition, must unfold within a framework in which multivalent systems both compete and conflict. Moreover, one must remain alert to the fact that, whenever people are recruited as research participants, an inherent risk for harm potentiates. Midwives, as with all healthcare professionals, need firstly to ensure any research proposal is morally, ethically, and culturally validated prior to commencement (Anderson & Thorogood, 2015).

Following the post-World War II Nuremberg trials for atrocities committed against humanity, the inherent need to minimise risk for future harm led to the establishment of international research ethics guidelines; including the Nuremberg Code, the Helsinki Declaration, The Belmont Report and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Jarmusik, 2019). These research ethics guidelines, when aligned with our nation's commitment to Te Tiriti ō Waitangi principles and bi-cultural considerations, ensure a legal framework within which advocacy for health policies that promote the tenants of social justice and informed choice and consent may be upheld (Burgess, 2008).

As Tangata Whēnua of Aotearoa/New Zealand, Māori have (as granted by the 1975 Treaty of Waitangi Act and 1988 Royal Commission on Social Policy), the right to optimal health and wellbeing, yet are disproportionately represented in the worst of our nation's social and health statistics (Ramsden, 2007; Perinatal and Maternal Mortality Review Committee [PMMRC], 2020). Therefore, while there is no formal requirement for ethical approval to be granted prior to undertaking an integrative review, Te Tiriti ō Waitangi key principles of self-determination, partnership, protection and participation (alongside our midwifery model of care and standards for professional practice) must continue to underpin Aotearoa/New Zealand's biomedical, ethical and cultural commitment to uphold human rights, medical accountability, patient dignity, appropriate treatment and effective communication for our most vulnerable populations, in particular Māori (NZCOM, 2015; Waikato District Health Board [WDHB], 2020). As such, Te Tiriti ō Waitangi provides the legal framework for identifying actual and potential Māori issues and ethical concerns and must be formally considered prior to undertaking any research project (Hudson et al., 2010; NZCOM, 2015).

BACKGROUND

Ko Rachel Taylor toku ingoa

Ko ahau te whaea ō nga tamahine ō te iwi ngati toa

Kia kaha wāhine toa

Tihei mauri ora

"Health is not merely the absence of disease or infirmity; it is a social phenomenon, the determinants of which cannot be separated from the social & cultural world in which we live" (Rose, 1992, as cited in Thorogood, 2015, p.59).

Prior to commencing work at the Waikato Institute of Technology (Wintec) I was employed as a rural caseload locum midwife in the South Waikato region, one of the largest, most diverse and geographically remote areas in New Zealand, representing 10% of the national birth rate in 2014 (Waikato District Health Board [WDHB, 2015). The birthing population in the South Waikato communities are predominantly Māori, often living in poverty with poor general health. The area is flanked by dairy farms and industrial zones, both of which spill environmental contaminants into the waterways and soil. Many homes built in the 1950s in response to the need to house the influx of workers to the region (and destined for demolition after 5 – 10 years), remain privately tenanted and dilapidated with deteriorating walls coated in lead-based paint and lined with asbestos. There is high ratio of fast-food outlets in the South Waikato urban areas and obesity affects as many as 70% of women. Up to 50% of women will continue to smoke throughout their pregnancy and more than 50% of children live in extreme social deprivation. More of these children will be born small and face long-term adverse health sequelae. Additionally, it is estimated that at least 10% of pregnant women in these areas will develop gestational diabetes mellitus and long-term Type II diabetes mellitus, both of which engender significant risk for lifelong hypertensive disorders and cardiovascular disease. The region has a higher (predominantly Māori) teenage birthing rate than other regions; a cohort now determined as one of the most at-risk pregnant populations in Aotearoa/New Zealand (Health Quality & Safety Commission [HQSC], 2019; WDHB, 2020). The number of young women I cared for over the years who suffered the consequences of preeclampsia and eclampsia (including kidney failure requiring transplant, severe essential hypertension, and stillbirth), is a sad yet insightful reflection on the preventable cycle of socio-economic deprivation and its engendered co-morbidities. Strong government policies that support improved and more accessible maternity and social services are essential in New Zealand if we are to successfully address and achieve better outcomes for our most vulnerable and at-risk populations.

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CHAPTER ONE – INTRODUCTION

1.1 Introduction to Preeclampsia

Written accounts of the history of preeclampsia as a uniquely human pregnancy condition date back as far as 5000 years, meaning there have been approximately three – five billion documented cases since *Homo sapiens* first walked upon the Earth (Robillard et al., 2016). According to the World Health Organisation (WHO) evaluation, preeclampsia afflicts approximately four million births every year, resulting in as many as 50,000 maternal deaths globally, the burden of which is largely carried by developing nations (WHO, 2011, as cited in Robillard et al., 2016).

Emergent research over the past decade has given rise to burgeoning evidence of links between genetic, immunological, inflammatory, and environmental factors and the pathogenesis of preeclampsia (Hutcheon et al., 2011). Furthermore, current research relating maternal systemic inflammatory responses to a predisposition for developing preeclampsia, continues to draw interest from clinicians worldwide. This will likely provide impetus for ongoing research and further insight into the preeclampsia disease pathology (Redman & Staff, 2015).

Globally, preeclampsia features as a leading cause of maternal, fetal and neonatal morbidity and mortality (Duley, 2009) and is associated with numerous pathophysiological changes leading to vascular dysfunction, and central nervous and systemic organ dysfunction; all of which engender significant risk for maternal and neonatal morbidity (August & Sibai, 2020).

This introductory chapter will provide a definition of hypertensive disorders of pregnancy in Aotearoa/New Zealand, discuss the background and aims of this research within a New Zealand midwifery model of care, and assess current challenges presented by health inequities and barriers to health care access, in particular by Māori, as Tangata Whēnua of Aotearoa/New Zealand. Finally, the structure of the thesis will be explained and summarised prior to moving to Chapter Two, which will examine the definition of preeclampsia, define it in terms of both incidence and prevalence, evaluate current criteria for accurate diagnosis, identify risk factors for preeclampsia, and assess the aetiology and pathophysiology of preeclampsia.

1.2 Hypertensive Disorders of Pregnancy in Aotearoa/New Zealand

Hypertensive disorders of pregnancy (HDP) in New Zealand are classified and coded by the Ministry of Health (MoH, 2018) into five categories, each aligning with the revised 2014 International Society for the Study of Hypertension in Pregnancy (ISSHP) statement to include:

- chronic/pre-existing hypertension
- gestational hypertension
- pre-eclampsia
- eclampsia
- HELLP syndrome (a variant of severe pre-eclampsia; elements of which include Haemolysis, Elevated Liver enzymes, and Low Platelet count).

HDP are the most commonly-reported cause for medical referral arising during pregnancy and are the second highest cause of pregnancy-associated hospital admissions in Aotearoa/New Zealand, occurring in approximately 5 – 10% of all pregnancies. Preeclampsia is diagnosed in 3 – 8% of all pregnancies, depending on region and individual District Health Board data and reporting (HQSC, 2019; MoH, 2018). Furthermore, women with HDP are more likely to experience pregnancy complications including placental abruption, premature delivery, fetal growth-restriction and neonatal demise (HQSC, 2019).

Known causes and risks for preeclampsia include genetic factors, ethnicity, immunologic processes, obesity (and other life-style factors), socio-economic and deprivation considerations, and environmental factors including pollution and geographic location, while in low and middle-income settings, preeclampsia and eclampsia feature in approximately 8% of all pregnancies, accounting additionally for 15 – 20% of all maternal morbidity and mortality statistics (Engjom et al., 2018).

1.3 Background to this Study

In 2013, a global and regional systematic review of the estimated incidence of preeclampsia was published by a collaboration of Argentinian and WHO researchers in the Department of Reproductive Health and Research, Geneva, Switzerland, with an aim to assess the methodological quality of eligible studies reporting incidence on HDP between 2002 – 2010 (Abalos et al., 2013). Preeclampsia and eclampsia have been identified as leading global causes of both maternal morbidity and mortality, and the reduction of maternal mortality is a key aim within the WHO Millennium Development Goals project, thereby

giving merit to the 2013 review which undertook an evaluation of the global and regional impacts of preeclampsia and other hypertensive disorders of pregnancy (Abalos et al., 2013).

Of 129 studies that met with the 2013 (Abalos et al., 2013) study's inclusion criteria, 74 reports obtained from 78 databases reporting on HDP were analysed. Data assessed represented close to 39 million women from 40 nations and determined an overall global incidence of 4.6% for preeclampsia and 1.4% for eclampsia. Limitations of the review were the comparatively small number of countries reporting on preeclampsia and eclampsia, with only seven reporting on national incidence. Furthermore, most articles reviewed emanated from North America and Western European countries, meaning reporting over global regions was limited and incidence rates therefore difficult to determine with any certainty (Abalos et al., 2013). Additionally, the Abalos et al. review defined preeclampsia as new-onset hypertension in the second half of pregnancy, with proteinuria as a requirement for diagnosis; a definition that was subsequently revised in 2014 to **remove proteinuria** (and include fetal growth restriction) as a requisite feature of the disease pathology (Abalos et al., 2013; Brown et al., 2018; Lowe et al., 2015).

This revised definition was then recommended for integration into New Zealand practice that same year, and further reinforced within the 2018 New Zealand's Ministry of Health updated publication of the *Diagnosis and treatment of hypertension and preeclampsia in pregnancy in New Zealand* guidelines (MoH, 2018). Given the 2013 Abalos global review drew upon this now-outdated definition criteria for preeclampsia, there is likelihood that diagnosis, coding and/or reporting may have been inaccurate, overlooked and therefore unreliable, giving merit to this integrative review, as well as highlighting implications for future research studies within an Aotearoa/New Zealand framework and context.

1.4 Aims of this Research

Although the pathogenesis of preeclampsia is extremely complex, multiple studies now suggest its aetiology may stem from a combination of several complex, multifactorial interactions, including genetic and environmental causes (Hutcheon et al., 2011). Furthermore, few studies since the 2013 systematic review (Abalos et al., 2013) have reported on either the global incidence or prevalence of preeclampsia, nor examined specific risk factors within individual nations, including Aotearoa/New Zealand. Moreover, due to reliance on now outdated diagnostic criteria, under-reporting of rates of preeclampsia may be suspected.

This research aims to:

1. Investigate and describe the incidence and prevalence of preeclampsia both globally and nationally,
2. Identify any environmental, cultural, and socio-economic factors that may be associated with preeclampsia incidence and prevalence in Aotearoa/New Zealand.

These aims will be achieved by critiquing and evaluating primary research studies and other published literature between January 2010 and August 2020; in particular, those meeting with defined inclusion criteria (see below) and which fulfil either cross-sectional, cohort or systematic review methodology. The quantitative method of an integrative review will be undertaken to critique and analyse existing international and national literature available over the past decade which comments on the mapping of the global incidence and prevalence of preeclampsia. Articles not relating specifically to preeclampsia incidence and/or prevalence will be excluded, along with any duplicates, articles not available in

English, and those involving animal rather than human participants. By assessing many forms of research, the existing body of knowledge can be evaluated and future areas for interest and research potential ascertained. Additionally, by evaluating current knowledge and understanding of the prevalence and incidence of preeclampsia (alongside any potential social and environmental influences), this research hopes to determine and identify any gaps in current Aotearoa/New Zealand hypertension in pregnancy guidelines to better inform future midwifery, maternity and health-care initiatives.

1.4.1 Factors for Consideration alongside the Research Aims:

While the pathogenesis of preeclampsia remains uncertain, multiple studies now suggest its aetiology stems from a combination of several complex, multifactorial interactions; including genetic and environmental considerations (Zhou et al., 2019). Furthermore, given much of the information currently available regarding risk stratification and the management of preeclampsia emanates from predominantly high-income countries, there is ongoing need for further investigation in countries reporting the highest incidence of maternal mortality related to preeclampsia (Dias et al., 2019). Additionally, due to sub-optimal reporting alongside inconsistent application of correct and current diagnostic criteria, the actual global incidence of preeclampsia is yet to be determined (Mayrink et al., 2019).

1.4.1.1 World-wide Incidence and Prevalence of Preeclampsia and Potential Risk Factors

World-wide incidence of preeclampsia may range anywhere from 2 – 17% (Poropet et al., 2018), and is responsible for 15 – 20% of severe maternal and perinatal morbidity and mortality cases, including 60,000 maternal deaths and more than 500,000 premature births each year (Ma'ayeh & Costantine, 2020), particularly in low-middle income countries (Elliot

et al., 2014). Incidence is estimated to be seven-times higher in developing nations such as India (Malik et al., 2019), while prevalence in certain Latin American countries is estimated to be greater than 25%, giving rise that differing rates globally may be attributed to unique geographic, social, economic and racial differences (Ma'ayeh & Costantine). A 2011 Canadian study examining the epidemiology of preeclampsia and other hypertensive disorders of pregnancy (Hutcheon et al., 2011) reported a 3% incidence in the United States of America (USA), 3.3% in New Zealand (based on a 1995 prospective study undertaken by Stone et al., 1995) 3% in Sweden, 4.5% in Denmark and 3% in Norway. Incidence rates were higher in certain North American regions (8.4% in Washington State and 8.7% in Nova Scotia respectively; both of which correctly defined preeclampsia without the previously required inclusion of proteinuria). Hutcheon et al. (2011) also noted a seasonal variation of incidence of preeclampsia; for example, in Northern regions, incidence is more common amongst winter births (Finnish women report a two-fold higher risk for preeclampsia than women in Southern Europe), while in Zimbabwe, there is marked variance in incidence between the dry and wet seasons. Additionally, global prevalence amongst pregnant adolescents (a high-risk birthing cohort) has been determined at 6.7% (Macedo et al., 2020). Overall, global rates have risen on average from 0.5 – 1% (depending on location and available data) between 1992 and 2002 (Hutcheon et al.).

1.4.1.2 Aotearoa/New Zealand Incidence and Prevalence of Preeclampsia and Potential Risk Factors

In Aotearoa/New Zealand, there are growing concerns around the impact of socio-economic disparity and health inequity amongst an ethnically diverse population (HQSC, 2019). National rates of preeclampsia are estimated to afflict between 3 – 6% of all pregnancies, resulting in multi-system pathologies and poor maternal, fetal and new-born outcomes (Mirzakhani et al., 2016).

1.4.1.3 Harm Potential of Preeclampsia for Women & Babies

Risks to women afflicted with preeclampsia include convulsions, placental abruption, cerebral haemorrhage and disseminated intravascular coagulation, renal failure and subcapsular liver haemorrhage, with increased risk for depression, cardiovascular disease and stroke in later life (Tanaka et al., 2007).

Risks for babies include growth restriction, oxidative stress, neonatal acidosis and hypoxaemia, neonatal encephalopathy, pre-term birth and death (Duley, 2009). Considering that each case of neonatal encephalopathy costs New Zealand taxpayers $55 million dollars (HQSC, 2019), meticulous antepartum care that includes early recognition and timely intervention for high-risk women is required alongside appropriate postpartum care.

Such undertaking will increase likelihood that early warning signs will not be missed, and that ongoing preeclampsia care and management strategies in Aotearoa/New Zealand are improved and enhanced.

1.5 Midwifery Model of Care in Aotearoa/New Zealand

Current incidence of preeclampsia in Aotearoa/New Zealand is estimated to affect 3 – 6% of all pregnancies (Mirzakhani et al., 2016) and may potentially be influenced by various environmental and socio-economic considerations as yet to be fully explored and investigated. Our country's unique model of midwifery and maternity care (based upon the tenants of partnership and continuity of care) may afford an appropriate pathway to explore the aims of this research in its commitment to maternity care provision that engages directly

with all women across a culturally diverse and often challenging primary-tertiary healthcare interface.

Midwifery care in Aotearoa/New Zealand is an autonomous practice that became an independent and registered health profession following the 1990 Nurses' Amendment Act (NZCOM, 2015). Following enaction of the 2003 Health Practitioners' Competency Assurance Act, midwifery has been regulated by the Midwifery Council of New Zealand (MCNZ) since 2004 (MCNZ, 2019). Alongside MCNZ competencies, midwifery standards for professional practice are determined by NZCOM, and placed in equal partnership alongside the profession's cultural competency framework of Turanga Kaupapa, gifted to the College in 2008 by the Māori midwifery collective, Ngā Maia (Ngā Maia 2006, as cited in NZCOM, 2015).

The term 'midwife' translates literally as 'with woman' and, in Aotearoa/New Zealand is an autonomous profession synonymous with the political struggles of the consumer-led feminist movement; the 'Save the Midwife' campaign, launched in the late 1970s by a "vociferous minority" of women intent on preserving their birth rites (and rights) against the encroaching tide of medicalised childbirth (Donley, 1992, p. 1). Midwifery, as a dynamic art as well as a science, is founded upon a collection of knowledge derived not only from research, obstetrics and associated health sciences, but from the lived experiences and stories of women; including their *her*story and philosophies placed alongside feminist theory, biculturalism, and the cultural frameworks within which this is grounded (NZCOM, 2015; Wintec, 2017, p. 4). Furthermore, as a holistic profession, the social, emotional, physical, spiritual, cultural and psychological ramifications of women's health experiences must be considered throughout the continuum of the midwifery partnership; seeking actively to

uphold, protect and promote women and their babies' wellness, alongside facilitation of understanding of these key issues within the wider community (NZCOM, 2015).

Midwives in Aotearoa/New Zealand are professionally responsible for the provision of all care, support and advice given to women and their families throughout the pregnancy, childbirth and labour, and up to six weeks' postnatally. They facilitate and support the physiological birthing process, identify any complications that may arise at any time in both or either mother and baby, ensure access to appropriate services, provide emergency care and assistance if required, as well as ensure and oversee all neonatal cares, breastfeeding education and assistance. If, at any time, a woman requires urgent or non-urgent referral for secondary and/or tertiary health care, New Zealand midwives do so in collaboration with other health professionals and associated providers. Additionally, and in accordance with key objectives of Section 88 of the Primary Maternity Services Notice 2007, they may practice in any setting, including the home, hospital or community and are fully responsible and accountable for the care they provide, as per the Midwifery Scope of Practice and Competencies as defined by the MCNZ (MCNZ, 2019). Furthermore, this care must be founded on Te Tiriti ō Waitangi principles which advocate for policies promoting social justice and informed choice and consent (NZCOM, 2015).

Midwifery, therefore, by its very definition, must take place in partnership with women, working within a framework that embraces continuity of care to both enhance and protect the normal physiological processes of pregnancy, childbirth and the postpartum period (NZCOM, 2015). As previously mentioned, the concept of partnership embraced by the profession expands far beyond that which exists simply between midwife, wāhine (woman) and whānau (family)*;* our recognition and commitment to the legal relationship

we uphold as a bicultural nation incorporates both Te Tiriti ō Waitangi and Turanga Kaupapa principles which are integral to midwifery professional standards and competencies for practice (Guilliland & Pairman, 1995; NZCOM, 2015; MCNZ, 2019).

The Turanga Kaupapa cultural framework and guidelines serve to enhance Ngā Maia Kaupapa and provide cultural competencies for midwifery care in Aotearoa/New Zealand, founded upon the four key Te Tiriti ō Waitangi principles as developed by the Royal Commission on Social Policy in 1988 (Hikuroa & Halliday, 2013). These fundamental tenants underpin Turanga Kaupapa and serve to strengthen our commitment as health practitioners to redress social and gender inequity and provide the women of New Zealand with a model of midwifery care that embraces inclusive practice, self-determination, empowerment and respect (NZCOM 2015; MCNZ, 2019; Ramsden, 2007).

Turanga Kaupapa

Whakapapa: *The wāhine and her whānau is acknowledged*

Karakia: *The wāhine and her whānau may use karakia*

Whanaungatanga: *The wāhine and her whānau may involve others in her birthing programme*

Te Reo Māori: *The wāhine and her whānau may speak Te Reo Māori*

Mana: *The dignity of the wāhine, her whānau, the midwife and others involved is maintained*

Hau Ora: *The physical, spiritual, emotional and mental wellbeing of the wāhine and her whānau is promoted and maintained*

Tikanga Whēnua: *Maintains the continuous relationship to land, life and nourishment; and the knowledge and support of kaumatua and whānau is available*

Te Whāre Tangata: *The wāhine is acknowledged, protected, nurtured and respected as Te Whāre Tangata (the "House of the People")*

Mokopuna: *The mokopuna is unique, cared for and inherits the future, a healthy environment, wai ū and whānau*

Manaakitanga: *The midwife is a key person with a clear role and shares with the wāhine and her whānau the goal of a safe, healthy, birthing outcome*

(Ngā Maia, 2006, as cited in NZCOM, 2015)

Thanks to strong professional adherence to these prerequisites (NZCOM, 2015; MCNZ, 2018), midwifery and midwifery education must, by proxy, reflect these key Treaty concepts alongside Turanga Kaupapa and social justice. These concepts are in close alignment with social reconstruction ideology, within which the purpose is to facilitate the redress of all racial, gender, social and economic inequalities (Schiro, 2013). The very heart of midwifery must therefore continue to embrace the fundamental partnership between woman and midwife alongside our professional commitment to honour bi-culturalism, improved health outcomes, equity, and literacy for all (Wintec, 2017, pp. 3-4).

Given that a primary aim of this research is to explore any potential environmental, cultural, and socio-economic factors that may be associated with preeclampsia incidence and prevalence in Aotearoa/New Zealand, our unique model of midwifery care is particularly well-suited to exploring these, given our privileged position of working directly and intimately with women, their babies, and families throughout their entire pregnancy, birthing and postpartum journey.

1.6 Health Inequity in Aotearoa/New Zealand

For midwives and health educators, the social determinants of health disparities and outcomes cannot be ignored. In June 2018, Dr Terry-Ann Clarke (keynote speaker and Māori advisor to the Ministry of Health) delivered a powerful message before the annual PMMRC in the form of her proposed Māori health rubric for addressing health inequity in Aotearoa/New Zealand. It is imperative moving forward that New Zealand health providers

and midwives continue to develop culturally responsible and responsive approaches and methodologies that will address these fundamental concerns.

Dr Clarke's rubric commits to upholding three simple key goals:

- ***Tika* – we address the needs of the people and interpret these needs correctly.**
- ***Mana* – we advance equity, self-determination and social justice.**
- ***Mahi tahi* – we establish relationships for positive change.**

(Clarke, 2018).

These three goals align and interweave synergistically with Turanga Kaupapa and Te Tiriti ō Waitangi principles that serve as both reference and guidance for midwives in Aotearoa/New Zealand to engage positively with women and their families for improved health outcomes within the wider community (NZCOM, 2015). Additionally, these key areas support a primary aim of this research to explore and determine any potential environmental, cultural, and socio-economic factors that may influence preeclampsia incidence and prevalence within Aotearoa/New Zealand.

In New Zealand, Māori and Pacific peoples currently experience greater challenges in achieving improved health outcomes due to poverty, discrimination, and poor access to appropriate and culturally responsive care. Māori women have the lowest uptake of first trimester maternity services and are less likely to receive acceptable levels of care despite clinical and medical indication (HQSC, 2019).

Furthermore, maternal and perinatal-related mortality rates vary significantly in New Zealand when the Index of Deprivation 2013 quintile categories are considered and applied; of particular concern are statistics involving babies of women living in the most deprived social circumstances and regions (quintile five), who experience far greater mortality rates than any other, with variation in mortality by scale of deprivation most noted in neonatal demise due to spontaneous premature birth, with mortality risk and incidence increasing

exponentially alongside increasing deprivation (PMMRC, 2019). In turn, deprivation deciles consider the distribution of deprivation throughout Aotearoa/New Zealand, and divide the country's population into ten parts, with 10% of the population represented in each one. For babies born to New Zealand European women, approximately 10% are represented each decile; however, for Maori, there are very few babies born into the higher deciles, and more than half are born into the most deprived deciles (8 – 10), proving a marked increased risk for deprivation amongst babies born to Māori mothers, with any baby born into a decile ten area experiencing the highest rate and risk of mortality. Furthermore, Māori are the most disproportionately affected population in New Zealand when considering the impact and burden of perinatal-related mortality alongside decile ratings, experiencing nearly twice as many deaths in this group than any other (PMMRC).

As such, research that seeks to identify trends and causes in health inequity for New Zealand's most vulnerable populations (with an aim to determine if modifiable factors such as environmental, geographical, cultural, and socio-economic considerations negatively impact current rates of preeclampsia) is overdue and warranted.

1.7 Structure of the Thesis

Chapter One has provided the context for this thesis aim, has defined and described the categories of hypertensive disorders of pregnancy in Aotearoa/New Zealand, discussed the background and aims of this research framed within the New Zealand midwifery model of care, and assessed current challenges presented by health inequities and barriers to health care access, in particular by Māori, as Tangata Whēnua of Aotearoa/New Zealand.

Chapter Two will explore and examine the current and revised definition of preeclampsia, define the disorder in terms of both incidence and prevalence, evaluate current criteria for accurate diagnosis, assess risk factors for preeclampsia and, finally, review the aetiology and pathophysiology of preeclampsia.

Chapter Three will briefly revisit the aim of the thesis and present the method by which the literature informing the incidence and prevalence of preeclampsia will be explored both globally and within Aotearoa/New Zealand, alongside considerations for any relevant environmental, cultural, and socio-economic factors. The integrative review method will be described and evaluated to explain the process of the literature search, analysis, and synthesis of the selected literature which will then be more closely scrutinised in subsequent chapters.

Chapter Four will synthesise and further evaluate both global as well as national incidence and prevalence of preeclampsia in Aotearoa/New Zealand and provide comment upon emergent themes of interest that may impact upon future practice and research opportunities. Additionally, it will briefly highlight any noted limitations of the research which may then be drawn upon to inform areas for future study and inquiry in Chapter Five.

Chapter Five will summarise the main findings of the integrative review, provide discussion on emergent themes and limitations captured during the review process, discuss key conclusions drawn by the thesis and provide advice regarding implications for future research opportunities.

1.8 Summary

This chapter has examined the current definition of hypertensive disorders of pregnancy in Aotearoa/New Zealand and discussed the background and aims of this study within a New Zealand midwifery model of care, while assessing current challenges presented by health inequities and barriers to health care access, particularly for Māori, as Tangata Whēnua of Aotearoa/New Zealand. The validity of the research aims has been established and the structure for the thesis discussed and summarised by way of introduction to subsequent chapters.

CHAPTER TWO - PREECLAMPSIA

2.1 Introduction

This chapter will explore the current and revised 2014 definition of preeclampsia, define preeclampsia in terms of its incidence and prevalence, evaluate current criteria for accurate diagnosis, assess known risk factors for the prediction of preeclampsia, and review the aetiology and pathophysiology of preeclampsia as a hypertensive disorder of pregnancy.

2.2 Definition of Preeclampsia

Pregnancy is essentially a vasodilatory state, during which there is an 8 to 10-fold increase in the vasodilator prostacyclin (Karumanchi et al., 2005). During the progression of a 'normal' pregnancy, blood pressure will begin to fall from the first trimester, generally reaching its lowest reading in the second trimester, then rising to pre-conceptual levels by term (Lowe et al., 2015).

With the hypertensive disorder preeclampsia, these normal pregnancy changes are altered or disrupted …
(Lowe et al., 2015).

The 2014 Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) *Guideline on Hypertensive Disorders of Pregnancy* defined gestational hypertension as a systolic blood pressure of greater or equal to 140mmHg and/or a diastolic blood pressure greater or equal to 90mmHg arising at or beyond 20 weeks' gestation (Lowe et al., 2015).

In 2018, the New Zealand MoH (MoH, 2018) adopted this definition in line with the 2014 revised ISSHP statement, and included consideration for chronic/pre-existing

hypertension, gestational hypertension, preeclampsia (either newly occurring (*de novo*) or superimposed on chronic hypertension, eclampsia and HELLP syndrome (now considered as a severe manifestation of preeclampsia) (Brown et al., 2018).

Preeclampsia, therefore, may be defined as a unique multi-organ pregnancy hypertensive disorder characterised by gestational or pre-existing hypertension and involvement of one or more other organ systems that may include placental dysfunction and/or the fetus. While it is important to note that hypertension (as defined above) is a common feature of preeclampsia (and additionally that an increase in baseline of 30 mmHg systolic or 15 mmHg diastolic may also be of clinical importance), an increase in blood pressure may not necessarily present as the initial feature of the disease pathology. Furthermore, proteinuria (previously used to elicit diagnosis of preeclampsia), is no longer a mandatory part of the diagnostic criteria for either preeclampsia or HELLP syndrome (Lowe et al. 2015; MoH, 2018).

2.2.1 Proteinuria

While proteinuria is no longer part of the diagnostic criteria for evaluation of preeclampsia, preeclampsia nonetheless remains the most common cause of severe proteinuria in pregnant women (August & Sibai, 2020). Proteinuria occurs secondary to impaired integrity of the glomerular barrier and altered tubular handling of filtered proteins (hypofiltration) leading to increased protein excretion (Norwitz & Repke, 2020). However, several clinical studies cited in Lowe et al. (2015) have demonstrated that neither the rate of increase nor the amount of proteinuria affects maternal or perinatal outcomes in the pathophysiology of preeclampsia, meaning repeated 24-hour urinary protein estimations are not useful. Once the threshold of 0.3g/24 hours or a protein/creatinine ratio (PCR) ≥30 is determined, repeated urinary PCR testing is both unnecessary and burdensome to the health

dollar. Furthermore, fetal growth restriction should be recognised early and managed appropriately, regardless of whether preeclampsia is formally diagnosed (Lowe et al., 2015). However, as many studies beyond 2014 continue to cite proteinuria as a critical element, exact rates of preeclampsia incidence and prevalence are likely to be inaccurately diagnosed, coded and reported.

2.2.2 Haemolytic Anaemia, Elevated Liver Enzymes & Low Platelets 'HELLP' Syndrome

HELLP may represent a severe form of preeclampsia, but the relationship between the two disorders remains controversial. While incidence is rare (approximately 0.1 – 0.8% of all pregnancies), 10 – 20% of those women with preeclampsia and/or eclampsia will develop the disease pathology. As 15 – 20% of women with HELLP syndrome will have no history of hypertension or proteinuria, some authorities have suggested it may be a separate disorder; however, it is generally accepted as a feature of the severe spectrum of the pathology (Sibai, 2020).

HELLP is associated with significant maternal and neonatal morbidity and mortality rates alongside its life-threatening risk for DIC, acute renal failure, pulmonary oedema and subcapsular liver haematoma (Blackburn, 2013). Although the exact pathology of the condition remains unclear, several contributing factors (including placental failure and immunological intolerance (between mother and baby)) are suspected (Thorogood & Donaldson, 2015). A 2012 (Anderson et al., 2012) cohort study on the impact of maternal body mass index (BMI) found that 34% of 178 pre-eclamptic women were obese (BMI>30) and were more likely to develop the disease pathology both in early and term pregnancy.

Increased BMI and risk for preeclamptic disorders can therefore be directly correlated as pro-inflammatory co-morbidities (Anderson et al., 2012). The key concern for health professionals regarding early recognition and appropriate management of HELLP is prevention of its associated risk for placental abruption and subsequent fetal demise (Sibai, 2020).

2.3 Definition of 'Incidence' & 'Prevalence'

2.3.1 Incidence

'Incidence' as a term, describes the rate of development of a disease within an identified cohort over a period (including its continuation and as well as any manifestation of new cases) by examining factors that are attributable to the disease's progress (Friedman, 2004).

2.3.2 Prevalence

In contrast, 'prevalence' refers to the proportion identified as having the disorder at any one point in time by examining the relationship between the disease and other variables of interest (Friedman, 2004).

For the purpose of this review, both **incidence** and **prevalence** were assessed in order to capture as much relevant data as possible.

2.4 Clinical Diagnosis of Preeclampsia

A diagnosis of preeclampsia can be made when hypertension manifests after 20 weeks' gestation, along with one or more of the following signs:

- Renal involvement including but not limited to significant proteinuria; typically, a urinary protein/creatinine ratio ≥30mg/mmol. This may be accompanied with rising serum creatine levels >90 μmol/L and potentially, oliguria <80mL over four hours. In the absence of proteinuria or other evidence of renal involvement, any other feature of end-organ damage alongside new-onset hypertension ≥20 weeks' gestation will also confirm suspicion for preeclampsia.
- Haematological and liver involvement including thrombocytopenia <100,000 /μL, red cell haemolysis, raised serum transaminases and liver necrosis, severe epigastric and/or right upper quadrant pain, increased levels of serum bilirubin and lactate dehydrogenase and, in severe cases, may include 'HELLP' syndrome which may precipitate disseminated intravascular coagulation (DIC) and uncontrolled haemorrhage.
- Neurologically, women may present with hyperreflexia with persistent clonus, severe headache that fails to resolve despite analgesia, visual disturbances, eclamptic seizure and stroke. They may also develop pulmonary oedema, which can prove fatal.
- Additionally, the placenta may be severely impaired and dysfunctional, typically noted alongside early or late-onset fetal growth restriction (Lowe et al., 2015; Malik et al., 2019; MoH, 2018).

2.5 Risk Factors for Preeclampsia

A prospective multicentre cohort study undertaken in 2011 found inherent clinical risk factors for preeclampsia included **nulliparity, advanced maternal age, hypertension, obesity**, **family history of preeclampsia and heart disease**, **low maternal birth weight**, and **history of antepartum bleeding** (North et al., 2011). And, while preeclampsia manifests typically in the primiparous population, its occurrence is also significant amongst multigravidas pregnant to new partners, suggesting that prior exposure to paternal antibodies is an important protective consideration (Karumanchi et al., 2005).

2.5.1 Other important risk factors for preeclampsia and eclampsia:

The New Zealand MoH *Diagnosis and treatment of hypertension and preeclampsia in pregnancy in New Zealand* guidelines (2018) additionally include an extensive list of risk factors for developing preeclampsia, including previous history of preeclampsia, assisted reproductive technology (oocyte donation), renal disease, chronic hypertension, previous history of HELLP syndrome, pre-existing diabetes, antiphospholipid antibodies, systemic lupus erythematosus, and family history of preeclampsia in either a mother or sister (MoH, 2018). Hydatiform moles and/or molar pregnancy have also been identified as presenting an additional potential risk factor for development of preeclampsia (Malik et al., 2019), while researchers in 2017 determined evidence for the protective properties of dietary nitrates, especially those found in leafy greens and beetroot (Cottrell et al., 2017).

2.5.2 Table 1 – Increased risk of developing preeclampsia if woman has pre-existing risk factors

Notable risk factors for preeclampsia:

Pre-existing risk factor	Relative risk/odds ratio	95% CI	Notes
Antiphospholipid antibodies/SLE*	9.72	4.34-21.75	MRF*
Previous history of preeclampsia	7.19	5.85-8.83	MRF
ART* (oocyte donation)	4.34	3.10-6.06	MRF
Renal disease	4.07	2.17-7.66	MRF
Chronic hypertension	3.6	2.0-6.6	MRF
Previous history of HELLP	3.7	0.9-16.1	MRF
Pre-existing diabetes	3.56	2.54-4.99	MRF
Family history of preeclampsia in mother or sister	3.3	1.5-7.4	MRF
Genetic ancestry ▪ African ▪ Indian ▪ Māori ▪ Pacific	 2.97 2.66 1.51 1.21	 1.98-4.4 1.29-5.48 1.16-1.96 0.99-1.57	
Nulliparity	2.91	1.28-6.61	
Multiple pregnancy	2.93	2.04-4.21	
Family history of preeclampsia Father of baby	2.9 2.1	1.70-4.93 1.0-4.3	
Change in partner	2.5	1.8-3.5	
Elevated BMI ≥35 (early/pre-pregnancy)	2.47	1.78-3.15	
Maternal age ≥40 (multiparous)	1.96	1.34-2.87	
Maternal age ≥40 (primiparous)	1.68	1.23-2.29	
Pregnancy interval >10 years	1.83	1.72-1.94	
ART* sperm donation	1.63	1.36-1.95	
Diastolic BP ≥80mmHg at booking	1.38	1.01-1.87	
Any ART*	1.17	1.10-1.24	

Note: This table was adapted using statistics obtained from the New Zealand MoH *Diagnosis and treatment of hypertension and preeclampsia in New Zealand* guidelines (MoH, 2018).

Adjusted odds ratio and relative risk data obtained from Duckitt and Harrington (2005), as cited in MoH, 2018.

*ART = assisted reproductive technology; BMI = body mass index; BP = blood pressure; CI = confidence interval; HELLP = Haemolysis, Elevated Liver Enzymes and Low Platelet count; MRF = major risk factor; SLE = systemic lupus erythematosus

2.6 Aetiology & Pathophysiology of Preeclampsia

Throughout the course of a healthy pregnancy, gas, nutrient and waste product exchange and removal between maternal and fetal circulation is dependent on well-functioning placental perfusion (Karumanchi et al., 2005). During the process of normal vascular invasion and placentation, invasive cytotrophoblasts of fetal origin enter the maternal spiral arteries, transforming them into high-calibre vessels capable of providing adequate perfusion for the developing embryo. The cytotrophoblast cells then differentiate from an epithelial to an endothelial phenotype, during a phenomenon known as *pseudovasculogenesis*. With preeclampsia however, cytotrophoblast cells fail to adopt an invasive endothelial phenotype, leading ultimately to placental ischaemia and fetal growth restriction (Brennan et al., 2013).

Impaired endothelial dysfunction is central to the risk associated with preeclampsia and is believed to be instigated by circulating factors released following placental ischaemia/hypoxia. Amongst these, an imbalance in pro- and anti-angiogenic factors and activation of immune mediators contributing to excessive inflammation are of relevance. In addition, the generation of reactive oxygen species (ROS) within the endothelium plays an important role in vascular dysfunction. Maternal endothelial dysfunction leads to increased systemic resistance, which reduces perfusion to all organs including the placenta, further exacerbating placental ischaemia and promoting a destructive cycle. Most symptoms of the disease pathology of preeclampsia, including HELLP syndrome, can now be definitively attributed to vascular and endothelial causes (Brennan, et al., 2013).

Additionally, intrauterine fetal growth restriction (IUGR) is a key marker in the diagnosis of preeclampsia and presently affects approximately 5% of all pregnancies (ISSHP, 2014). IUGR is associated with numerous short and long-term adverse outcomes, including the complications that iatrogenic prematurity (as a side-effect of early labour induction) may present for new-born babies and their mothers alike. While there are numerous factors that increase the risk for IUGR (including smoking, high blood pressure, IVF pregnancy, preeclampsia and HELLP syndrome), abnormal placentation is now considered as key to the pathophysiology of 'placental' or early-onset preeclampsia (Enkhmaa et al., 2016).

As maternal systemic endothelial dysfunction accounts for many of the pathological markers of preeclampsia, minimum diagnostics should include full blood count including platelets, serum creatinine, aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), urinary protein:creatinine ratio and formal obstetric ultrasound assessment (Norwitz & Repke, 2020). While in Aotearoa/New Zealand we generally investigate ALT levels in addition to AST, the advantage to AST is that it is a single test that reflects both hepatocellular necrosis as well as red cell haemolysis (Sibai, 2020). Additionally, a rising serum haematocrit can indicate haemoconcentration (suggesting contraction of intravascular volume and progression to more severe disease manifestation), while a falling haematocrit may be a sign of haemolysis. Furthermore, while an elevated serum indirect bilirubin concentration may be a better marker of red cell haemolysis, an elevated lactate dehydrogenase (LDH) can also determine severity of the disease pathology, including the onset of HELLP syndrome (Norwitz & Repke, 2020).

2.7 Important Differentiations between Early and Late-Onset Preeclampsia

2.7.1 Definition of Early-Onset Preeclampsia

Early-onset preeclampsia (EOP) is commonly defined as disease manifestation prior to 34 weeks' gestation, frequently aligned with severe fetal growth restriction and is considered 'placental' in causation (Redmann & Staff, 2015). Placental ischaemia is commonly noted with early-onset preeclampsia, which in turn is associated with placental production of numerous inflammatory circulating factors leading ultimately to systemic maternal endothelial dysfunction (Brennan et al., 2013). EOP therefore appears to result from inadequate trophoblast and placental implantation and occurs in 30% of all documented cases worldwide (Robillard, 2017).

With 'placental' preeclampsia, suboptimal perfusion is believed to be initiated by insufficient trophoblastic invasion of the uterine spiral arteries in early pregnancy, a process that may be addressed with the simple inclusion of low-dose aspirin and calcium supplementation from as early as 11 weeks' gestation and preferably prior to 20 weeks' gestation (Meher et al., 2017; Roberge et al., 2017). Malperfusion leads to placental ischaemia and the release of cytokines and other antiangiogenic agents which, in turn, initiate maternal endothelial cell activation.

2.7.2 Definition of Late-Onset Preeclampsia

Late-onset preeclampsia (LOP) occurs at term, from 37 weeks' onwards. The intermediate onset of the disease between these times is likely a mixture of the two (Yung et al., 2014). Recent studies support that LOP may be classified (in terms of its pathophysiology) as 'maternal' causation, often due to pre-existing conditions such as obesity

and diabetes. LOP is the predominant form of preeclampsia globally (90% of all reported cases), particularly in developed nations where both the means and ability to undertake and publish research are available (Robillard, 2017).

However, while both EOP and LOP result in varying degrees of placental malperfusion (Redmann & Sargent, 2007, as cited in Robillard et al., 2017), given preeclampsia manifests in both molar and ectopic pregnancies, neither the fetus nor uterus can be considered as uniquely significant contributors (Hung & Burton, 2006, as cited in Yung et al., 2014).

2.8 Summary

This chapter has explored the 2014 revised and updated definition of preeclampsia, defined preeclampsia in terms of its incidence and prevalence, and evaluated current criteria for accurate diagnosis of preeclampsia. Additionally, it has assessed predetermined and known risk factors for the prediction of preeclampsia and reviewed both the aetiology and pathophysiology of preeclampsia as a hypertensive disorder of pregnancy.

Chapter Three will again revisit the aim of the research and present the method by which the research will explore the literature informing the incidence and prevalence of preeclampsia both globally and within Aotearoa/New Zealand. The integrative review method will be described to explain the process of literature analysis, synthesis and integration that will be evaluated in the chapters which follow.

CHAPTER THREE – RESEARCH METHOD: An Integrative Review

While all research generates evidence, not all evidence is necessarily robust ...
(Shields & Smyth, 2016).

3.1 Introduction

As previously described, the aim of this research is to 1) describe the incidence and prevalence of preeclampsia both globally and nationally, and 2) identify any environmental, cultural, and socio-economic factors which may be associated with preeclampsia incidence and prevalence in Aotearoa/New Zealand.

By drawing upon an integrative review study design method, this research also aims to determine whether there has been a research review undertaken in the past decade of the geographical incidence of preeclampsia within Aotearoa/New Zealand.

To achieve these aims, a rigorous integrative review will be undertaken in order to both critique and analyse all current and existing international and national literature, namely primary research studies and other relevant published literature which inform this study's research aims between January 2010 and August 2020; in particular, those meeting with cross-sectional, cohort or systematic review criteria. Key word searches will be undertaken within the Wintec 'OneSearch' library access of major data bases. Any articles not relating specifically to preeclampsia incidence and/or prevalence will be excluded along with any duplicates, articles not available in English, and those involving animal rather than human participants. By assessing many forms of research, the existing body of knowledge can be further scrutinised and evaluated and future areas for interest and research potential determined. This section on research methodology will also describe and evaluate the process required to search, review and synthesis the selected literature.

Much of what we know and identify as quantitative research methods have been developed from the discipline of epidemiology, championed as early as the mid-19th century by Florence Nightingale when she developed statistical tests which were then used to produce evidence regarding outcomes for sick and wounded soldiers during the Crimean War (Shields & Smyth, 2016). Modern epidemiology (drawn from the Greek word meaning 'the study of people) involves the study of health-related events including pathophysiology and disease patterns amongst human populations and aims, essentially, to achieve three goals (Shields & Smythe, 2016):

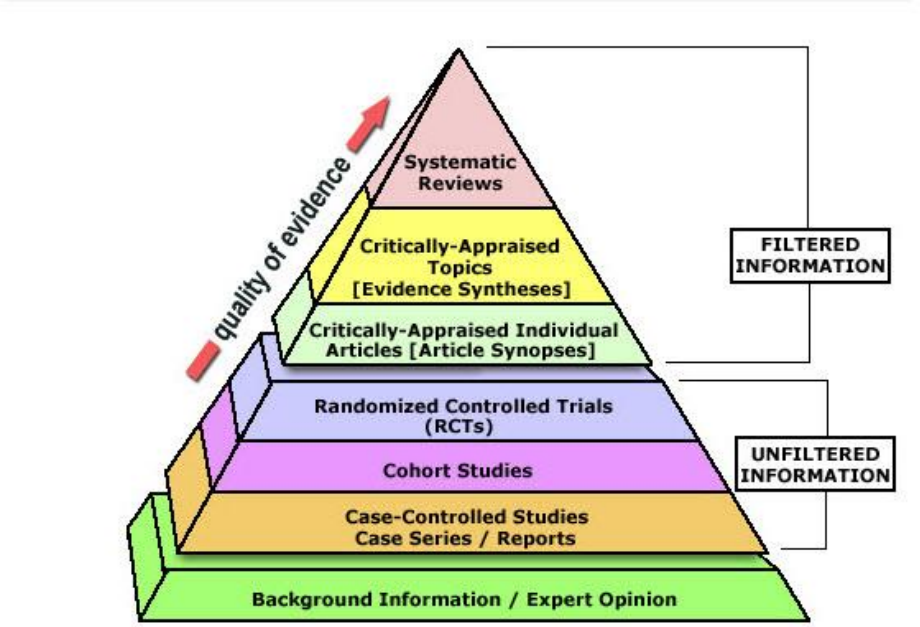
1. Identify and describe disease patterns
2. Identify the cause(s) of these disease patterns (aetiology)
3. Provide data that will then be examined and disseminated in order to inform ongoing and/or future management, evaluation and service-planning for the prevention, control and treatment of the pathology (Shields & Smyth, 2016).

Quantitative or structured research methodology has its roots in the philosophy of rationalism and adheres to a structured and pre-determined set of procedures to explore data to quantify an objective and transparent result that is generalisable and will hold rigour to scrutiny (Kumar, 2014).

3.2 The Evidence Pyramid

The evidence pyramid is a useful, visual tool by which the rigour of quantitative research may be assessed according to its methodology. The highest (and therefore strongest) level of evidence includes systematic reviews, meta-analyses and critical appraisals. The integrative review, while not positioned at the very top of the pyramid, is a well-used approach to undertaking meta-analysis that does not wish to be limited to inclusion of only one type of study (Glover et al., 2006). While a common research approach, there are few

integrative reviews undertaken within the field of midwifery, meaning scope for inquiry using this method is warranted as an appropriate design by which to evaluate this study's research question.



(Glover et al., 2006).

To enhance, develop and promote better and improved health and maternity services throughout Aotearoa/New Zealand, it is vital that best-evidence practice is incorporated within our autonomous model of midwifery care. The integrative review is one of the more academically rigorous methods to ensure this aim, as it requires collection, inclusion, and examination of all current, existing research evidence, which is then systematically critiqued and extensively evaluated (Shields & Smyth, 2016). Given the very nature of an integrative review signals inclusivity, both qualitative and quantitative research can be examined in a purposeful and systematic way, affording an enhanced exploration of the research aim(s). The integrative review process affords a theoretical background to the investigative research proposed by linking that which has already been studied with that which is to be examined.

Additionally, it cements and establishes the level of expertise in the field of interest as expected and helps to ground emergent areas of interest and study within the existing body of knowledge (Kumar, 2014). The integrative review sits within the top frame of the evidence pyramid and affords deeper and critical appraisal of the subject analysis and evidence synthesis by aiming to summarise past research, while evaluating overall conclusions drawn from the available and current body of literature (Whitehead & Maude, 2016).

3.3 The Integrative Review Method – A Definition

The integrative review method affords inclusion of studies with diverse methodologies to be assessed and examined in detail, as all studies that may address either related or identical research questions may potentially be included in the final body of literature (Whitehead & Maude, 2016).

According to Whittemore and Knafl (2005), the integrative review is the only research approach which affords examination of a combination of diverse methodologies, thereby presenting strong potential to inform evidence-based practice in the realm of midwifery research. However, while strategies to enhance data collection and extraction are well developed within the method design, methods of analysis, synthesis, and conclusion drawing may be potentially not as robust when compared with the method of a systematic review incorporating meta-analysis.

For the purpose of this research and, in order to be afforded the opportunity to evaluate as much data and journal articles as possible, the method of an integrative review was selected as the most suitable, due to its potential to allow diverse and holistic primary

research methods to play a greater role within evidence-based practice initiatives (Whittemore & Knafl, 2005).

Whittemore and Knafl (2005) describe the integrative literature review as "a modified framework for research … (in order) to address issues specific to the integrative review method" (p. 546). Their design calls for specification of the review purpose, a comprehensive review of the available literature and evaluation of data from primary sources that is then analysed, results presented and finally discussed (Whittemore & Knufl, 2005).

There are very few integrative reviews published to date that have focused on the field of preeclampsia, and even less so within a midwifery research context. Furthermore, there is no evidence of one having previously been undertaken within Aotearoa/New Zealand. In recognition of this recognised deficit, the integrative review method has been evaluated as an appropriately robust and suitable design for the completion of this research, with the aim that future opportunities will be both identified and justified.

3.4 Review Objectives

The objective of this integrative review is to evaluate and present the best available evidence in order to explore the following research questions:

- What is the incidence and prevalence of preeclampsia both globally and within Aotearoa/New Zealand?
- Is there potential for further exploration of the environmental, cultural and social/socio-economic factors that influence and/or impact on the incidence and prevalence of preeclampsia within an Aotearoa/New Zealand framework?

3.5 Review Method

"An integrative review is a specific review method that summarizes past empirical or theoretical literature to provide a more comprehensive understanding of a particular phenomenon or healthcare problem ..."
(Whittemore & Knafl, 2005, p. 546).

As described in Chapter One, the aim of the following integrative review is to explore the global and national incidence of preeclampsia and evaluate any environmental, cultural and/or social factors that may influence prevalence of the disorder in Aotearoa/New Zealand.

An integrative review seeks to synthesise all relevant and pertinent literature available on a particular topic, with the view to stimulate new perspectives and impetus for further research (Ferrero et al., 2016; Torraco, 2016). As there are few published with a specific midwifery focus, those that are may be cited and drawn upon by research scholars across the

national and international scope (Torraco, 2016). Having identified that the last comprehensive review of global incidence and prevalence of preeclampsia was conducted in 2013 (Abalos et al., 2013), there is merit in revisiting this topic. Furthermore, given the 2013 review drew upon (now defunct) diagnostic criteria for preeclampsia requiring inclusion of proteinuria, reliable reporting of its incidence and prevalence are likely inaccurate. Future investigation of other emergent and possible causes of preeclampsia is also warranted.

3.6 Inclusion Criteria & Search Strategy

To comply with the requirements of an integrative review study design and method meeting with quantitative evaluation, primary research studies and other relevant published information informing the topic were examined, having met firstly with broad appraisal for meeting with either cross-sectional, cohort or systematic review criteria. Critical analysis and oversight of the selected published research affords identification of both the strengths and weaknesses of the literature. Additionally, any omissions or deficiencies may be identified which can then assist with clarification and identification of future research pathways.

The review will then discuss recommendations for ongoing research aiming to critically assess and evaluate the impact of any potential environmental, geographical, cultural and/or social factors that may influence both the incidence and prevalence of preeclampsia within an Aotearoa/New Zealand context.

The aim of the literature search was to capture all relevant, internationally published journal research articles between January 2010 and August 2020 that focused on either cross-sectional (or prevalence) studies and/or cohort (or incidence) studies. Any articles that did not specifically relate to preeclampsia incidence and/or prevalence in the country of the research origin were excluded. Additionally, any trials that involved animal rather than human participation were also excluded. Exact duplicates were removed during each keyword process and the sixth and final keyword search was later abandoned following early identification of a significant number of search double-ups. Additionally, any articles not available in English were also excluded.

The quality and merit of the individual studies included and assessed for the purpose of this review will be discussed in further detail in Chapter Three and then further analysed in Chapter Four. The author will then evaluate if the review process has identified whether previous studies are sufficiently current to continue to inform our understanding of preeclampsia rates both globally and within Aotearoa/New Zealand and determine what other factors may influence its prevalence and incidence.

For the purpose of this research, the author has chosen to adapt the 2005 Whittemore and Knafl design for writing an integrative review (Whittemore & Knafl, 2005), while additionally drawing reference and guidance from the updated 2019 Joanna Briggs Institute Model for Evidence-Based Healthcare (Jordan et al., 2019).

Articles from a wide range of databases and relevant journals meeting with each keyword search criteria published between January 2010 and August 2020 were included following review of each article's abstract, introduction, results and discussion sections (see p. 48). These were then further scrutinised for relevancy, including consideration for each study's definition and diagnostic criteria for preeclampsia, which was revised for wider Australasia in 2014 and again, specifically for New Zealand, in 2018 (Lowe et al., 2015; MoH, 2018). These revisions were undertaken to align with the 2014 ISSHP amendments that made recommendations to exclude proteinuria as a definitive pre-requisite for preeclampsia diagnosis and include fetal growth restriction (ISSHP, 2014, as cited in Wojtowicz et al., 2019). All research trials meeting with this study's criteria and identification process were collected and further examined for relevancy for inclusion and further examination. During the undertaking of Search Five (and due to acknowledgement that the revision of the preeclampsia diagnostic definition in 2014 was yielding potentially outdated results), all articles published prior to 2014 were from then on excluded due to a lack of relevancy alongside likelihood of inaccurate reporting of the prevalence, incidence and rate of preeclampsia globally.

In total, 64 studies from around the globe were analysed from full-text PDF format, with an additional four studies perused for general interest and comment.

3.7 Keyword Searches

Six major and robust key word searches were undertaken within the Wintec 'OneSearch' library access of key data bases, including:

- Academic Search Complete
- CINAHL Complete
- Clinical Trials
- Complementary Index
- Computers and Applied Sciences Complete
- Directory of Open Access Journals (DOAJ)
- Engineering Source
- Gale Academic One File
- Gale Health and Wellness
- PLOS/ONE
- Science Direct

An additional search of Google Scholar was also undertaken, when full-text articles could not be obtained via the 'OneSearch'* library access search engine.

*'OneSearch' is the name accorded to the Wintec Library's search tool (powered by EBSCO Discovery Service), which provides a single search box for accessing a range of electronic resources, including several research databases as denoted above. 'Complementary Index', while technically not a subscription database, is an index of full-text resources that are used for linking search content. Additionally, DOAJ and PLOS/ONE are separate databases linked to the 'OneSearch' tool.

3.7.1 Keyword Search One

‘preeclampsia’ AND ‘geographic location’

This search resulted in 39 articles of which six were extracted for further scrutiny.

3.7.2 Keyword Search Two

‘preeclampsia’ AND ‘geograph*’

This search yielded 262 results of which 22 were reviewed in closer detail.

3.7.3 Keyword Search Three

‘preeclampsia’ AND ‘altitude’

This search yielded 133 results. Once exact duplicates were discounted, 58 articles were then scrutinised, of which four met with inclusion criteria.

3.7.4 Keyword Search Four

‘preeclampsia’ AND (‘international’ or ‘geographic’ or ‘worldwide’) AND (‘distribution’ or ‘spread’)

This search yielded 234 results of which fourteen were selected for further scrutiny. Of these, 10 met with inclusion criteria.

3.7.5 Keyword Search Five

'preeclampsia' AND ('global' or 'international' or 'worldwide') AND ('occurrence' or 'incidence')

Keyword search five initially yielded 2154 results. When article publication dates were limited to between January 2015 – August 2020 (in order to attempt to exclude any study whereby proteinuria was a pre-requisite of diagnostic criteria) results were reduced to 1649 results. Once any double-ups, non-human trials and articles published in any language other than English were excluded, results were further reduced to 993. When this was then further limited to academic journal articles, the search was reduced to 830. Articles were then perused and any immediately identifiable as adhering to pre-2014 diagnostic criteria for preeclampsia were excluded, alongside any in which the true incidence of preeclampsia for that specific country could not be clearly determined. The result was then reduced to 132 articles that met with inclusion criteria for closer investigation, of which 44 were perused in close detail.

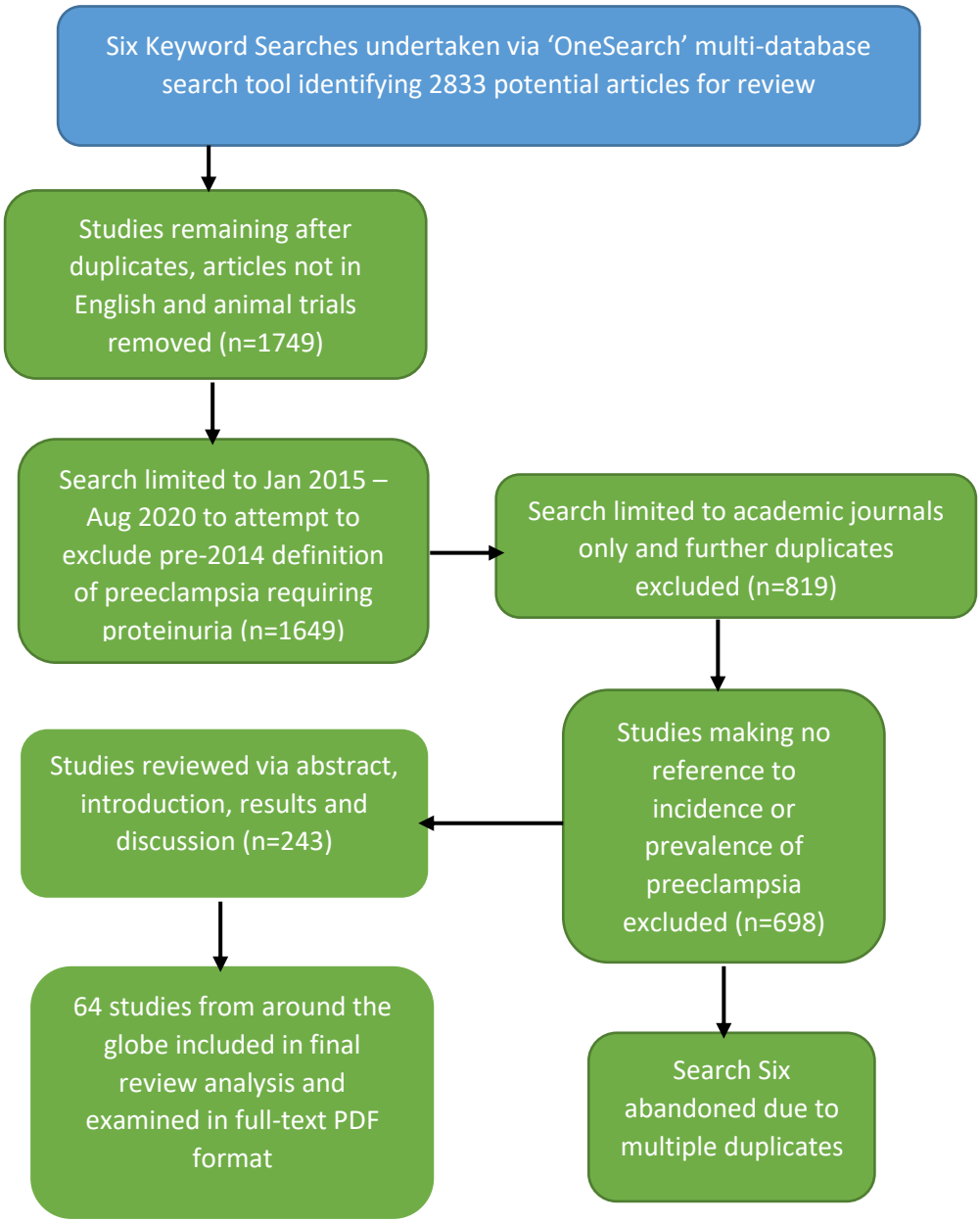
A sub-search of the Directory of Open Access Journals Search One database was then undertaken using the keywords 'preeclampsia' AND 'regional' AND 'international', yielding eleven results, of which four met with review criteria.

3.7.6 Keyword Search Six

As previously detailed, a sixth and final keyword search was quickly abandoned following early identification of a significant number of search double-ups.

3.7.7 Figure 1 – Flow Diagram of the Research Article Selection Process

Flow diagram of the research article selection process for the integrative review - adapted from PRISMA



Databases searched via Wintec 'OneSearch' Engine:

- Academic Search Complete / CINAHL Complete / Clinical Trials / Complementary Index / Computers and Applied Sciences Complete / Engineering Source / Gale Academic One File / Gale Health & Wellness / PLOS/ONE / Science Direct /
- Directory of Open Access Journals (DOAJ)
- Google Scholar

3.7.8 Table 2 – Characteristics of Included Studies

Author/s	Country	Research Method	Participants Number / Inclusion Criteria	Overall reported rate of preeclampsia %	Proteinuria required as part of diagnostic criteria? yes / no
Asgharnia et al., 2017.	Iran	Cross-sectional study	160 women with preeclampsia	8.1% rate of hypertensive disorders of pregnancy reported	no
Aung et al., 2018.	South Africa	Case-Control Study (CCS) (facility-based)	357 South African Black primigravid pregnant women diagnosed with preeclampsia (cases) and 246 South African Black normotensive primigravid pregnant women (controls) n=603	12% reported rate from a previous 2016 single-facility study in Durham, South Africa	yes
Bakwa-Kanyinga et al., 2017	Brazil	Cross-sectional study	533 teen pregnancies	5.3%	no
Benfatah et al., 2018.	Morocco	Retrospective Cohort Study (RCS)	401 women with preeclampsia	7.1%	yes
Bernardes et al., 2019.	Netherlands	Linked cohort study of 1st & 2nd pregnancies	272,551 women from the Dutch Perinatal Registry 2000 - 2007	2.5% and 0.9% respectively	yes
Besnard et al., 2014.	French Polynesia	Retrospective univariate and multivariate data analysis	Preeclampsia linked to 29% of preterm births	not disclosed	not disclosed
Browne et a., 2011.	Bolivia	Cross-sectional case study	187 Andean pregnant women living at high altitude. Those with PE n=20	10.7%	yes
Cho et al., 2016.	South Korea	Retrospective population-based study	212,463 primiparous women birthing between January 2011 – December 2012	3.1%	yes
da Silva Gama et al., 2020.	Brazil	Quasi-experimental study	720 births involving women with hypertension from July 2015 – July 2016 in a tertiary facility in NE Brazil	39.9% (all women were admitted with hypertension)	no
Dias et al., 2019.	Brazil	Stepped wedge cluster randomised trial proposal (PREPARE Trial)	Not yet recruited at time of writing	5% worldwide rate of PE cited	no

Author/s	Country	Research Method	Participants Number / Inclusion Criteria	Overall reported rate of preeclampsia %	Proteinuria required as part of diagnostic criteria? yes / no
Endeshaw et al., 2016.	Ethiopia	CCS (facility-based)	151 women diagnosed with preeclampsia (cases) and 302 healthy women (controls) n=453	8.4%	yes
Engjom et al., 2018.	Norway	Population-based retrospective cohort study	6,367,738 births in Norway, 1999 - 2009	5.6% in nulliparous women; 2.6% in multiparous women	yes
Ferrero et al., 2016.	USA, New Zealand, Sweden, Slovenia, Czech Republic	Literature search of 18 multivariate studies of preterm birth risk factors	4.1 million singleton pregnancies	4.2%, 3.4%, 5.7%, 2.8% and 4.8% respectively	not disclosed
Fox et al., 2017.	Ireland	Cross-sectional study using Irish data from the SCOPE study	1774 women, 68 of whom developed PE	3.8%	yes
Gagliano et al., 2016.	Haiti	Retrospective cohort study	436 pregnant women presenting between January 2013 and July 2015	18% incidence	yes
Hendy et al., 2017.	United Kingdom (UK)	Audit of 16 NHS sites in Wales & England		1.92%	not disclosed
Ivankiv et al., 2018.	Ukraine	Small scale pregnancy examination	25 pregnant women with preeclampsia	Reported incidence of 6–16%	yes
Jayanti et al., 2017.	Indonesia	Analytical observational cross-section study	161 midwives selected using total sampling technique	7-10%	not disclosed
Kaduma et al., 2019.	Tanzania	1:2 Matched CCS (two facilities in Mwanza City)	131 women diagnosed with preeclampsia (cases) and 262 healthy women (controls) n=393	1.4% (based on a previous Tanzanian facility-based study)	yes
Khader et al., 2017.	Jordan	National study of perinatal mortality	21,928 women	1.3%	not disclosed

Author/s	Country	Research Method	Participants Number / Inclusion Criteria	Overall reported rate of preeclampsia %	Proteinuria required as part of diagnostic criteria? yes / no
Khan et al., 2020.	UK	Retrospective comparison study	66,964 singleton pregnancies January 2011 – June 2018	2.8% (n=1870) ISSHP-old 3.0% (n=2019) ACOG 2013 3.4% (n=2301) ISSHP-new 2014	no
Khanapurkar et al., 2016.	India	Cohort study	60 women with severe preeclampsia between 2014 - 2015	6-8%	yes
Kharaghani et al., 2016.	Iran	Systematic review and meta-analysis	132,737 participants from 1996 - 2013	0.7%	yes
Kongwatanakul et al., 2018.	Thailand	Retrospective descriptive study (facility-based)	11,199 deliveries between January 2012 – December 2016	1.9%	no
Li et al., 2018.	China	Retrospective cross-sectional cohort study (facility-based)	199 pregnant women from September 2014 – May 2016	~7%	yes
Lisonkova et al., 2014.	Washington State, USA	Retrospective cohort study	670,120 singleton deliveries between 2000 - 2008	2.9% (2000) increased to 3.1% (2008)	yes
Liu et al., 2019	China	Population-based cohort study in 2 Southern Chinese provinces	205,605 singleton pregnant women	2.4%	yes
Liwang & Bhargah, 2018.	Indonesia	Literature review		Commented only on certain global rates	yes
Maáyeh & Costantine, 2020.	Ohio, USA	Literature review		3-8%	no
Macedo et al., 2020.	Brazil & Italy	Systematic review & meta-analysis	291,247 pregnant adolescents worldwide since 1969	6.7%	no
Malik et al., 2019.	India	Literature review		Revised definition now indicates incidence rate ~28%	no
Marchand et al., 2016.	Mongolia	Cross-sectional study	221 urban (n=136) and nomadic (n=85) women in Ulaanbaatar & regional provinces	4.1%	no

Author/s	Country	Research Method	Participants Number / Inclusion Criteria	Overall reported rate of preeclampsia %	Proteinuria required as part of diagnostic criteria? yes / no
Markin & Medvyedyeva, 2017.	Ukraine	Single unit case-control study	300 singleton pregnancies delivered between June 2014 – June 2017	Specific PE rates not reported	no
Mayrink et al., 2019.	Brazil	Nested case-control multicohort study (Preterm SAMBA)	1373 healthy nulliparous participants of which 1165 complete pregnancy data was available	7.5%	no
Mihiri et al., 2020.	French Guiana	Observational & non-interventional single unit study	1243 women who birthed in the unit between January 2019 and February 2019	7.6%	no
Miyoshi et al., 2018.	Zambia	RCS (facility-based)	1712 deliveries reviewed; 25 cases of preeclampsia and 8 cases of eclampsia identified, n=33	1.93%	yes
Morikawa et al., 2020.	Japan	Retrospective cohort study (facility-based)	94 women diagnosed on admission with preeclampsia	not disclosed	yes
Moyene et al., 2016.	Democratic Republic of Congo (DRC)	CCS	88 women hospitalised with preeclampsia (cases) and 88 healthy women (controls), n=176	6 – 13% (with noted seasonal variation; rainy season versus dry season)	yes
Mrema et al., 2018.	Tanzania	Prospective registry-based study (facility-based)	17738 singleton births; 582 cases of preeclampsia identified.	3.3%	yes
Murmu & Dwivedi, 2020.	India	Prospective observational study (facility-based)	200 pregnant women	3%	not disclosed
Mutabazi et al., 2020.	Rwanda	Combined Retrospective & Prospective Study (2 tertiary facilities in Kigali).	19746 deliveries reviewed; 454 cases of preeclampsia/eclampsia identified.	2.3%	yes
Nakagawa et al., 2016.	Hawaii, USA	Retrospective cohort study	271, 569 deliveries between January 1995 – December 2013	3.3% overall incidence (2.0-4.6%) higher rates noted in ethnic minorities than Europeans	not disclosed

Author/s	Country	Research Method	Participants Number / Inclusion Criteria	Overall reported rate of preeclampsia %	Proteinuria required as part of diagnostic criteria? yes / no
Ngwenya, 2017.	Zimbabwe	Retrospective Descriptive Cohort Study (facility-based)	9086 deliveries reviewed; 121 cases of severe preeclampsia/eclampsia identified.	1.3%	yes
Ngwenya et al., 2019.	Zimbabwe	Single-centre Retrospective Cross-Sectional Study (Proposal)	Not applicable	1.3% rate of severe preeclampsia and eclampsia – reported from 2017 study in same facility	yes
Obi et al., 2019.	Nigeria	Four-year Retrospective CCS (facility-based)	6585 deliveries; 92 cases of preeclampsia identified	1.4%	yes
Olaoye et al., 2019.	Nigeria	Descriptive Cross-sectional study	110 health care providers interviewed; including 75 nurses, 9 obstetric consultants and 26 general practitioners	2 – 16.7%	yes
Osoti et al., 2019.	Kenya	Prospective Cohort Study (facility-based)	266 post-partum women, with or without preeclampsia	32% rate of gestational hypertension (including preeclampsia)	no
Osungbade & Ige, 2011.	Nigeria	Literature Review	Unspecified number of included review articles	2 – 16.7%	yes
Ozimek et al., 2016.	California, United States of America (USA)	Retrospective Cohort Study (facility-based)	386 cases screened for severe maternal morbidity at time of delivery admission (Jan 2012 – June 2014)	10.7% of cases of severe maternal morbidity were attributed to preeclampsia	not disclosed
Pretorius et al., 2018.	South Africa	Systematic Review and Meta-Analysis	6 RCTs from nine publications	14% of all maternal deaths caused by hypertensive disease of which 26% are due to proteinuric hypertension	yes
Rana et al., 2020.	India	Prospective observational cohort study	200 pregnant women	8-10%	not disclosed

Author/s	Country	Research Method	Participants Number / Inclusion Criteria	Overall reported rate of preeclampsia %	Proteinuria required as part of diagnostic criteria? yes / no
Ray et al., 2016.	Ontario, Canada	Retrospective Population-based Cohort Study	881,700 singleton live births between 24-42 weeks' gestation, April 2003 – December 2012	1.2 – 8.3% depending on maternal country of birth (average 4%)	not disclosed
Sacks, et al., 2018.	Israel	Population-based cohort study	231,298 deliveries in a regional tertiary unit between 1991 - 2014	4.1%	not disclosed
Schlembach et al., 2018.	Germany	Economic impact study		2%	No
Serra et al., 2020.	Barcelona, Spain	Prospective cohort study of singleton pregnancies	6893 pregnancies included for analysis	2.3% general rate of PE; 0.2% rate of EOP	No
Shankar et al., 2019.	India	Retrospective observational study (facility-based)	208 women diagnosed with preeclampsia	6.3%	Yes
Thornton et al., 2013.	Australia	Retrospective data analysis	691,738 singleton births from 2000 - 2008	3.3% overall incidence of PE, declining from 4.6 – 2.4%	not disclosed
Toledo-Jaldin et al., 2019.	Bolivia	Report aimed at informing and revising updates to practice		not disclosed	not disclosed
US Preventative Services Task Force, 2017.	USA	Literature & Evidence Review for a Recommendation Statement		4%	No
Vahiddastjerdy et al., 2016.	Iran	Descriptive-retrospective cohort study	5,094,317 deliveries between March 2009 – March 2012	7.7% of all maternal deaths	not disclosed
Vata et al., 2015.	Ethiopia	Retrospective Observational Study (ROS) (hospital-based)	172 women diagnosed with or presenting with symptoms associated with preeclampsia	2.23%	Yes
Wagnew et al., 2016	Ethiopia	Five-year RCS (hospital-based)	1809 women with preeclampsia/eclampsia from 43 hospitals in Addis Ababa	2.2 – 5.58% with 4.2% overall average	Yes
Wahabi et al., 2016.	Saudi Arabia	Multicentre cohort study	14,568 women from November 2013 – March 2015	1.1%	Yes
Wojtowicz et al., 2019.	Poland	Single tertiary unit retrospective cohort study	214 women diagnosed with preeclampsia (singleton pregnancies)	1.7% of 13,716 deliveries 2013 - 2017	No

Author/s	Country	Research Method	Participants Number / Inclusion Criteria	Overall reported rate of preeclampsia %	Proteinuria required as part of diagnostic criteria? yes / no
Xiao et al., 2014.	China	Retrospective cohort study in three regional facilities	67,746 pregnant women from 2002-2011	1.91% overall prevalence	yes
Ye et al., 2014.	China	Multi-centre cross-sectional retrospective study	112,386 pregnant women between January 2011 – December 2011 (n=5969 with HDP)	5.22% with HDP – specific rates of PE not reported	yes
You et al., 2018.	Taiwan	Retrospective population-based cohort study	2,884,347 singleton pregnancies ≥20 weeks with live or stillborn babies January 2001 – December 2014	1.7% rising trend noted following 2014 ISSHP diagnostic criteria revision	no
Yu et al., 2020.	Taiwan	Nationwide study	1,347,672 live births between 2004 - 2011	2.7%	not disclosed

3.8 Search Results – Synthesis of Findings from Table 2

In total, four studies from the USA were analysed, two from Canada, five from Brazil, two from Bolivia, one each from French Guiana and Haiti, one each from Israel, Jordan and Saudi Arabia, two from Iran, one each from Hungary, Ireland, Norway, Poland, Germany, the Netherlands and Spain, two each from the United Kingdom and the Ukraine, one each from Australia, Hawaii and French Polynesia, four from China, five from India, one each from Mongolia, South Korea, Japan and Thailand, two each from Taiwan and Indonesia, one each from Morocco, the Democratic Republic of Congo, Rwanda, Zambia, and Zimbabwe, two from South Africa and three each from Ethiopia and Nigeria. There were no studies emanating from New Zealand that met with this thesis' inclusion criteria, meaning scope for future research is warranted.

Additionally, many of the studies included beyond 2014 (when ISSHP revision of diagnostic criteria for preeclampsia came into effect) either required proteinuria for inclusion and/or did not report on their country's overall rate or incidence. Furthermore, many studies that retrospectively examined reporting of preeclampsia incidence in line with the 2014 revisions, noted and/or were suggestive of, higher rates of the disorder, once new criteria were applied.

Outcomes and reporting on the incidence and prevalence of preeclampsia in each of the included studies will be examined more comprehensively in Chapter Four.

3.9 Summary

Chapter Three has evaluated the research method drawn upon to guide this thesis and its critique of the global and national incidence and prevalence of preeclampsia. The method of an integrative review design method has been described and explored to provide evidence of validity. Additionally, the process undertaken to effectively search, review and synthesise studies meeting with the inclusion criteria has been described for reader clarification.

Merits of the quantitative evidence pyramid (referencing the structure of an integrative review) have been described and defined. Review objectives have been evaluated, and the method of the integrative review explored in depth to provide rationale for merit of selection. Inclusion criteria of selected studies and the applied search strategy have been clearly defined by way of explanation of each keyword search undertaken. Inclusion of visual explanations via implementation of a search flow diagram and integration of a table of

characteristics of included studies were also incorporated to both support and enhance further understanding of the integrative review process.

Chapter Four will now explore and further evaluate both the global as well as national incidence and prevalence of preeclampsia in Aotearoa/New Zealand and provide comment upon emergent themes of interest that may impact upon future practice and research opportunities. Additionally, it will briefly highlight any noted limitations of the research that may be drawn upon to inform areas for future study and inquiry in Chapter Five.

CHAPTER FOUR – OUTCOMES & CRITICAL ANALYSIS

"Where disease occurs is a matter of great importance ... (as) ... comparison of disease rates in different places may strongly suggest aetiological factors or serve as a stimulus to further fruitful investigation …"
(Friedman, 2004, p. 72).

4.1 Introduction

Chapter Four will explore and further evaluate the global and national incidence and prevalence of preeclampsia in Aotearoa/New Zealand and comment upon emergent themes of interest that may impact upon future practice and research opportunities. Additionally, any noted limitations of this research review project will be highlighted as areas of interest for future research study and inquiry.

4.2 Global Incidence & Prevalence of Preeclampsia 2010 - 2020

4.2.1 Table 3 – Estimates of the Global Impact of Preeclampsia 2010 - 2020

Estimated global incidence & prevalence of preeclampsia	2 – 7%
Estimated rates of global maternal & perinatal morbidity due to preeclampsia	15 – 20%

Global incidence of preeclampsia may range anywhere from 2 – 17% (Poropet et al., 2018), and is responsible for 15 – 20% of severe maternal and perinatal morbidity and mortality cases, including 60,000 maternal deaths and more than 500,000 premature births each year (Ma'ayeh & Costantine, 2020), particularly in low-middle income countries (Elliot et al., 2014; Deng et al., 2019). Incidence is estimated to be seven-times higher in developing nations such as India (Malik et al., 2019), while prevalence in certain Latin American countries is estimated to be greater than 25%, giving rise that differing rates globally may be attributed to unique geographic, social, economic and racial differences (Ma'ayeh & Costantine, 2020).

A 2011 Canadian study examining the epidemiology of preeclampsia and other hypertensive disorders of pregnancy reported a 3% incidence in the USA, 3.3% in New Zealand (based on a 1995 prospective study; Stone et al., 1995) 3% in Sweden, 4.5% in Denmark and 3% in Norway. Incidence rates were higher in some North American regions, including 8.4% in Washington State and 8.7% in Nova Scotia (which correctly defined preeclampsia without required inclusion of proteinuria) (Hutcheon et al., 2011). Authors additionally noted a seasonal variation of incidence of preeclampsia; in Northern regions of the globe, incidence is more common amongst winter births, with Finnish women reporting a two-fold higher risk for preeclampsia than women in Southern Europe. Additionally, in Zimbabwe, there is marked variance in incidence between the dry and wet seasons (Hutcheon et al., 2011).

Overall, global rates have risen since the last systematic review and meta-analysis was undertaken in 2013.

4.2.2 Emergent Themes of Interest:

- Geographic, social, economic and racial differences may account for differing global rates of preeclampsia.
- Environmental impacts alongside a noted seasonal variation of preeclampsia rates warrant further exploration.
- Low to middle-income nations (including New Zealand) report higher rates of preeclampsia compared with wealthier countries.
- Global prevalence and incidence of preeclampsia has risen since the last large-scale meta-analysis was undertaken in 2013.

4.2.3 North America

United States of America

In the USA, preeclampsia affects approximately 4% of pregnancies and is the second leading cause of maternal mortality and serious perinatal morbidity, including eclamptic seizure, multi-organ dysfunction, fetal growth restriction, low birth weight and perinatal demise (US Preventative Services Task Force, 2017). This rate (or reported rate) has increased slightly from an earlier study emanating from Washington State in 2014, where the preeclampsia rate was noted to have increased from 2.9 to 3.1 per 100 singleton births between 2000 and 2008, with rates of early and late-onset manifestation reported as 0.3% and 2.7% respectively (Lisonkova et al., 2014). However, inclusion of proteinuria as a requirement for diagnosis may account for under-reporting prior to acceptance of the new diagnostic criteria in 2014 (ISSHP). This rate of 3% was also reported in a 2019 US study, which similarly drew upon the 2013 American College of Obstetricians and Gynecologists (ACOG) definition of preeclampsia requiring proteinuria as a definitive diagnostic feature, meaning that a 4% estimate may indeed be more accurate when drawing upon the updated 2014 ISSHP guidelines (Calimag-Loyola & Lerma, 2019).

Additionally, preeclampsia is noted second only to previous preterm birth as a leading independent risk factor for preterm birth, a morbidity factor which incurs a burden of more than USD$26 billion per annum upon the US health service (Ferrero et al., 2016). Similarly, another 2016 study undertaken in California at the Cedars-Sinai Medical Centre reported preeclampsia and eclampsia as the second most common cause of severe maternal morbidity (10.7%) after haemorrhage (71.3%) (Ozimek et al., 2016). Given that preeclampsia and eclampsia may lead to and/or exacerbate haemorrhage and disseminating intravascular coagulation (DIC), and considering that this study did not provide a clear definition of the

diagnostic criteria for preeclampsia, incidence and prevalence of the disorder may possibly be frequently and consistently under-reported and recognised.

Canada

In Canada, preeclampsia incidence has increased from 2.64% of deliveries in 1989 to 5.06% in 2012 (Auger et al., 2015, as cited in Sacks et al., 2018). A 2016 retrospective population-based cohort study from April 2013 to December 2012 additionally ascertained that risk for preeclampsia alongside preterm birth between 24 and 36 weeks' gestation differed significantly according to maternal origin; specifically, Canadian-born women were far less likely to experience this outcome (4.0 per 1000) compared to residing Canadian immigrant women, especially those hailing from Nigeria, the Philippines, Colombia, Jamaica and Ghana (6.6 per 1000 to 8.3 per 1000 rate in sequential order), confirming ethnicity and socio-economic factors as pre-disposing risks for preeclampsia (Ray et al., 2016).

4.2.4 Central & South America

Bolivia

In Bolivia, the maternal mortality rate has, for many years, been consistently reported at more than twice the rate of all other Latin American countries and is currently decreasing by only 3.5% per annum, half the recommended reduction target. Preeclampsia is currently Bolivia's second highest cause for maternal death (and likely also associated with the first cause, postpartum haemorrhage) and afflicts as many as 20% of all pregnancies. For those mothers and babies who do survive, the risk for developing long-term cardiovascular and other associated co-inflammatory conditions (including chronic hypertension and diabetes

mellitus) is high. While limited health care resources and socio-economic deprivation are contributing factors, two-thirds of Bolivians live in high-altitude (often remote rural) areas, a factor linked to poor fetal growth and pregnancy-associated hypertensive disorders, including preeclampsia (Toledo-Jaldin et al., 2019). Given that early-onset preeclampsia is particularly dangerous (and more likely to be severe) amongst indigenous Andean populations living at high altitude, investigating other influences such as serum levels of pro-inflammatory cytokines may help to determine genetic risk factors and enable timely and early preventative medical interventions, including low-dose aspirin and oral calcium supplementation (Davila et al., 2012). Additionally, with statistics confirming that Andean (and Tibetan) women have a two to four-fold increased incidence of preeclampsia yet lower risk for small-for-gestational-age (SGA) babies than their low-altitude neighbours, further investigation into genetic adaptations to altitude (which could support the theory that the aetiologies of preeclampsia and SGA differ) are warranted (Browne et al., 2011).

Brazil

In Brazil, preeclampsia accounts for 18% of all preterm births and is a major contributing factor towards both short and long-term neonatal morbidity rates, including the consequences of iatrogenic prematurity and growth restriction. Additionally, hypertensive disorders (including preeclampsia) are recognised as the leading cause of death in Brazil and are collectively responsible for 23% of all maternal deaths (Bakwa-Kanyinga et al., 2017; Dias et al., 2019). Of 27 referral hospitals assessed in a 2019 nationwide cross-sectional surveillance PREPARE stepped wedge trial, 10 were recognised as providing inadequate care, exacerbating risk for severe maternal morbidity (Dias et al., 2019). Incidence of hypertensive disorders of pregnancy in Brazil ranges from 14.4 – 18.4%, with an overall preeclampsia rate of approximately 7.5 – 8.9% (Bergamo et al., 2015 as cited in Kharaghani

et al., 2016; Mayrink et al., 2019; da Silva Gama et al., 2020). Associated risk factors for preeclampsia in the Brazilian population include diabetes mellitus and obesity, giving rise to serious maternal adverse outcomes such as postpartum haemorrhage, chronic hypertension, placental abruption, renal and hepatic failure and death (Bakwa-Kanyinga et al., 2017). Researchers involved with the aforementioned 2019 PREPARE trial also assert there may be additional pathophysiological influences and risk factors relevant to Brazil (and perhaps also with other low to low-middle income countries) that may account for this high prevalence, including poorly funded health services that may lead to iatrogenic early delivery (possibly both hastily and unnecessarily), via (predominantly) caesarean section (Dias et al., 2019).

The Preterm SAMBA (Screening & Metabolomics in Brazil and Auckland) trial (also published in 2019) was conducted in five different health centres throughout Brazil and involved 1165 eligible (healthy and primiparous) participants (Mayrink et al., 2019). This study also reported an overall incidence of preeclampsia of 7.5%, with 16.1% developing early-onset preeclampsia (prior to 34 weeks' gestation), while the remainder developed it at or after 34 weeks' gestation (Poon et al., 2010; Mayrink et al., 2019). Poor maternal and neonatal outcomes for those afflicted with preeclampsia were noted, including increased risk for caesarean section, prolonged hospital admission, preterm delivery at less than 34 weeks' gestation, low birth weight, Apgar scores of less than 7 at 5 minutes of age and increased risk for fetal demise. Data analysis was able to identify three factors that attributed to significant risk for development of preeclampsia, namely increased or rapid maternal weight gain in pregnancy, pre-existing maternal obesity, and a diastolic blood pressure at 20 weeks' gestation of ≥75mmHg (Mayrink et al., 2019).

French Guiana

In French Guiana, reported rates of preeclampsia range from 2 – 8%. However, a 2020 study involving 1243 women birthing in a tertiary unit in the capital Cayenne reported a 12.6% rate of pregnancy-related hypertensive disorders, of which preeclampsia accounted for 61.4% of cases with an overall incidence of nearly 8%; due likely to the tertiary status of the hospital, to where women diagnosed with hypertension in pregnancy would be referred. Additionally, there is a higher rate of chronic hypertension amongst the French Guiana population (23.5%) when compared with other South American nations. 52.4% of women included in the study were South American, 45.1% were from the Caribbean and one woman was of African origin; all of whom have been identified as at particular risk for preeclampsia. Co-morbidities were determined as gestational and pre-existing diabetes mellitus and low-socio-economic status. Proteinuria was not a requirement for diagnosis (as per 2014 updated criteria) but was noted as significant (≥0.3g/L protein:creatinine ratio) in nearly 60% of cases (Mhiri et al., 2020).

The only recent data available reporting incidence of preeclampsia in Argentina was cited in a 2016 Moroccan study at 3.2% (Marchand et al., 2016). Data from other Central and South American countries was not extrapolated from the keyword search or may have not been available as an English-language publication.

4.2.5 The Caribbean

Haiti

In Haiti, the incidence of preeclampsia is reported to be as high as 18% (Raghuraman et al., 2014, as cited in Gagliano et al., 2016). Furthermore, the prevalence of hypertension-induced preeclampsia contributes to nearly 40% of all maternal deaths (WHO, 2016, as cited in Gagliano et al., 2016). In a small rural birthing cohort in Haiti (436 women), 13.1% met with criteria for diagnosis of pre-partum hypertension (systolic pressure of greater than 140mmHg and/or diastolic pressure of greater than 90mmHg on at least two occasions at least four hours apart), with an astounding 65.5% of women being diagnosed with postpartum hypertension only, suggesting that preeclampsia may have been missed antenatally due to the inclusion of proteinuria as an antepartum diagnostic requirement. Rates of preeclampsia in Haiti may in fact be far higher than has been reported, likely due to various considerations, including poor access to advanced health care services, extreme poverty, as well as political and geographical challenges (Gagliano et al., 2016).

4.2.6 Western & Central Eastern Europe

The European continent is reported to have an overall approximated incidence of preeclampsia of 3.8%
(Nwanodi, 2016).

Germany

In Germany, preeclampsia complicates approximately 2% of pregnancies while hypertensive disorders of pregnancy are the most common cause for maternal mortality in Europe, giving researchers impetus to examine the economic feasibility for use of predictive serum blood tests for preeclampsia, specifically the soluble fms-like tyrosine kinase 1: placental growth factor ratio (sFlt-1:PlGF) (Schlembach, et al., 2018). Results indicate that use of this test is likely to reduce unnecessary hospitalisation for low-risk women while ensuring those identified at high-risk will receive appropriate care and management, resulting in significant health dollar savings (Schlembach et al., 2018).

Hungary

A study undertaken in Hungary in 2015 examined the impact of hypertensive disorders of pregnancy comparing results based on the 2013 ACOG criteria for preeclampsia diagnosis (requiring proteinuria) and the ISSHP 2014 criteria (Rigo et al., 2015). 775 women admitted to the Semmelweis University obstetrics and gynaecology department diagnosed with hypertensive disorders and singleton pregnancies between January 2012 and December 2014 were enrolled. Results found that the redefining of preeclampsia diagnosis according to the ACOG 2013 criteria increased the rate of preeclampsia by 8.2% and by a staggering 17.2% when the ISSHP 2014 criteria were applied (when compared with earlier 2002 ACOG classification). Additionally, while the incidence of preeclampsia was indeed increased when

applying the new diagnostic criteria, perinatal outcomes were not significantly influenced (Rigo et al., 2015).

Iceland

A 2018 Icelandic study concluded that hypertensive disorders of pregnancy complicate up to 10% of pregnancies in that country, with preeclampsia affecting approximately 3.2% of these. Of 63,014 children analysed between the ages of nine and fifteen years, 2026 had been exposed to preeclampsia in-utero. Not only were those children more likely to have been born SGA and prematurely with lower Apgar scores, but incidence of preeclampsia was found to be higher in urban as opposed to rural settings (Fridgeir et al., 2018).

Ireland

In Ireland, preeclampsia affects 2 – 3 % of all pregnancies and 5 – 7% of nulliparous pregnancies and has significant impact on the economic health costs (Fox et al., 2017). Given that this study required proteinuria onset as a diagnostic pre-requisite for preeclampsia, under-reporting of the disorder may be suspected, meaning economic impact estimations are also lacking.

Netherlands

A 2019 Dutch study determined the rate of preeclampsia to account for approximately 3% of all pregnancies in Holland, with prevalence at 2.5% for first pregnancies and 0.9% for second pregnancies, following a linked cohort of 272,551 women whose data had been collated by the Dutch Perinatal Registry between 2000 and 2007 (Bernardes et al., 2019). However, given that the criteria for confirmation of preeclampsia required proteinuria

alongside hypertension during the period of data collection, under-reporting can be suspected, given the current, revised diagnostic criteria.

Norway

In 2015, the rate of preeclampsia in Norway was reported as 3.8% for the nulliparous population, with a 4.3% overall occurrence (Austdal et al., 2015). The study however only included a small cohort of 599 women, all with moderate to high risk for developing preeclampsia (including nulliparity, previous hypertension or risk based on first trimester urine and serum metabolomic results). Furthermore, researchers determined proteinuria as a diagnostic inclusion requirement (Austdal et al., 2015).

Another (2017) Norwegian study examining seasonal and other preventable environmental contributors to preeclampsia (including smoking) determined that preeclampsia risk was indeed related to season, with higher risk associated with spring conceptions and lower risk associated with autumn conceptions (Weinburg et al., 2017).

Yet another (2018) Norwegian population-based cohort study of 630255 pregnancies between 1999 and 2009 found that the rate of preeclampsia was 5.6% amongst primiparous women and 2.6% for multiparous women. Furthermore, the risk of eclampsia and HELLP syndrome was 3.5% for those women diagnosed with preeclampsia, meaning the impact on the Norwegian health service structure was significant (Engjom et al., 2018). A limitation of this study, however, was the requirement for proteinuria as part of the diagnostic criteria, meaning once again, under-reporting of preeclampsia incidence may be suspected.

Poland

A comprehensive cohort study of 214 women between 2013 – 2017 examined laboratory and clinical findings according to the 2014 ISSHP criteria in Krakow University Hospital in Poland (Wojtowicz et al., 2019). The study found that the overall incidence of preeclampsia according to the new diagnostic criteria was 1.7%, while those diagnosed with early-onset preeclampsia (<34 weeks' gestation) had higher risk for severe perinatal and maternal adverse pregnancy outcomes, including cardiorespiratory and haematological complications (Wojtowicz et al., 2019). Limitations of the study were the comparatively small cohort and further, larger-scale studies on a nationwide scale are warranted.

Turkey

A 2011 Turkish study of women admitted with preeclampsia, eclampsia and/or HELPP syndrome between 1998 and 2002 to the Atatürk University, Obstetrics and Gynaecology Department in Ankara sought to determine a distribution map of the effects of altitude upon the rate of HELLP syndrome and eclampsia. Authors concluded that rates of HELLP and eclampsia were raised at high altitude when compared with their low-dwelling counterparts, and that early diagnosis was vital in order to prevent significant maternal morbidity and mortality risk (Kumtepel et al., 2011).

Spain

In Spain, a prospective cohort study of 7908 pregnancies (of which 6893 were included in the final data analysis) in two Barcelona hospitals between March 2014 and September 2017 reported an incidence of 2.3% of preeclampsia, with incidence of early-onset preeclampsia (< 34 weeks' gestation) reported at 0.2% (Serra, et al., 2020). The study sought to assess the multivariate Gaussian distribution model as a reliable screening tool for early-

onset preeclampsia (including maternal risk factors, early placental growth factor determination at 8 weeks' gestation and other biophysical variables) and found it a feasible predictor between 11 to 13 weeks' and 6 days' gestation. Authors concluded that the model should now be compared with other predictor tools (using regression analysis) and that a nationwide trial could also be considered (Serra et al., 2020).

Ukraine

A 2017 case-control study of 300 singleton pregnant women (aged 16 – 43 years; 100 diagnosed with EOP, 100 with LOP and 100 as a control) who delivered either a live or still birth in the obstetric department at the L'viv Regional Clinical Hospital in the Ukraine between June 2014 to June 2017 sought to evaluate differences in risk factors and birthing outcomes when comparing early versus late-onset preeclampsia (Markin & Medvyedyeva, 2017). Although the study relied on the former 'gold standard' definition of preeclampsia (that is, to include proteinuria in diagnostic criteria), maternal age > 35 years, smoking during pregnancy, pre-existing obesity and hypertension were associated with significant risk for both early and late-onset disease manifestation, while chronic hypertension and fetal congenital anomalies were more strongly associated with early-onset preeclampsia. Diabetes, nulliparity, and teenage pregnancy were additionally cited as strongly identified risk factors for late-onset preeclampsia. Overall, early-onset preeclampsia was associated with increased risk for IUGR, prematurity (largely due to iatrogenic pre-term delivery) and severe neonatal morbidity and mortality, while late-onset preeclampsia rarely led to fetal or neonatal demise (Markin & Medvyedyeva). However, overall incidence of preeclampsia in the Ukraine was not commented on.

A later (2018) Ukrainian study examining vaginal and mammary gland skin microbiota in 25 women with preeclampsia and 25 ‘healthy’ women experiencing a normal physiological pregnancy, cited the incidence of preeclampsia in the Ukraine to range from 6 – 16% but did not offer any comment on why this range variation was so wide. Furthermore, classification of preeclampsia was according to a 1995 amendment to the Order of the Ministry of Health of Ukraine (2004), in which proteinuria was part of the mandatory diagnostic criteria, meaning many cases were potentially missed (Ivankiv et al., 2018).

United Kingdom

An audit undertaken in sixteen National Health Service (NHS) sites across both England and Wales between 2016 and 2017 found the incidence of preeclampsia to range from 3.25% to 0.3%, with an overall mean of 1.92%, lower than previously reported, which was unexpected, although diagnostic inclusion criteria was not described (Hendy et al., 2017). Authors commented however, that accurate and recent data reporting on the incidence of preeclampsia in high-income countries is currently extremely limited and their own findings were potentially flawed due to coding inaccuracies and/or missed diagnosis, concluding that there is an opportunity for future important research opportunities (Hendy et al.).

Leading from this, a 2020 retrospective study of 66,964 singleton pregnancies between January 2011 and June 2018 who delivered at King’s College Hospital in London (of whom 2.8% were previously identified as having preeclampsia based on former ACOG and ISSHP criteria) were reviewed according to ‘new’ ACOG 2013 and ISSHP 2014 criteria (the latter of which no longer requires proteinuria as a diagnostic prerequisite) (Khan et al., 2020). Following this review, incidence of preeclampsia climbed to 3% using ‘new’ ACOG criteria and 3.4% when ‘new’ ISSHP 2014 criteria were applied, meaning overall incidence at

the time of data collection was significantly under-reported. Authors concluded that the new definition of preeclampsia resulted in an increase of diagnosis but added that the additional identified cases manifested milder pathogenic symptoms, inferring that early diagnosis could both critically and positively impact on pregnancy and perinatal outcomes, alongside maternal morbidity and mortality risk (Khan et al., 2020).

4.2.7 The Middle East

Iran

In Iran, preeclampsia may account for as much as 7.7% of the total mortality rate (Vahiddastjerdy et al., 2016), with the prevalence of hypertensive disorders in pregnancy reported at 8.1% (Asgharnia et al., 2017). Following a 2016 systematic review and meta-analysis (in which 36 separate international and Iranian studies were assessed) an increasing prevalence in preeclampsia (from 0.3% between 1996 – 2005, to 0.7% between 2010 – 2013) was noted alongside a marginal decline in eclampsia (Kharaghani et al., 2016). However, authors reported a wide discrepancy in the results following meta-analysis, meaning a precise rate of incidence could not be determined. Furthermore, the systematic review definition criteria for study inclusion adhered to the former (now defunct) diagnostic definition of preeclampsia (requiring proteinuria alongside hypertension after 20 weeks of pregnancy), meaning under-reporting and / or inaccurate coding is likely.

Israel

A 2018 Israeli population cohort study examining 231,298 deliveries between 1991 and 2014 in a regional tertiary medical centre determined a 4.1% rate of preeclampsia, although no diagnostic definition of preeclampsia was described. The study sought to examine congenital cardiovascular predispositions and cardiovascular risk factors in children exposed in-utero to preeclampsia and found a significant association between the two (Sacks et al., 2018). However, given the cohort included in the study drew upon former diagnostic criteria requiring proteinuria, under-estimation of rates of preeclampsia may be suspected.

In 2020, an Israeli retrospective cohort study sought to explore the environmental effects of climate change secondary to global warming alongside emergent evidence suggesting the impact of environmental factors upon the pathophysiology of preeclampsia. Additionally, and as supported by other international studies previously cited, the impact of socio-economic status alongside environmental factors including rural lifestyle and seasonality effects was also considered (Shashar et al., 2020). Of 64,566 deliveries (from 31,101 women) that met with inclusion criteria in the Negev region of Southern Israel, 7% of women and 4.1% of deliveries were affected by preeclampsia, with their babies more likely to have lower Apgar scores and lower birth weights. Women diagnosed with preeclampsia were likely to be older, and of Jewish ethnicity, with diagnosis occurring mostly in late pre-term gestations between 34 and 36+6 weeks resulting in pre-term delivery. However, seasonal variance was also confirmed to increase likelihood for preeclampsia when the majority of the pregnancy occurred during the summer months – in this instance, women were more likely to be rural and poorer; namely nomadic women of Bedouin-Arab ethnicity when compared with their urban, wealthier and mostly Jewish counterparts, for whom air-conditioning and air-filtration systems are more common, particularly during warmer periods. Authors concluded therefore that environmental (alongside socio-economic) factors may

indeed affect maternal heat homeostasis, causing reallocation of maternal resources away from the developing fetus, thereby increasing risk for preeclampsia. This, when placed alongside global warming and increased socio-economic deprivation, validates further exploration of these risks alongside the potential for a rise in preeclampsia incidence (Shashar et al., 2020).

Jordan

In 2017, a national study of perinatal mortality was undertaken in Jordan, with one objective focused on estimating the incidence of preeclampsia, its associated risk factors, and impact on neonatal morbidity and mortality rates (Khader et al., 2018). Diagnostic criteria again included proteinuria, meaning that the reported 1.3% overall incidence rate amongst the 21,928 women included in the study is likely unreliable. Authors did note a higher rate of low birth weight, risk for prematurity and neonatal encephalopathy and neonatal mortality rate in those babies born to women with preeclampsia, although further exploration with more recent diagnostic criteria for preeclampsia is warranted.

Saudi Arabia

A multi-centre cohort study undertaken in three Riyadh hospitals in Saudi Arabia between November 2013 and March 2015 determined a 1.1% incidence of preeclampsia amongst the 14,568 women participants (Wahabi et al., 2016). However, given that diagnostic criteria for preeclampsia required the inclusion of proteinuria alongside new onset of hypertension at ≥ 20 weeks' gestation, under-reporting is highly likely. Saudi Arabia is a high-income country with a well-serviced health care system, and is predominantly mono-cultural (70% Saudi population) with a rapid rise in urbanisation and Westernisation, resulting in rates of obesity and gestational diabetes that rank amongst the world's highest

(Wahabi et al., 2016). As both these co-morbidities increase risk for preeclampsia, likelihood of a further increase in preeclampsia rates may be anticipated in the absence of preventative health measures and initiatives.

4.2.8 The African Continent

The African continent is reported as having the highest international incidence of preeclampsia, estimated to afflict 4 – 10% of all pregnancies, with sub-Saharan rates reported to be as high as 44% (Benfateh et al., 2018; Nwanodi, 2016; Vata et al., 2015).

Morocco

A small review of 401 preeclamptic cases reported in a Casablanca Hospital between 2010 – 2011 found an incidence of 7.1%, with key risk factors for preeclampsia identified as primiparity, limited antenatal care, obesity and chronic hypertension (Benfateh et al., 2018). Diagnostic criteria for preeclampsia included hypertension (blood pressure ≥ 140/90mmHg) alongside significant proteinuria (≥0.3g/24 hour collect or ≥2+ protein on urinary dipstick screening), meaning accuracy of reporting may be unreliable.

Democratic Republic of Congo

Kinshasa, capital city of the Democratic Republic of Congo (and second-most densely populated area within the sub-Saharan region) reports an overall high annual incidence of preeclampsia (approximately 9%) but with significant rate variation noted between the wet and dry seasons, respectively 6% versus 13% (Moyene et al., 2016). Alongside a lack of readily-available fresh fruit and vegetables (a known risk factor for preeclampsia) during the dry season, authors of a 2016 Kinshasa seasonal case-control study (of healthy women and

those diagnosed with preeclampsia in the rainy season between March and April 2011 and the dry season from July to September 2011) additionally acknowledged the correlation between pro-oxidant metals (including lead) and associated risk for preeclampsia (Moyene et al., 2016). Serum lead levels have been determined to increase during dryer months due to greater likelihood of lead-contaminated soil dust inhalation (Laidlaw et al., 2005; Moyene et al.). Once again, diagnostic criteria for preeclampsia required the presence of proteinuria, meaning both coding discrepancy and inaccuracy of reporting could be possible.

Ethiopia

In Ethiopia, prevalence of preeclampsia may account for 8.4% of all adverse pregnancy outcomes, ranking as third amongst the top four causes of maternal mortality and contributing significantly to risk for maternal death (Endeshaw et al., 2016). A facility-based case-control study undertaken in Bahir Dar City in north-western Ethiopia sought to evaluate the risk of obesity and dietary habits on incidence of preeclampsia but was limited by its small scale, interviews reliant on self-reporting, and diagnostic inclusion criteria defining the disorder as "hypertension accompanied by proteinuria, with or without generalised oedema" (p. 2), making it therefore difficult to predict reliability of the study's figures (Endeshaw et al.).

An earlier (2015) assessment of prevalence of preeclampsia in the Dilla region of Ethiopia between January 2009 and December 2012 found the incidence rate to be 2.23% yet reiterated that confirmation of proteinuria alongside hypertension was a requisite part of the diagnostic inclusion criteria. Additionally, authors acknowledged that no in-depth studies on preeclampsia in Ethiopia have thus far been undertaken, calling for urgent government publication of a guideline for the management and prevention of preeclampsia (Vata et al., 2015).

In 2016, a retrospective cross-sectional study reviewing five years of medical records in selected government hospitals throughout the capital city Addis Ababa as well as other Ethiopian regions, determined that rates of preeclampsia had increased from 2.2% in 2009 to 5.58% in 2013. For preeclampsia to be determined, authors defined the disorder as "new onset of hypertension and proteinuria after 20 weeks' gestation in a previously normotensive woman" (p.2), meaning reliable reporting of actual rates and incidence may be queried (Wagnew et al., 2016).

Rwanda

A 2020 combined retrospective and prospective study undertaken in two teaching hospitals in Kigali, Rwanda sought to determine prevalence of preeclampsia and eclampsia and whether there were seasonal variations (Mutabazi et al., 2020). Over a two-year period (December 2015 – August 2017) involving close to 20,000 births, a 2.0% rate of preeclampsia was reported. Risk factors identified were obesity, a history of hypertension, pre-existing and gestational diabetes. While two-thirds of women diagnosed with preeclampsia presented during the rainy season, timing of conception was not noted as significant (Mutabazi et al.). However, despite international revision of preeclampsia diagnosis criteria in 2014 (ISSHP, 2014; SOMANZ, 2014) this study maintained a requirement for proteinuria alongside hypertension for case inclusion, meaning under-reporting is once again likely.

Nigeria

Nigeria reports a rate of preeclampsia ranging from 2 – 16.7% (Osungbade & Ige, 2011), with more than 30,000 women dying each year from the disorder. There is marked regional variation, with preeclampsia accounting for 40% of all maternal mortality cases in North Nigeria, while prevalence in the south ranges from 5.6 – 7.6% (Olaoye et al., 2019). Low socio-economic status, poverty, poor diet, poor access to health and maternity care, previous history of hypertensive disorders and a generalised lack of knowledge about the disorder amongst health care providers, are noted as key risk factors (Olaoye et al.).

A 2018 retrospective study of 89 obstetric patients admitted to a Southeast Nigerian hospital between the 1st of January 2012 and December 2013 reported a 6.7% rate of severe preeclampsia, a 22.5% rate of eclampsia, and a further 36% rate of uterine rupture. Lack of antenatal care, inadequate health care services and low socio-economic status were significantly associated with increased maternal mortality risk. However, given the study drew upon proteinuria as a diagnostic requirement for preeclampsia, likelihood of under-reporting of preeclampsia (until manifestation of severe preeclampsia was identified) may be suspected (Ozumba et al., 2018).

Another (2019) retrospective case-control study undertaken in the Alex Ekwueme Federal University Teaching Hospital in Abakaliki, Nigeria between January 2012 and December 2015 determined a preeclampsia prevalence of 1.4% amongst 6585 deliveries (Obi et al., 2019). Again, proteinuria was required alongside gestational hypertension as part of the diagnostic inclusion criteria.

Zambia

In Zimba Mission Hospital, Zambia, a 2018 study of all 1712 deliveries in 2017 found and reported an overall rate of 2.5% for all pregnancy hypertension disorders and 1.5% rate of preeclampsia and drew on the current and revised diagnostic criteria for hypertension alongside proteinuria and/or evidence of other organ failure (Miyoshi et al., 2018). Given the rate of eclampsia was determined at 19%, failure to diagnose and treat preeclampsia in a timely manner with interventions such as magnesium sulphate (administered intramuscularly in this setting for low-income women as part of hospital protocol) was identified by authors as a significant barrier contributing to the nation's high maternal mortality rate (Miyoshi et al.).

Tanzania

Limited reporting has thus far emanated from Tanzania, with data from one medical centre reporting a preeclampsia rate of 1.6% (Kaduma et al., 2019). Given the small size of the study (393 women) and diagnostic inclusion criteria requiring proteinuria, many cases may not have been adequately captured. An earlier 2018 retrospective population study of 17,738 singleton deliveries (drawn from data from the Kilimanjaro Christian Medical Centre Birth Registry between July 2000 and May 2013) reported a preeclampsia rate of 3.3%, and noted the association between maternal obesity and risk for preeclampsia, but again relied upon proteinuria for diagnostic inclusion (Mrema et al., 2018).

Zimbabwe

Overall incidence of severe preeclampsia and eclampsia in Mpilo Central Hospital in Bulawayo, Zimbabwe was determined to be 1.3% in 2017 (Ngwenya, 2017, as cited in Ngwenya et al., 2019), although diagnostic inclusion criteria for preeclampsia required manifestation of significant proteinuria alongside hypertension after 20 weeks' gestation. Other studies reporting specific rates and/or national incidence of preeclampsia in Zimbabwe have not yet been determined and/or were not available at the time of writing this thesis.

South Africa

Between 2011 and 2013, hypertensive disorders accounted for 14.8% of all maternal deaths in South Africa (Pretorius et al., 2018). Depending on ethnicity, overall incidence of preeclampsia is estimated to range from 3 – 7% in healthy primigravid women and between 1 – 3% in multigravida pregnancies (Aung et al., 2018). However, prevalence of preeclampsia amongst South African Black primigravid women is reported to be as high as 12% and accounts for 10-15% of all maternal deaths, highlighting the severe impact of the disorder on indigenous women when compared with other ethnic populations (Aung et al.).

There were no other studies undertaken in African nations that met with search criteria, although figures related to incidence in Uganda and Angola (3.7% and 0.9% respectively) were cited (but not explored) in a 2016 cross-sectional study undertaken in Mongolia (Marchand et al., 2016).

4.2.9 Central & South East Asia

Mongolia

A 2016 cross-sectional study of 236 urban and 85 rural (including nomadic) women conducted in two maternity hospitals in the Mongolian capital of Ulaanbaatar found an overall incidence rate of preeclampsia of 4.1%, when diagnostic criteria for new-onset of hypertension after 20 weeks' gestation alongside proteinuria (protein:creatinine ratio of ≥0.3 and/or dipstick reading > +1) was applied (Marchand et al., 2016).

China

Prevalence of preeclampsia in China may account for approximately 5 – 7% of all pregnancies (Li et al., 2018; Liang et al., 2019), although there have been very few studies to date that focus on the specific rate of preeclampsia throughout China. Additionally, those that have, predominantly include proteinuria alongside new onset of hypertension ≥ 20 weeks' gestation as a requisite for diagnosis.

A retrospective analysis study conducted between January 2002 to December 2011 in the Yulin Shaanxi Province of China collected data from three large tertiary hospitals (involving 62,925 women who had given birth after 20 weeks' gestation) reported an overall preeclampsia rate of 1.92% amongst the nulliparous, ethnic Han Chinese population, when compared with resident Caucasian women; suggesting Chinese ethnicity may attribute to lower risk for developing preeclampsia (Xiao et al., 2014). The study, however, did include proteinuria as a diagnostic pre-requisite for preeclampsia, meaning some cases may not been adequately captured.

A 2011 survey on hypertensive disorders in pregnancy (HDP) involving 112,386 pregnant women across 38 secondary and tertiary hospitals in Mainland China found an overall prevalence of 5.22%; of which mild preeclampsia accounted for 15.13%, severe preeclampsia 39.96%, and eclampsia 0.89% (Ye et al., 2014). There were however, significant differences between the various geographical regions, with North China provinces showing the highest incidence of HDP and Central China the lowest (Ye et al.), meaning that further exploration of these geographic differences (aside from noted risk factors including nulliparity, multiple pregnancy, age of >35 years, obesity, history of hypertension and diabetes) is warranted.

In a large population-based study involving 205,605 singleton pregnant women undertaken in two Southern Chinese provinces between October 1993 and September 1995, the overall incidence of preeclampsia was reported as 2.4% (Liu et al., 2019). However, due to the period in which data was included, diagnosis for preeclampsia drew upon the now-outdated requirement for evidence of concurrent 1+ of proteinuria on dipstick screening alongside hypertension ≥20 weeks' gestation, meaning likelihood of under-reporting may be suspected. Further exploration of incidence of preeclampsia in China is therefore now warranted and overdue.

India

In India, preeclampsia may affect as many as 6 – 10% of all pregnancies although current data to support this remains insufficient (Khanapurkar et al., 2016; Rana et al., 2020).

According to the 2005-2006 nationwide Indian National Family Health Survey, incidence of preeclampsia and eclampsia (based on self-reported symptoms from women who had a live birth in the five years preceding survey publication), incidence of preeclampsia

was estimated to be as high as 28%. Additionally, India reports the highest number of pre-term births (<37 weeks' gestation) in the world, with 36% of those attributed directly to preeclampsia (Malik et al., 2019).

A retrospective comparative study of 208 women diagnosed with preeclampsia between January 2014 and December 2016 in Tamil Nadu (Kelambakkam region of India) reported an overall preeclampsia rate of 6.3%, but included proteinuria (≥300mg/24 hours or ≥1+ on dipstick urinalysis) as part of the diagnostic inclusion criteria (Shankar et al., 2019).

Additionally, a prospective observational study involving 184 women recruited between 13 and 18-weeks' gestation with uncomplicated, normotensive, singleton pregnancies in the Tata Main Hospital in Jamshedpur in India, 14.67% went onto develop gestational hypertension ≥ 20 weeks of pregnancy with 22.22% of these diagnosed with preeclampsia. However, diagnostic criteria for defining preeclampsia was not included and the cohort was insufficiently large in order to be deemed statistically significant (Murmu & Dwivedi, 2020).

South Korea

A study of 212,463 South Korean primiparous women with no previous history of hypertension who birthed between January 2011 and December 2012 reported a 3.1% overall incidence of preeclampsia. Additionally, rates of preeclampsia were found to be as high as 7.3% in those women diagnosed with metabolic syndrome prior to becoming pregnant (1.2% of total participants) (Cho et al., 2016).

Japan

According to the most recent Japanese diagnostic criteria for hypertension disorders in pregnancy, preeclampsia is defined as new-onset hypertension from 20 weeks' gestation with evidence of one or more other maternal complications (including liver dysfunction, neuropathy including cerebral stroke, and evidence of placental dysfunction, such as IUGR and stillbirth, with or without fetal anomalies) following on from manifestation of proteinuria (Watanabe et al., 2018, as cited in Morikawa et al., 2020). Overall incidence of preeclampsia in the greater Western Pacific region (which includes Japan) is estimated at 4.2%, the highest of all middle to high-income global populations (Nwanodi, 2016).

Thailand

A 2018 retrospective descriptive study conducted in one north-eastern tertiary care facility in Thailand (involving 11,199 deliveries between January 2012 and December 2016) identified a specific regional 1.9% preeclampsia incidence when applying revised 2013 ACOG guidelines, which required proteinuria as part of their inclusion criteria but not fetal growth restriction (Kongwattanakul et al., 2018). Incidence in Thailand has previously been reported as high as 4.7% (Pitakkarnkul et al., 2011, as cited in Kharaghani et al., 2016) while rates between 2002 – 2012 were cited at 2.2%. Authors of the more recent 2018 study recognised, however, that revision of the 2013 ACOG diagnostic criteria could potentially result in changes to incidence rates, alongside other, associated, maternal, perinatal and neonatal outcomes and impacts, with scope for future nation-wide research identified (Kongwattanakul et al.).

Taiwan

Following a nationwide study assessing data from 1,347,672 live births born between January 2004 and December 2011 in Taiwan, prevalence of preeclampsia was determined at 2.27%, although definitive diagnostic criteria for preeclampsia was neither clearly defined nor described within the scope of the study (Yu et al., 2020). Additionally, authors decided to combine gestational hypertension and preeclampsia as a composite outcome, recognising that mild cases of preeclampsia may have been missed or inaccurately diagnosed and therefore incorrectly coded.

An earlier 2018 retrospective population-based cohort study of all singleton pregnancies of ≥ 20 weeks' gestation resulting in either live or stillbirth babies (n=2,884,347) between January 2001 and December 2014, found an incidence of 1.7%, following a rising trend since 2012, with a steady increase in (notably) early-onset preeclampsia but also late-onset preeclampsia (You et al., 2018). Advanced maternal age, primiparity, stroke, diabetes, chronic hypertension and hyperthyroidism were all determined as risk factors for preeclampsia; again, criteria for diagnosis of preeclampsia was not specified (You et al.).

Indonesia

In Indonesia, preeclampsia, eclampsia, infection and bleeding account for 75 – 85% of all maternal deaths, with incidence of preeclampsia estimated to be between 3 – 10% of all pregnancies, with most recent figures citing a rate of 4.6% (Jayanti et al., 2017; Suparman et al., 2018; Sufriyana et al., 2020). Additionally, more recent Indonesian maternal mortality rates arising directly from preeclampsia are reported at 4.91% (Liwang & Bhargah, 2018). Between 2006 and 2008, 542 cases of preeclampsia were reported in 7285 deliveries in the Dr Hasan Sadikin Hospital (7.44% incidence), with an associated maternal and perinatal mortality rate of 0.3% and 0.21% respectively (Suparman et al.). Preeclampsia was attributed

to enhanced risk for both maternal, perinatal and neonatal mortality and morbidity, notably from placental abruption, intrauterine fetal growth restriction and preterm (often iatrogenic) birth (Sufriyana et al., 2020).

There were no other studies undertaken in either Central or South East Asia that met with the search criteria, although figures related to incidence in Philippines and Vietnam (5.6% and 1.2% respectively) were cited (but not explored) in the aforementioned 2016 cross-sectional study undertaken in Mongolia (Marchand et al., 2016).

Similarly, incidence in Bangladesh was also cited at 12% (Jahan et al., 2015, as cited in Kharaghani et al., 2016) but with no further exploration of this estimate proffered.

In Pakistan, incidence of preeclampsia is estimated to be as high as 55.3% amongst obese, primigravid women, but no figures pertaining to the nation's overall rate were available at the time of writing this thesis (Hussain et al., 2019).

Finally, no evidence of reporting of either rates or incidence of preeclampsia in North Korea was available at the time of writing.

4.2.10 Australia & the Pacific Region

The greater Western Pacific region (including Australia, Japan, South Korea, New Zealand and Singapore) collectively reports an overall preeclampsia incidence of 4.2%, the highest of all middle to high-income global populations (Nwanodi, 2016).

Australia

In 2013, the incidence of preeclampsia in Australia between 2000 and 2008 was reported as 3.3% overall, with a decrease from 4.6% in 2000 to 2.3% in 2008 (Thornton et al., 2013). The study also drew upon (now outdated) diagnostic criteria for preeclampsia to include new onset proteinuric hypertension at ≥ 20 weeks' gestation, meaning a more accurate and recent data revision and investigation is now warranted.

The 2014 Australasian, United Kingdom and Irish *Screening for Pregnancy Endpoints* (SCOPE) international cohort study examined incidence of preeclampsia in 5573 women between 2004 and 2011 and found the overall rate in those countries to be 4.9%, a figure which cannot be applied with any vigour to any one specific country (Kenny et al., 2014, as cited in Schalekamp-Timmermans et al., 2016).

French Polynesia

In Tahiti, 29% of cases of neonatal prematurity (204 in total between January 2007 and December 2011) were attributed to maternal preeclampsia (Besnard et al., 2015), yet data relating specifically to the incidence of preeclampsia was neither included nor discussed.

Hawaii

In Hawaii, a 2016 retrospective study on state-wide data for birthing outcomes between January 1995 and December 2013 found that incidence of preeclampsia varied widely between ethnicities, once confounders including age, multiple gestation, multiparity, chronic and pre-existing hypertension, pre-existing diabetes mellitus, obesity and smoking had been accounted for (Nakagawa et al., 2016). After analysing 271,569 post-delivery hospital discharge records, overall rates of preeclampsia ranged from 2.0% for Chinese women (lowest risk) to 4.6% for both Native Hawaiian and Filipino women, followed closely by 'other' Pacific Island women at 4.5%. European and Japanese women were reported at 2.9% and 2.5% respectively, with 'other' Asian women reported at 2.5% and an overall average incidence of 3.49% (Nakagawa et al.). Again, preeclampsia diagnosis was dependent on onset of proteinuria alongside mid-gestational hypertension, meaning under-reporting of incidence may have occurred.

4.3 Incidence & Prevalence of Preeclampsia in Aotearoa/New Zealand 2010 - 2020

"To date, there is limited research mapping geographical incidence of preeclampsia within a New Zealand context" …

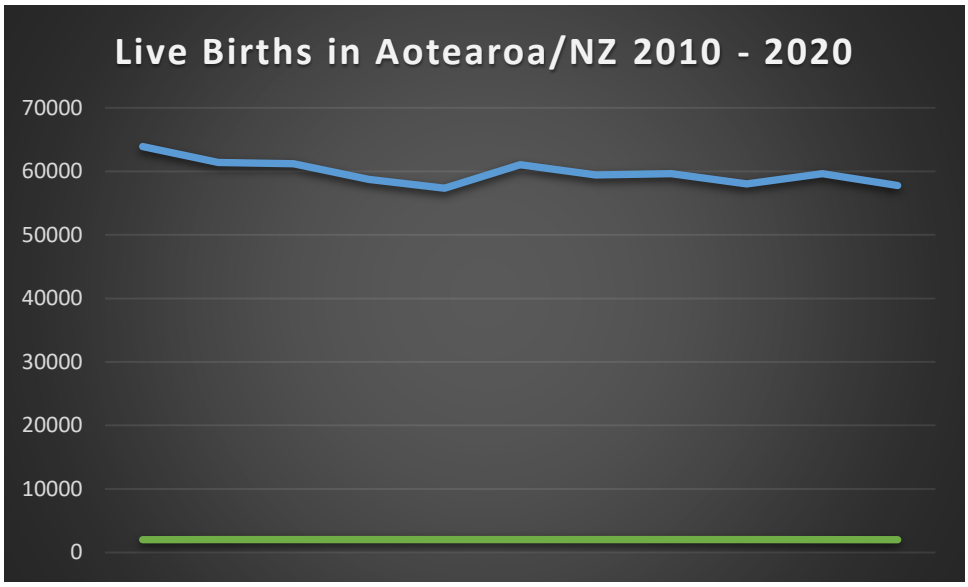
(Associate Professor Katie Groom, On Track Network Trial, Auckland, New Zealand, personal communication, February 20, 2020)

The rate of live births over the past ten years in Aotearoa/New Zealand has averaged 60,308 annually. However, this rate has steadily fallen by approximately 3% per annum since 2017, with the lowest recorded birth rate since 2005 (57,744) reported in 2020; 57,753 live births in 2020 compared with 59,637 the previous year (Statistics New Zealand, 2020).

4.3.1 Live Births in Aotearoa/New Zealand 2010 - 2020

Figure 2

Live Births in Aotearoa/New Zealand, 2010 – 2020.



Note: This figure was created using data obtained from Statistics New Zealand (Statistics NZ, 2020).

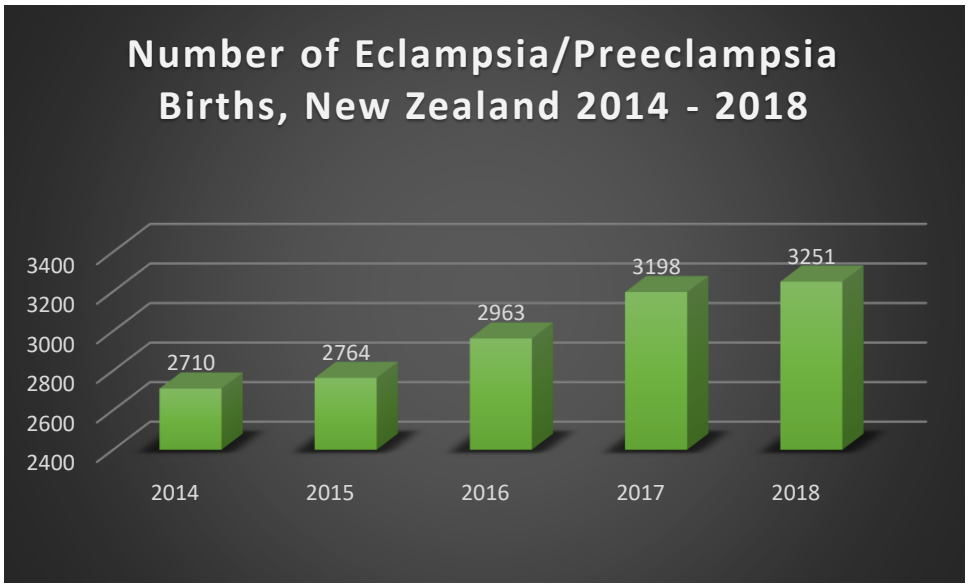
Meanwhile, research assessing the incidence and prevalence of preeclampsia in Aotearoa/New Zealand is extremely limited, with only very few studies available for further scrutiny and evaluation at the time of submitting this thesis.

However, recently published statistics from the New Zealand National Maternity Collection denote a steady rise in the number of births affected by eclampsia / preeclampsia, increasing from 2710 documented cases in 2014, to 3251 documented cases in 2018 (see below, Figure 3).

4.3.2 Number of Eclampsia/Preeclampsia Births, Aotearoa/NZ

Figure 3

Number of Eclampsia/Preeclampsia Births, New Zealand, 2014 – 2018.



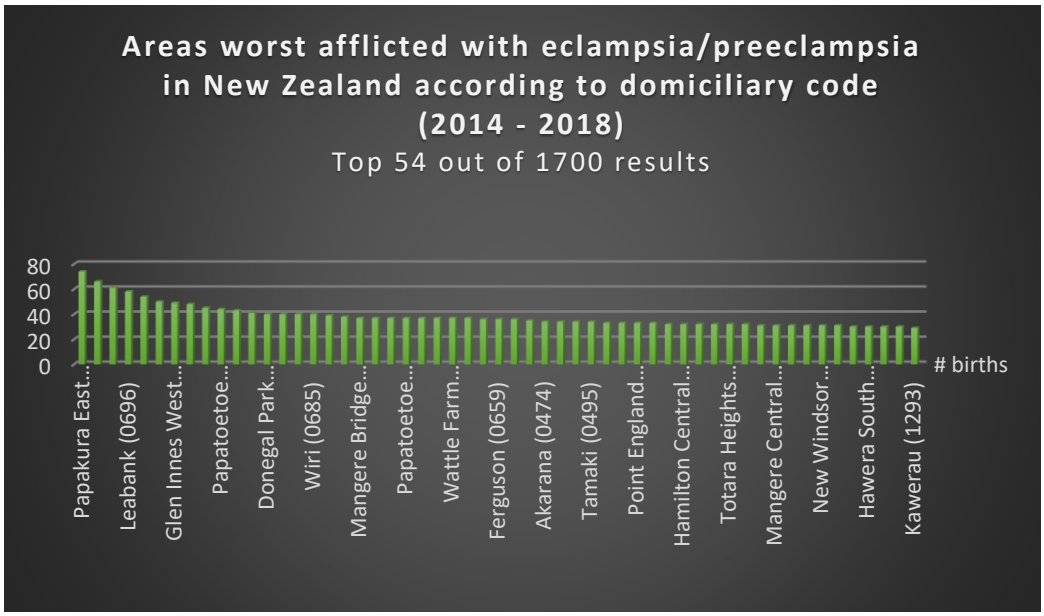
Note: This figure was created using statistics obtained from the National Maternity Collection, New Zealand (MoH, 2020).

The following visual graph (Figure 4) denotes the regional domiciles recording the highest rates of eclampsia and preeclampsia within Aotearoa/New Zealand. However, data differentiating between the two disorders is not currently available for evaluation or comment.

4.3.3 Areas worst afflicted with Eclampsia/Preeclampsia, Aotearoa/NZ

Figure 4

Areas worst afflicted with eclampsia/preeclampsia in New Zealand according to domiciliary code (2014 – 2018)



Note: This figure was created using statistics obtained from the National Maternity Collection, New Zealand (MoH, 2020).

While the author recognises the value of analysing and proffering comment on all 1700 domiciliary results for rates of preeclampsia in Aotearoa/New Zealand, this is acknowledged as a limitation of the aims of this research. Further and future analysis of these results is warranted and should therefore be evaluated and explored at a later opportunity as

part of an ongoing research project. Nonetheless, emergent themes from the 54 domiciliary results as denoted in the graph above should be noted and commented upon:

Of the regions reporting the highest incidence of preeclampsia in Aotearoa/New Zealand, there is direct correlation between that and socio-economic deprivation, whether the domiciliary area is urban (and therefore more highly populated), industrial, or rural. A geo-coded map of the above data superimposed upon the reporting of socio-economic deprivation and quintile scales would afford greater analysis of this theme and has merit for further investigation. Geocoding is a scientific algorithm that enables addresses to be matched to specific geographic locations and is an important step in using Geographic Information Systems (GIS) typically to determine association between environmental exposure assessment and adverse health outcomes (Avanasi, et al., 2016, p. 505). Such a project would afford greater insight into the established links between socio-economic deprivation, environmental pollution and disease that current and emergent research is now determining as definitive causation for the pathogenesis of preeclampsia (Hutcheon et al., 2011).

While the author could find no current New Zealand publications specifically assessing either incidence or prevalence of preeclampsia in Aotearoa/New Zealand, several journal articles and national reports and reviews were perused and are included below for comment:

A 2012 New-Zealand-based prospective cohort study (Anderson et al., 2012) examining the impact of maternal body mass index on the phenotype of preeclampsia reported a higher risk for disease diagnosis and progression amongst women who were overweight or obese in early pregnancy. However, the study did not report on specific rates of prevalence or incidence of preeclampsia in Aotearoa/New Zealand.

In 2018, a systematic review and meta-analysis examining the efficacy of maternal folic acid supplementation for the prevention of preeclampsia noted that the global incidence of preeclampsia was estimated at approximately 4.1% with regional differences ranging from 1 – 7% worldwide, while in New Zealand, rates of preeclampsia were approximated as affecting 3% of all pregnancies, with higher rates noted in nulliparous women (Bulloch et al., 2018).

In 2016, the Neonatal Encephalopathy Working Group (NEWG) in Wellington, New Zealand reviewed a series of 47 babies diagnosed with neonatal encephalopathy (NE) between 2013 and 2015 following an acute peripartum event; including placental abruption and uterine rupture, eclampsia and preeclampsia, shoulder dystocia, cord prolapse and emergency caesarean section. More than 13% of all cases involving NE were determined as attributable to maternal hypertensive disorders, including preeclampsia. In two-thirds of all cases of NE that were reviewed, mortality and severe morbidity outcomes were considered potentially avoidable (PMMRC, 2018).

The 2018 PMMRC determined that the neonatal mortality rate has not reduced in New Zealand in the past decade when compared with other comparable countries such as the United Kingdom and Australia, remaining at 2.5/1000 live births in 2016. Furthermore, there are significantly higher death rates for babies without congenital anomalies amongst Māori, Pacific and Indian women, particularly those babies born to young mothers (aged under 20 years of age) in these same ethnic groups (PMMRC, 2018). In Aotearoa/New Zealand, inequities in health and health determination are marked, with the burden of adverse health outcomes carried predominantly by Māori women, who are disproportionately and adversely afflicted with risk for maternal morbidity and mortality (HQSC, 2019). Additionally, social inequity and institutional racism was highlighted as a dominant precursor for sub-optimal maternal and neonatal outcomes, with findings from the report confirming the association

between maternal health inequalities, fetal growth restriction and socio-economic deprivation (PMMRC, 2018; PMMRC, 2019).

The Maternal Morbidity Working Group (MMWG) Annual Report from September 2017 to August 2018 received 468 notifications of maternal morbidity for 437 women between September 2017 and 31 August 2018. While the leading cause for high-dependency unit (HDU) and intensive care unit (ICU) admission was postpartum haemorrhage (33.9%), this was closely followed by hypertensive disorders of pregnancy (30.2%), including preeclampsia. Once again, Māori women were over-represented in the notifications of women admitted to an HDU or ICU when compared with non-Māori women and show that Māori and Pacific women in particular, face greater likelihood of poorer birth outcomes, perinatal and maternal morbidity and mortality (HQSC, 2019).

4.4 Synthesis of Findings

Global incidence and prevalence of preeclampsia has been difficult to determine in exact measures, due to limitations in both reporting, likelihood of internal coding errors and missed diagnosis due to use of conflicting diagnostic criteria and requisites. As previously mentioned, 64 studies from around the globe were analysed from their full-text PDF format, with an additional four studies perused for general interest and comment. Each study was evaluated for its reporting on both or either the incidence and/or prevalence of preeclampsia in its nation of origin with emergent themes commented on throughout. In particular (and despite preeclampsia diagnostic criteria revision in 2014), many studies included beyond 2014 continued to require proteinuria for confirmation of preeclampsia diagnosis and/or did not report on their country's overall rate or incidence. Furthermore, many studies that went

on to re-examine previous reported rates of preeclampsia in line with the 2014 ISSHP and 2015 SOMANZ revisions, either noted and/or were suggestive of higher rates of the disorder, once new criteria were applied.

There were no studies emanating from New Zealand that resulted from any of the key word searches undertaken, meaning further exploration of emergent themes pertaining to the influence of environmental, geographic, genetic and social factors on preeclampsia incidence and prevalence within an Aotearoa/New Zealand framework is warranted.

4.5 Summary

Chapter Four has explored and further evaluated each of the included review literature to examine and critique the incidence and prevalence of preeclampsia both globally and within an Aotearoa/New Zealand framework. This chapter has also drawn attention to significant research deficits in this field of study and provided comment upon emergent themes of interest that will bear impact upon future research opportunities. Chapter Five will now examine and discuss the implications of the research findings, conclusions and indications for future research pathways.

CHAPTER FIVE – REVIEW FINDINGS & IMPLICATIONS FOR FUTURE RESEARCH

5.1 Introduction

Chapter Five will briefly summarise the main findings of the integrative review, provide discussion on emergent themes and limitations captured during the review process, discuss key conclusions drawn by the research and provide advice regarding implications for future research opportunities.

5.2 Discussion

This research has sought to critique and evaluate all literature meeting with the study's inclusion and search criteria, in order to:

1) investigate the incidence and prevalence of preeclampsia both globally and within Aotearoa/New Zealand and
2) identify any environmental, cultural and socio-economic factors that may be associated with preeclampsia incidence and prevalence in Aotearoa/New Zealand

This evaluation has been necessary to determine feasibility for ongoing research into the impact of environmental factors alongside geographical, cultural and socio-economic considerations when assessing risk for preeclampsia within a New Zealand maternity population.

Preeclampsia, a sub-set of hypertensive disorders diagnosed during pregnancy, is a complex pregnancy-induced syndrome occurring 20 weeks' gestation. Preeclampsia and eclampsia account for one- third of severe maternal morbidities and, collectively, are responsible for 10–15% of maternal mortality rates in low to middle- income countries and 30– 35% of pre-term births worldwide. (Duley, 2009). While the exact pathogenesis of preeclampsia remains unclear, multiple studies suggest aetiology may stem from a combination of several complex, multifactorial interactions; including genetic and environmental considerations (Zhou et al., 2019).

Genetic and epigenetic factors including life-style considerations such as obesity, age, nutrition and pre-existing chronic hypertension all play an important role in the development and pathophysiology of preeclampsia. Moreover, geographical location, altitude, pollution and exposure to environmental toxins are now becoming more commonly recognised as significant yet potentially modifiable risks. Many of the smaller and larger scale Chinese studies assessed during the undertaking of the research report genetic factors associated with risk for preeclampsia, although incidence amongst the different populations and ethnicities is yet to be fully explored (Zhou et al., 2019). Additionally, known causes and risks for preeclampsia (aside from genetic and lifestyle factors) have been evaluated to include immunologic processes, socio-economic and environmental factors (Engjom et al., 2018).

However, given that many studies perused for the purpose of writing this research provided no definition of preeclampsia, both reporting of incidence as well as reliability of data cannot necessarily be relied upon as suitably robust. Additionally, and despite a century of inquiry, the exact pathogenesis of preeclampsia remains largely undetermined. However, emerging research now seems to implicate either 'placental' or 'maternal' causes as two key culprits (Redmann & Sargent, 2005 as cited in Brennan et al., 2013; Robillard, 2017; Robillard et al., 2018).

Given these two causes were considered neither in the 2013 global and regional investigation (Abalos et al., 2013), nor within the literature commented on throughout the course of this thesis, no meaningful findings pertaining to the onset of preeclampsia or the differentiation between early and late-onset preeclampsia could be extrapolated. Furthermore, the difference between these two variants is yet to be applied to global and national reporting on the incidence and prevalence of preeclampsia. Considering the inherent risk for serious maternal and fetal morbidity and mortality arising from the timing of the onset of preeclampsia, this too should be considered within an Aotearoa/New Zealand context alongside evaluation of the significance of key emergent themes (namely environmental, geographic, cultural, and social considerations) when assessing rates of preeclampsia.

5.3 Review Recommendations

Given much of the information currently available regarding risk stratification and management of preeclampsia emanates from high-income countries and, while only limited research has thus far been undertaken in the geographic localities featuring the highest incidence of maternal mortality, there is ongoing need for further investigation (Dias et al., 2019). This should additionally be considered within an Aotearoa/New Zealand context alongside determination of any environmental, geographic, cultural, and social considerations of both prevalence and incidence of preeclampsia.

5.4 Review Limitations

To date, and despite global revision of criteria for accurate preeclampsia diagnosis in 2014, recent data reporting on the incidence of preeclampsia in both high and middle-income countries is remains extremely limited and potentially flawed due to coding inaccuracies, missed diagnosis and continued use of outdated diagnostic inclusion criteria.

Furthermore, other than two studies sourced from the Ukraine, no other data from the former Soviet Union, modern-day Russia or North Korea has been reported or made academically available, meaning little can be currently inferred or commented upon regarding the incidence or impact of preeclampsia amongst those nations' large and (in the case of Russia) ethnically-diverse populations.

Of eleven international studies included in a 2016 meta-analysis of fetal sex-specific differences in gestational age at delivery alongside preeclampsia, only four included data from 2010 onwards, with only one including data from 2014 when international guidelines redefined diagnostic criteria for preeclampsia, once again indicating that global reporting to date has been extremely poorly captured (Schalekamp-Timmermans et al., 2017).

Furthermore, no evidence of a nationwide study of this research aim could be determined within an Aotearoa/New Zealand context or framework.

5.5 Implications for Future Research

There remain significant deficits in the exact determination of both global and national incidence and prevalence of preeclampsia, as well as little or no evidence of examination of any social and/or environmental risks, causes or assessments. Furthermore, as no evidence of a nationwide study of this nature within Aotearoa/New Zealand can be determined, the validity of future research and investigation has been proven. The author proposes the merit of progressing to a PhD thesis proposal, phase one of which would seek to firstly undertake an observational study to map the incidence of preeclampsia by domiciliary code/region in Aotearoa/New Zealand and determine whether there is:

a) geographic variation in rates of preeclampsia in Aotearoa/New Zealand;
b) variation in environmental pollution levels (specifically lead and other relevant toxins) according to domicile/region in Aotearoa/New Zealand;
c) establish feasibility of any link between socio-economic deprivation and preeclampsia in Aotearoa/New Zealand.

5.6 Conclusion

Preeclampsia is a leading cause of severe maternal morbidity and mortality, with global rates increasing incrementally each year. Preeclampsia bears many serious social and economic ramifications for both the women and families impacted and the nations who shoulder the largest share of the financial burden and implications of the long-term health sequelae presented by the disorder. Worldwide, the exact incidence and prevalence of the disease remains largely unknown, particularly in lower and middle-income nations, including Aotearoa/New Zealand. Furthermore, accurate coding, reporting and diagnosis of preeclampsia remains suboptimal.

Globally, there are few studies which analyse the distinction, cause or incidence of early and late-onset manifestation of the disease pathology, as recommended in the revised 2014 ISSHP criteria. More importantly, there are no such studies to date of this nature within an Aotearoa/New Zealand context or framework. Additionally, accurate data reporting on the incidence and/or prevalence of preeclampsia is sparse and extremely limited, while coding inaccuracies and inconsistent application of both the ISSHP, SOMANZ and Ministry of Health's 2018 revised guidelines and diagnostic criteria are suspected and probable. Furthermore, many countries that re-evaluated their preeclampsia statistics following the 2014 ISSHP diagnostic revisions, found the impact of the disorder to be greater than initial findings had suggested (Khan et al., 2020). Overall, global rates have risen since the last systematic review and meta-analysis was undertaken in 2013 (Abalos et al., 2013).

Additionally, epigenetic and pro-inflammatory biological factors which determine increased risk for preeclampsia (and which continue to unfold as a result of a global rise in the incidence of diabetes mellitus and obesity) cannot be ignored. Furthermore, emergent evidence of the influence of environmental factors on the disease pathology, including pollution and geographic location, as well as ethnic and socio-economic factors (namely poverty and its engendered co-morbidities), bears significant influence and impact upon both risk for, incidence and prevalence of preeclampsia.

In Aotearoa/New Zealand, Māori and Pacific peoples currently experience greater challenges in achieving improved health outcomes due to poverty, engendered discrimination and poor access to appropriate and culturally responsive care. Māori women have the lowest uptake of first trimester maternity services and are less likely to receive acceptable levels of care despite clinical and medical indication. Future research examining these preventable factors is warranted within an Aotearoa/New Zealand framework in order to better inform

future government policy and achieve improved health outcomes for our most vulnerable and at-risk populations.

CONFLICT OF INTEREST DECLARATION

The author declares no conflict of interest nor financial gain procured in the writing of this thesis.

AUTHORSHIP DECLARATION

The author declares this work to be her own, with all resources drawn upon acknowledged and appropriately referenced.

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