SOMANZ

SOCIETY OF OBSTETRIC MEDICINE OF AUSTRALIA AND NEW ZEALAND

SOMANZ

Hypertension in Pregnancy Guideline

2023

Electronic Document

ISBN Online: XXXXXXXXXXXX (TBA)

Published: XXXXXXXXX (TBA)

Preferred Citation: Society of Obstetric Medicine Australia and New Zealand, Hypertension in Pregnancy Guideline, Sydney; 2023.

Disclaimer

This guideline document is based upon literature searches last conducted in December 2020, and updated in December 2022. It is designed to assist with decision-making in matter related to the care of women with hypertension in pregnancy. It is not intended to define the standard of care but rather should be interpreted by clinicians based on the individual needs, preferences and values of their patient, the resources available to them and other constraints to practice that be unique to an institution. It is not compulsory to apply these guidelines and they do not override the responsibility of the clinician to make decisions appropriately.

The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) has made every effort to ensure there were no conflicts of interest between the members of the working group and their personal, professional or business interests. All members of the working group were required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as, or are actual conflicts of interest. Disclosures are published in the appendix of this document and are also held on file at SOMANZ.

These are the recommendations of a multidisciplinary working party convened by SOMANZ. They reflect a thorough assessment of the current medical literature and the clinical experience of members of the working party.

Foreword

SOMANZ (Society of Obstetric Medicine in Australia and New Zealand) was established in 2005 to improve the outcomes for all women with medical disorders related to pregnancy. The landscape has changed over the decades; women are choosing to become pregnant despite pre-exiting medical disorders and the knowledge and understanding of pregnancy related disorders has significantly improved. SOMANZ has previously published version of guidelines related to hypertension in pregnancy that have provided clinicians practical and pragmatic advice on how to manage these disorders. However, we felt it important to update those guidelines (last updated 2015) in an academically robust and rigorous manner given the increase in the evidence available that could be assessed.

Given the importance of this guideline to clinicians and women alike, we thus undertook the work to ensure it would be of the standard to be an 'NHMRC approved guideline'. The NHMRC approval indicates to users that a guideline is of high quality, is based on the best available scientific evidence, and has been developed to rigorous standards. They are recognised in Australia and internationally as representing current knowledge and best health practice. We anticipate the next update of these guidelines will be undertaken in a similar manner.

In contrast to the previous versions of guidance, this guideline update features a combination of both graded recommendations and practice points. Graded recommendations were based on a systematic review of the evidence and are graded for both strength of the recommendation (level 1, "strong" or level 2, "weak") and quality of the evidence (A, "high"; B, "moderate"; C, "low"; or D, "very low") using GRADE criteria. Practice points are consensus-based statements representing the expert judgment of the Work Group and are not graded as there was insufficient evidence to do so.

Thanks first and foremost must go to Dr Renuka Shanmugalingam for leading this multidisciplinary initiative, her tireless efforts, and her dedication to the process. This work would also not have been possible without the continued efforts of the Working Group members who volunteered their time and expertise to this update. Dr Zachary Munn was instrumental in undertaking this work. His guidance on the methodology of undertaking the assessment of the evidence and the grading was crucial.

In keeping with SOMANZ and NHMRC's policy for transparency and rigorous public review during the guideline development process, the draft guideline was made available for open commenting. The feedback received from the public review was carefully considered by the Work Group members and the guideline revised, as was deemed appropriate, for its formal release.

Prof Angela Makris
Chair of SOMANZ Guideline Committee

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(Members' full profile and disclosures are available under section 'Member Profile and declarations')

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Contents

List of Tables

List of Tables

List of Figures

List of Patient Information Sheets

List of Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitoring
ACOG	American College of Obstetricians and Gynecologists
ACR	albumin to creatinine ratio
ADP	Adenosine diphosphate
AFI	amniotic fluid index
ALT	Alanine transaminase
APLS	Antiphospholipid syndrome
AST	Aspartate transaminase
ATL	asprin triggered lipoxin
BMI	body mass index
COX	cyclooxygenase
CTG	cardiotopography
DBP	Diastolic Blood pressure
DHA	Docosohexaenoic acid
DVP	deepest vertical pocket
EOPE	early onset preeclampsia
EPA	Eicosopentaenoic acid
EPDS	Edinburgh postnatal depression scale
ET	endothelin
EtD	Evidence to Decision
EUC	electrolytes, urea and creatinine
GI	gGastrointestinal
GTN	Glyceryl trinitrate
HBPM	home blood pressure monitoring
HDP	hypertensive disorders of pregnancy
HELLP	Haemolysis, elevated liver enzymes and low platelets
HES	Hydroxyethyl starch
HMG-CoA	hydroxymethylglutaryl-coenzyme A
HUVEC	Human umbilical vein endothelial cells
ICU	intensive care unit
IL	interleukin
IM	Intramuscular
IPD	individual patient data
IR	Immediate Release
ISSHP	International Society for the Study Of Hypertension In Pregnancy
IUGR	Intrauterine growth restriction
IV	Intravenous
K1-5	Korotkoff Sound 1-5
LCPUFA	Long Chain polyunsaturated fatty acids
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LFT	Liver function test
LMWH	low molecular weight heparin
LOPE	late onset preeclampsia
MH	masked hypertension
NICE	National instiute for Health and Care Excellence
NICU	Neonatal intensive care unit
NMDA	N-methyl-D-aspartate
NO	Nitric oxide
NSAID	Non steroidal anti inflammatory drug
OR	Odds Ratio
PCOS	Polycystic ovarian syndrome
PCR	protein to creatinine ratio
PGI2	Prostglandin I2
PI	Pulsatility Index
PlGF	Placental growth factor
PP	Practice Point
PPI	proton pump inhibitor
RANZCOG	Royal Australian and New Zealand College of Obstetrics and Gynecology
RCOG	Royal College of Obstetricians and Gynecologists
RCT	Randomised control trials
RR	Risk Ratio
SBP	Systolic blood pressure
sEng	soluble endoglin
sFlt-1	soluble fms-like tyrosine kinase-1
SGA	small for gestational age
SLE	systemic lupus erythematosus
SoF	Summary of Findings
SOMANZ	Society of Obatetric Medicine Austrlia and New Zealand
TGA	Therapeutic Guidelines of Australia
TIA	Transient ischaemic attack
TNFa	Tumour necrosis factor alpha
TXA	Thrombaxane A
UAD	umbilical artery Doppler
UtA-PI	uterine pulsatility index
VCAM	vascular cell adhesion molecule
VTE	venous thromboembolism
WCH	white coat hypertension
WHO	World Health Organisation

Methodology

Appointment of working group members and methodology development

The SOMANZ Hypertension in Pregnancy Guideline 2023 was developed with the aim of providing evidence-based clinical practice guideline in screening, preventing and managing pregnant women who are at risk of hypertensive disorders in their pregnancy, both antenatally and beyond.

This guideline adheres to national and international best practices for guideline development and was developed strictly following the "Procedures and requirements for meeting the NHMRC Standards for Clinical Practice Guidelines". In adhering to the recommended best practices, the following processes were undertaken in developing this guideline:

- Appointment of working group members and conflicts declared (Refer to Member Profile and Declared Conflict(s) of interest)
- Development and review of guideline development methodology
- Defining scope and topics of the guideline
- Identification of clinical questions: Population, Intervention, Comparator, Outcome, Methods (PICO) and MeSH keywords
- Literature search and review
- Meta-analysis and GRADE assessment
- Development of recommendations based on meta-analysis
- Public and stakeholder consultation of recommendations

Defining the scope of the guidelines and identification of clinical questions

The working group determined the scope of the guideline and identified clinical questions based on clinical and research development since the last version of the SOMANZ Hypertension in Pregnancy (2015) guideline (1).

Each clinical question was framed using the 'PICO' framework as follows:

- Population or Problem
- Intervention (for a treatment intervention question), or Indicator or exposure (for a prognosis or aetiology or question), or Index test (for a diagnostic accuracy question)
- Comparator
- Outcome

Outcomes examined were in keeping with the core outcome set for preeclampsia research (2, 3).

Literature search and review

Members of the panel undertook a workshop conducted by JBI Australia. The workshop was led by the group's methodologist and was designed to train the team members on conducting meta-analysis, GRADE assessment and development of recommendation based on outcome of meta-analysis.

Literature search was conducted through three main electronic databases (Medline, Cochrane Library, Embase) based on pre-determined MeSH keywords specific for each clinical question. Literature search included all studies from 1970 to 2022.

Exclusion criteria included:

- Non-English literature (except for where data from non-English manuscripts were accessibly through publicly available Cochrane Systematic Review RevMan folders)
- Non-pregnant subjects
- Animal and cell studies

The titles and abstracts resulting from the searches were screened by the lead and chair of the group who independently assessed retrieved abstracts and, if necessary, the full text, to exclude studies that met the specified exclusion criteria. Any disagreement on exclusion of studies were resolved by discussion with a third member of working group.

Following which, a second round of literature review was conducted in duplicates by two group members for each clinical question to select articles based on the preference below:

- Meta-analysis, systematic review of randomised controlled trials (interventions)
- Randomised controlled trials (RCT)
- Cohort studies
- Case control studies and case series

Meta-analysis, systematic reviews and randomised controlled studies were given preference over cohort studies and case-controlled studies. Where there were adequate randomised controlled studies, cohort studies and case-controlled studies were excluded from the meta-analysis.

Outcome of literature review for each clinical question was assessed for agreement. Where there were disagreements between both reviewers, a third group member would adjudicate.

Meta-analysis, GRADE assessment and development of recommendations

Data extraction from selected studies within each clinical question was performed independently by 2 members of the working group. Where there was disagreement on inconsistency with data extraction, a third member from the working group would adjudicate. Extracted data was populated into Review Master (RevMan) to generate meta-analysis and forest plots.

Where a Cochrane systematic review with a similar PICO was identified, the publicly available Cochrane RevMan was reviewed and adapted for our analysis.

Evidence synthesis and meta-analysis: Results for dichotomous outcomes were expressed as risk ratio (RR) with 95% CI. For continuous scales of measurement, mean difference (MD) with 95% CI was used. Data were pooled using the Mantel–Haenszel random-effects model for dichotomous outcomes with 2 or more studies while fixed-effects model was used for dichotomous outcomes with less than 2 studies.

The diagnostic tool analysis (DTA) meta-analyses were conducted by the DTA team (Refer to member profile). STATA was utilised to conduct bivariate model analysis and generate sensitivity and specificity.

Critical appraisal of quality of evidence (GRADE assessment): The meta-analysis for each outcome within each clinical question was critically appraised through the GRADE system (conducted through the GRADE PRO software) **(https://www.gradepro.org/)** which consisted of an assessment of the following domains:

(a) Risk of bias assessment

Majority of meta-analysis conducted consistent of RCTs. For these reviews, the Cochrane Risk of Bias tool was used to assess individual studies for risk of bias. The risk of bias assessments was conducted individually by two members of the working group. Where there were disagreements, a third member from the working group was consulted. The domains in the risk of bias assessment were as listed below:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias (other biases)?

For observational cohort studies, the ROBINS-i risk of bias assessment tool was utilized. For diagnostic tool assessment (DTA) reviews, the QUADRAS, CHARM and PROBAST risk of bias tools was utilized.

Overall risk of bias for each outcome was assessed based on the number of studies, weight of each study and number of domains consisting of high (red), uncertain (yellow) or low (green) risk of bias. Based on which, risk of bias was determined to be either not serious (0), serious (-1) or very serious (-2).

(b) Assessment for inconsistency (heterogeneity)

Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes and of risk ratios, and c2 tests. A P <0.05 was used to denote statistical heterogeneity, with an I2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance. A I2 value of ≥60% was deemed serious (-1) and ≥ 80% was deemed very serious (-2) for heterogeneity.

(c) Assessment for indirectness

Indirectness was assessed based on the relevance of the population in the studies to the clinical question examined. All studies selected excluded studies with non-pregnant subjects, therefore, minimizing the risk of indirectness.

(d) Assessment for impression

Impression was assessed based on event size relative to sample size and the associated confidence intervals (CI). Wide confidence interval relative to the event size were deemed either serious (-1), very serious (-2) or extremely serious (-3) based on the extend of difference between confidence intervals relative to the event size.

(e) Publication bias

Publication bias was assessed with the use of funnel plots when sufficient number of studies were available (i.e., more than 10 studies).

For observational studies and other study types, the quality of the evidence was upgraded from low quality of the evidence (where appropriate) according to the specified criteria.

Based on the domains assessed, an overall quality of evidence of either high, moderate, low or very low is generated for each outcome examined. Further details on the GRADE approach for rating quality of the evidence can be found at **https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence**

Summary of finding (SoF) tables were generated by the group lead through the GRADEPRO software. The SoF tables consist of results from data synthesis as relative and absolute effect estimates and the overall quality of evidence for each outcome. The data summary tables in this document have been generated based on the SoFs. The authors of this guidelines can be contacted for access to the full SoF documents.

Development of recommendations: Evidence to decision (EtD) framework flowsheets were generated by the group lead through the GRADEPRO software in facilitating the development of recommendations (ref). The EtD consist of a summary of the clinical question, meta-analysis, quality of evidence, balance of effect of intervention (where applicable), feasibility and equity in recommending intervention (where applicable) and proposed recommendation. The EtD for each clinical question along with the SoFs were distributed to all members of the working group electronically through the GRADEPRO software. Members were required to vote and comment on the proposed recommendations electronically. Outcomes of the votes were discussed and finalised through two videoconferences. All members of the working group provided input on initial and final drafts of the recommendation statements and guideline text and approved the final version of the guideline.

Funding

All members of the working group underwent a virtual training session with JBI. The cost of the training session, JBI consultation fees and DTA meta-analysis by the DTA team were paid for by SOMANZ. No external funding was obtained.

Limitations

Studies published in any language other than English were excluded due to our inability to access professional translational service (except for where data from non-English manuscripts were accessibly through publicly available Cochrane Systematic Review RevMan folders). Where data was not available or not extractable, we did not contact the nominated authors of the study.

How to Use This Guideline

Type of recommendations

This guideline consists of evidence-based recommendations and practice points (Table I.I)

Evidence based recommendation	Practice points (PP)
Meta-analysis and quality of evidence analysis conducted	Inadequate data to conduct meta-analysis (no meta-analysis conducted)
Recommendation generated based on evidence meta-analysis and quality of evidence analysis	Recommendation generated based on consensus statement (limited or no data)
Guidance is based on evidence and is clinically actionable	Guidance to be used at the discretion of the clinician

Table I.I Summary of differences between evidence-based recommendations and practice points

Evidence based recommendation: Evidence based recommendations have been made based on meta-analysis and quality of evidence analysis (Described in Methodology section of this document). Each recommendation is followed by an assessment of the **strength of the recommendation (strong - level 1 or weak - level 2)** and the **quality of the evidence (A, B, C, D)** (Table I.II and I.III).

Strength of recommendation	Implication
Level 1 (Strong)	Most patient should receive the recommended course of action
Level 2 (Weak)	Different choices will be appropriate for different patients. The decision on treatment options should be made through a shared informed decision-making process with the patient

Table I.II Description of types of strength of recommendation

Grade	Quality of evidence	Meaning
A	High	The working group members have a lot of confidence that the true effect is similar to the estimated effect
B	Moderate	The working group members believe that the true effect is probably close to the estimated effect
C	Low	The working group members believe that the true effect might be markedly different from the estimated effect
D	Very low	The working group members believe that the true effect is probably markedly different from the estimated effect

Table I.III: Description of types of quality of evidence

The recommendation statements are followed by key information such as summary of literature reviewed, summary of evidence (based on summary of finding, SoF), rationale for recommendation, comparison of recommendation with other key guidelines such as:

- International Society of Hypertension in Pregnancy Guideline (ISSHP) 2022
- Australian Pregnancy Care Guidelines 2019
- NICE, UK Guideline (2019) (and 2022 where updated version was available)
- SOMANZ Hypertension in Pregnancy Guideline 2015

A section on current literature gaps and future research topics is also provided at the end of every clinical question. Access the meta-analysis forest plots, SoF tables and EtD flow charts can be obtained by submitting a written request to SOMANZ.

Practice points (PP): In addition to evidence-based graded recommendations, this guideline includes "practice points" to help clinicians better evaluate and implement guidance from the working group. Practice points are consensus statements about a specific aspect of care where no formal systematic evidence review was undertaken, or if there was insufficient evidence to provide a graded recommendation. Practice points represent the expert judgment of the guideline working group, but and may be based on limited or emerging evidence. Unlike evidence-based recommendations, practice points are not graded for strength of recommendation or quality of evidence. Clinicians should use practice points as expert guidance and use it as they see fit in making shared, informed decisions with the women under their care.

Clinician information/flow sheets

This guideline provides illustrated flow charts and clinician information sheet to help clinicians utilise the recommendations made in this guideline. The information sheets were generated based on both evidence-based recommendations and practice points and are identified accordingly. The information sheets were produced and reviewed by the members of the working group specifically for the purpose of this guideline.

Patient information sheet

This guideline provides summarised information for patients and consumers to provide them with the ability to participate in their own care. The information sheets were generated by the working group members with significant input from our patient/consumer representatives to help women understand their diagnosis, treatment and/ or prognosis with clarity in helping them make informed decisions with their clinicians. The information sheets in the current version of the guideline are presented in English only. We aim to include information sheets in other key languages in future versions of this guideline. All patient information sheets in this guideline should be used in conjunction with clinical counselling by the treating clinician or midwife. The information sheet does not replace the importance of clinical counselling.

Executive Summary of Recommendations

Chapter 2: Screening for women at risk of preeclampsia

Clinical question	Type of Recommendation	Recommendation	Rating of Recommendation
2. Screening for women at risk of developing preeclampsia			
2.1	Evidence based recommendation	The use of maternal risk factors (maternal characteristics, medical and obstetric history) to screen all pregnancies for risk of preeclampsia is strongly recommended (Table 2.1)	1A
2.2	Evidence based recommendation	The use of a combined first trimester screen (combined maternal features, biomarkers and sonography) to identify women at risk of developing preeclampsia is conditionally recommended based on local availability and access to the required resources.	2B

Chapter 3(A): Prevention of preeclampsia (Pharmacological)

Clinical question	Type of Recommendation	Recommendation	Rating of Recommendation
3A.1 Aspirin			
3A.1.1	Evidence based recommendation	Initiation of aspirin in women at high risk of developing preeclampsia, prior to 16 weeks of gestation, is strongly recommended	1B
3A.1.2	Evidence based recommendation	The use of 150mg/day of aspirin is recommended.	1B
3A.1.3	Evidence based recommendation	The use of bedtime aspirin is conditionally recommended	2C
3A.1.4	Evidence based recommendation	Cessation of aspirin between 34 weeks of gestation and delivery is conditionally recommended. The exact timing of cessation should be based on individualised clinical judgment and informed, shared decision making with the patient.	2B
3A.1.5	Evidence based recommendation	Universal aspirin in low-risk nulliparous women is conditionally recommended against Informed, shared decision making with the patient is recommended where appropriate risk stratification is not possible	2B
3A.1.6	Practice point	Counselling on the use of aspirin in pregnancy is recommended to improve adherence to aspirin in pregnancy (Patient Information Sheet 3A.1)	PP
3A.2 Oral supplemental calcium			
3A.2.1	Evidence based recommendation	The use of supplemental calcium is strongly recommended in pregnant women with low dietary calcium intake (<1g/day)	1C
3A.2.2	Practice point	Assess dietary calcium intake prior to recommending oral calcium supplementation (Flow chart 3A.2)	PP
3A.2.3	Practice point	Consider assessing serum corrected calcium prior to commencement of calcium oral supplementation (to ensure the absence of underlying hypercalcaemia)	PP
3A.3 Oral omega-3 LCPUFA	Evidence based recommendation	The use of oral omega-3 LCPUFA supplementation for the prevention of preeclampsia is recommended against until more data is available	2B

Clinical question	Type of Recommendation	Recommendation	Rating of Recommendation
3A.4 Oral garlic supplementation	Evidence based recommendation	The use of oral garlic supplementation for prevention of preeclampsia is recommended against until more data is available.	2D
3A.5 Oral antioxidants (Vitamin C and E)	Evidence based recommendation	The use of oral Vitamin C and E supplementation for prevention of preeclampsia is recommended against until more data on the risk of harm is available.	2B
3A.6 Oral magnesium	Evidence based recommendation	The use of oral magnesium replacement for the prevention of preeclampsia, is recommended against until more data is available.	2C
3A.7 Progesterone	Evidence based recommendation	The use of progesterone for prevention of preeclampsia, is recommended against until more data is available.	2B
3A.8 Statin	Evidence based recommendation	The use of statin for prevention of preeclampsia is recommended against until more data is available.	2B
3A.9 Low Molecular weight Heparin			
3A.9.1 Low Molecular weight heparin in addition to aspirin for prevention of preeclampsia	Evidence based recommendation	The use of low molecular weight heparin (LMWH) in addition to aspirin for prevention of preeclampsia in women without a history of thrombophilia or APLS is conditionally recommended against. The decision to use LMWH in addition to aspirin should be individualised based on the patient's clinical and obstetric history and through shared- decision making.	2C
3A.9.2 Low Molecular weight heparin alone (without aspirin) for prevention of preeclampsia	Evidence based recommendation	The use of low molecular weight heparin (LMWH) alone (without aspirin) in women without a history of thrombophilia or APLS can be considered if a contraindication to aspirin is present. The decision to use LMWH (at a prophylactic dose) should be individualised based on the patient's clinical and obstetric history and through a shared, informed decision-making process. LMWH should not replace the use of aspirin in women without contraindications to aspirin.	2D
3A.10 Nitric Oxide	Evidence based recommendation	The use of nitric oxide (either in donor or precursor forms) for the prevention of preeclampsia is recommended against until more data is available	2C
3A.11 Metformin	Evidence based recommendation	The use of oral metformin, specifically for the prevention of preeclampsia is recommended against until more data is available	2C
3A.12 Oral Vitamin D	Evidence based recommendation	The use of oral Vitamin D supplementation for the prevention of preeclampsia is recommended against until more data is available	2B
3A.13 Oral Proton Pump Inhibitors (PPIs)	Practice point	The use of proton pump inhibitors for prevention of preeclampsia is recommended against until more data is available.	PP
3A.14 Clopidogrel	Practice point	The use of clopidogrel for prevention of preeclampsia is recommended against until human data is available	PP

Chapter 3(B): Prevention of preeclampsia (Non-pharmacological)

Clinical question	Type of Recommendation	Recommendation	Rating of Recommendation
3B.1 Exercise/ Physical activity	Evidence based recommendation	Moderate intensity exercise, in the form of aerobic, stretching and/ or muscle resistance exercises, for a total of 2.5-5 hours a week, as recommended as part of routine pregnancy wellbeing has the added benefit of reducing the risk of hypertensive disorders of pregnancy. Adherence to the current recommended exercise regimen for general pregnancy wellbeing is encouraged.	2D
3B.2 Dietary salt restriction	Evidence based recommendation	Dietary salt restriction, for prevention of preeclampsia, is recommended against until more data is available	2D

Chapter 4: Diagnosis of preeclampsia

Clinical question	Type of Recommendation	Recommendation	Rating of Recommendation
4.1 Urine assessment for proteinuria			
4.1.1	Evidence based recommendation	Urine dipstick can be used for initial screening, however, dipstick alone is inadequate to diagnose proteinuria in pregnancy. A confirmatory quantifying method of urine protein assessment (i.e. urine protein to creatinine ratio) should be used in women with clinical suspicion of preeclampsia	2B
4.1.2	Evidence based recommendation	Urine protein to creatinine ratio (uPCR) with a cut off ≥30mg/mmol can be used to diagnose proteinuria in pregnancy.	1B
4.1.3	Evidence based recommendation	Urine albumin to creatinine ratio (uACR) with a cut off ≥8mg/mmol can be used an alternative if urine protein to creatinine ratio (uPCR) is not available to diagnosed proteinuria in pregnancy.	2B
4.1.4	Practice point	Cut off for abnormal urinary protein excretion in multi-gestational pregnancy remains unclear and therefore urine PCR, ACR and 24-hour urine assessment should be interpreted with caution	PP
4.1.5	Practice point	Repeated urinary protein assessment in women with proteinuria from preeclampsia (in the absence of other indications) is not recommended. There is inadequate data to determine the severity of preeclampsia or timing of delivery based on urine protein assessment.	PP
4.2 Use of sFlt-1/PlGF ratio			
4.2.1	Evidence based recommendation	Utility of sFlt-1/PlGF (≤38) in ruling out preeclampsia within 1- 4 weeks of testing in women where there is a clinical suspicion of preeclampsia is conditionally recommended where a clinically validated ratio assessment is available in a timely manner.	2D
4.2.2	Evidence based recommendation	The use of the sFlt-1/PlGF ratio in diagnosing preeclampsia, determining fetal outcomes, severity of disease, timing of delivery and its used in routine screening in asymptomatic women is not recommended until more data is available to support its use in these settings	2D
4.2.3	Practice point	The SFlt-1/PlGF ratio should be used as an adjunct to clinical assessment. The use of the ratio should not replace clinical assessment and management decisions should not be made based on the ratio alone (Flowsheet 4.2)	PP
4.3 Use of PlGF-based testing			
4.3.1	Practice point	More data on the clinical application of PlGF-based testing in predicting preeclampsia in women with clinical suspicion of preeclampsia is required prior to clinical implementation of PlGF-based testing in Australia and New Zealand	PP
4.3.2	Practice point	Use of the PlGF value (alone) from the sFlt-1/PlGF ratio assay (ROCHE COBAS) for the use of PlGF-based testing has not been clinically validated and is not recommended	PP

Chapter 5: Management of chronic or gestational hypertension in pregnancy

Clinical question	Type of Recommendation	Recommendation	Rating of Recommendation
5.1 Blood pressure target in women with chronic or gestational hypertension	Evidence based recommendation	Women with gestational or chronic hypertension should have tight blood pressure control to a target of ≤135/85mmHg	1C
5.2 Home BP monitoring (HBPM) in monitoring women with stable chronic or gestational hypertension			
5.2.1	Evidence based recommendation	Where appropriate, HBPM with the use of a validated blood pressure device can be utilised in women with chronic or gestational hypertension. The use of HBPM, however, should not replace the minimum recommend frequency of antenatal review according to the woman's parity and stage of pregnancy.	1B
5.2.2	Practice point	Compliance and technique with home blood pressure monitoring (Patient information sheet 5.2.1 and 5.2.2) should be reassessed at each review to ensure ongoing suitability	PP
5.3 Antihypertensives in the management of stable hypertension			
5.3.1	Evidence based recommendation	Oral agents labetalol, methyldopa and/or nifedipine can be used in managing stable hypertension in pregnancy (gestational hypertension, chronic hypertension, non-severe hypertension in preeclampsia). The choice of agent should be individualised based on access to agent, women's clinical history and through a shared informed decision-making process (Flowchart 5.3)	2C
5.3.2	Practice point	In addition to the agents above, oral hydralazine can be used in managing stable hypertension in pregnancy	PP
5.4 Timing of birth in women with chronic hypertension or gestational hypertension	Evidence based recommendation	There remains inadequate data to suggest the need for planned birth between 36 and 37^{+6} weeks of gestation in women with gestational or chronic hypertension. The decision on the timing of birth should be individualised based on the patient's clinical and obstetric history and through a shared, informed decision-making process	2D
5.5 ABPM or home BP monitoring to diagnose masked and white coat hypertension			PP
5.5.1	Practice point	Ambulatory blood pressure should be considered to exclude white coat hypertension in women with isolated hypertension in pregnancy (in the absence of an established diagnosis of preeclampsia, chronic hypertension, or gestational hypertension)	PP
5.5.2	Practice point	Where there are poor pregnancy outcomes in current or previous pregnancies that could not be explained by other factors, we suggest an ABPM to assess for masked hypertension	

Chapter 6: Management of preeclampsia

Clinical question	Type of Recommendation	Recommendation	Rating of Recommendation
6.1 Antihypertensives in the management of stable hypertension in preeclampsia	Evidence based recommendation	Oral agents labetalol, methyldopa and/or nifedipine can be used in managing stable hypertension in pregnancy (gestational hypertension, chronic hypertension, non-severe hypertension in preeclampsia). The choice of agent should be individualised based on access to agent, women's clinical history and through a shared informed decision-making process. (Flowchart 5.3)	2C
6.2 Management of acute hypertension (≥160/110mm Hg) in preeclampsia			
6.2.1	Evidence based recommendation	Short acting agents such as IV hydralazine, IV labetalol, oral immediate release (IR) nifedipine or IV diazoxide should be used in managing acute hypertension (Flow chart 6.2). The choice of short acting antihypertensive should be based on the unit's access and familiarity with agent of choice.	2C
6.2.2	Practice Point	Acute (severe) hypertension should be treated to a target of <160/110 mmHg	PP
6.3 Timing of birth in preeclampsia			
6.3.1	Evidence based recommendation	Delivery plan should be initiated women with preeclampsia at ≥37 weeks	2D
6.3.2	Evidence based recommendation	Decision for expectant management or immediate delivery in women with preeclampsia <37 weeks should be made based on maternal and fetal clinical stability in weighing the risk preterm birth (Table 6.3.2). The decision should be made through an informed shared decision-making process with the patient	2D
6.3.3	Practice point	Delivery should be considered at any gestation in the event of deterioration (Table 6.3.2)	PP
6.3.4	Practice point	Women with preeclampsia at risk of early preterm birth (<34 weeks) should be considered for a transfer to a unit with appropriate level of neonatal and paediatric care	PP
6.3.5	Evidence based recommendation and practice point	There is limited data to support the use of angiogenic biomarkers in determining timing and indication of delivery (Recommendations 4.2 and 4.3)	2B
6.3.6	Evidence based recommendation	Where appropriate, consider the use of corticosteroid and magnesium sulphate in women at risk of early preterm birth (Recommendations 6.5 and 6.6)	2A
6.4 Corticosteroid in women with preeclampsia at risk of preterm delivery			
6.4.1	Evidence based recommendation	Use of corticosteroid (either betamethasone or dexamethasone) is recommended in women with preeclampsia who are at risk of delivery <34 weeks of gestation.	2A
6.4.2	Evidence based recommendation	There is insufficient data to recommend routine use of corticosteroid in women with preeclampsia who are at risk of delivery between 34-36 weeks of gestation. The use of corticosteroid in this setting should be individualised based on clinical assessment and through an informed shared decision-making process with the patient	2B

Chapter 6: Management of preeclampsia

Clinical question	Type of Recommendation	Recommendation	Rating of Recommendation
6.4.3	Evidence based recommendation	Redosing of corticosteroid can be considered in women with preeclampsia who remain at risk of delivery <34 weeks of gestation 7-14 days following initial single dose of corticosteroid	2A
6.5 Magnesium sulphate for fetal neuroprotection in women at risk of preterm delivery			
6.5.1	Evidence based recommendation	The use of magnesium sulphate for fetal neuroprection in women with preeclampsia at risk of preterm delivery <30 weeks of gestation is strongly recommended	2A
6.5.2	Practice point	Decision on the use of magnesium sulphate for fetal neuroprotection in women with preeclampsia at risk of delivery between 30-34 weeks of gestation should be individualised based on clinical assessment and through a shared informed decision-making process with the patient	PP
6.6 Magnesium sulphate in minimizing the risk of eclampsia and treating eclampsia			
6.6.1	Evidence based recommendation	Prophylactic magnesium sulphate with an intravenous loading dose of 4g followed by maintenance at 1g/hr for 24 in total or time of last seizure is strongly recommended in women at risk of eclampsia or recurrent eclampsia. (Flow chart 6.6)	1A
6.6.2	Evidence based recommendation	There is inadequate evidence to support an alternative magnesium regimen or the use of anticonvulsants for the prevention of eclampsia	2C,2D
6.7 Corticosteroid in the management of HELLP syndrome	Evidence based recommendation	The use of corticosteroid in managing HELLP syndrome is recommended against until more data is available.	2C
6.8 Thromboprophylaxis in women with preeclampsia			
6.8.1	Practice point	Women's risk of venous thromboembolism (VTE) and need for VTE prophylaxis should be made based on the current local hospital or state-based protocol or policy. In the absence of which, the included VTE risk in pregnancy assessment tool (Flowchart 6.8) can be utilised	PP
6.8.2	Practice point	Risk assessment should be conducted in early pregnancy (first trimester) or pre-conception, at every admission into hospital, at the time of diagnosis of preeclampsia or new intercurrent medical issue and in the immediate post-partum period	PP
6.9 Plasma expansion in women with preeclampsia	Evidence based recommendation	Routine plasma expansion for management of preeclampsia is recommended against until more data is available	2C

Chapter 7: Immediate/short term post-partum care

Clinical question	Type of Recommendation	Recommendation	Rating of Recommendation
7.1 Routine use of non-steroidal anti-inflammatory drugs (NSAIDs) for post-partum pain management in women with preeclampsia			
7.1.1	Evidence based recommendation	The routine use of non-steroidal anti-inflammatory drugs (NSAIDs) in post-partum pain management in women with preeclampsia is recommended against until more data on safety is available.	2C
7.1.2	Practice point	Short term, in-patient use can be considered in the absence of an alternative analgesics	PP
7.2 Routine use of loop diuretics in managing post-partum hypertension in women with preeclampsia	Evidence based recommendation	The short-term use of loop diuretics ,in the in-patient setting, can be considered where clinically indicated (ie pulmonary oedema, clinical features of fluid overload) in managing post partum hypertension in women with preeclampsia	2C
7.3 Antihypertensives in post-partum period	Evidence based recommendation	There remains inadequate data to suggest the superiority of a single agent or group of agents in selecting antihypertensives for the management of hypertension in the post-partum period. The choice of antihypertensive (beta-blockers, methyldopa, hydralazine, nifedipine, enalapril, clonidine) should be made through a shared decision-making process, particularly in lactating women.	2D

Chapter 8: Long term post-partum care

Clinical question	Type of Recommendation	Recommendation	Rating of Recommendation
Long term post-partum care			
8.1.1	Practice point	Women should be informed of the long-term risks associated with preeclampsia and the importance of post-partum follow up prior to discharge from hospital (Patient information sheet 8.1)	PP
8.1.2	Practice point	Women should be reviewed by their general practitioner within 1 week of discharge from hospital to ensure stable blood pressure post discharge	PP
8.1.3	Practice point	At 3-6 months post-partum, a follow up review of blood pressure (consider a 24-hour blood pressure monitor if not previously done), urine protein assessment (uACR and/or uPCR), BMI and metabolic profile (fasting blood glucose and fasting cholesterol assessment) should be considered. Interventions for any abnormalities (ie: further investigations, specialist referral, weight management, lifestyle changes, smoking cessation) should be discussed (Clinician check list 8.1)	PP
8.1.4	Practice point	A yearly follow up of blood pressure, urine protein assessment, BMI and metabolic profile should be considered in identifying early abnormalities in the first 5-10 years post-partum (Clinician check list 8.1)	PP
8.1.5	Practice point	At every review, women should be opportunistically screened for post-partum depression and anxiety. The Edinburgh Postnatal Depression Scale (EPDS) can be used as an initial screening tool (Clinician check list 8.1)	PP
8.1.6	Practice point	At every review, women should be counselled on the risk of preeclampsia in subsequent pregnancies and the importance of pre-conception medical optimisation, contraception (where indicated) and risk minimisation strategies (ie : prophylactic aspirin) (Clinician check list 8.1)	PP

PART 1: Definitions of Hypertensive Disorders of Pregnancy

Hypertension in pregnancy is defined as:

- Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg

These measurements should be confirmed by repeated readings (with three consecutive readings at least ~ 2 minutes apart). The BP should be repeated in at least 4hours to confirm true hypertension. Elevations of both systolic and diastolic blood pressures have been associated with adverse maternal and fetal outcome and therefore both are important.

Measurement of blood pressure in pregnancy

Accurate blood pressure measurement is important as blood pressure variations may result in changes in clinical management. The following measures are recommended to minimise erroneous blood pressure readings:

- The woman should be seated comfortably with her legs resting on a flat surface and her arm resting at the level of her heart.
- In labour, the blood pressure may be measured in lateral recumbency. Supine posture should be avoided due to the risk of supine hypotension syndrome (4)
- The systolic blood pressure is accepted as the first sound heard (Korotkoff sound 1(K1) and the diastolic blood pressure the disappearance of sounds completely (K5). Where K5 is absent, K4 (muffling) should be accepted (5, 6).
- Correct cuff size is important for accurate blood pressure recording. A large cuff with an inflatable bladder covering 80% of the arm circumference should be used if the upper arm circumference is greater than 33 cm but less than 44 cm and a thigh cuff used if the upper arm circumference is greater than 44 cm (7). This helps to minimise over-diagnosis of hypertension during pregnancy.
- The rate of deflation of the cuff should be ≤2 mm per second to avoid underestimating systolic blood pressure (8).
- Healthcare providers must ensure that devices for measuring blood pressure are properly validated, maintained and regularly recalibrated according to manufacturers' instructions as recommended by the British and Irish Hypertension Society (BIHS) **(https://bihsoc.org/bp-monitors/for-specialist-use/)** or European Hypertension Society **(https://stridebp.org/bp-monitors).**

Classification of hypertensive disorders in pregnancy

The classification of the hypertensive disorders in pregnancy reflects the pathophysiology of the constituent conditions as well as the risks and potential outcomes for both mother and baby. Classification is as follows:

- Preeclampsia
- Gestational hypertension
- Superimposed preeclampsia
- Chronic hypertension
- White coat hypertension
- Masked hypertension

Preeclampsia

Preeclampsia is a multi-system disorder defined as the new onset of hypertension (systolic blood pressure ≥140 mmHg and/ or diastolic blood pressure ≥90 mmHg) after 20 weeks gestation accompanied by one or more of the following signs of new onset organ involvement:

- Renal involvement (any one of the following):
  - Significant proteinuria – spot urine protein/creatinine ratio ≥ 30mg/mmol (Recommendation 4.1). Proteinuria is the most recognised additional feature after hypertension but should not be considered mandatory to make the diagnosis of preeclampsia
  - Serum creatinine > 90 µmol/L
- Liver involvement:
  - Raised serum transaminases (from a normal baseline, in the absence of alternative diagnoses for such changes)
- Haematological involvement (any one of the following)
  - Thrombocytopenia (<150,000 µ/l)
  - Features of haemolysis: decreased haptoglobin with or without fragmented red cells, elevated LDH
  - Disseminated intravascular coagulation (in the absence of alternate diagnoses for such changes)
- Neurological involvement (any one of the following):
  - Convulsions (eclampsia)
  - Features of cerebral irritability: hypereflexia with sustained clonus, persistent headache, persistent visual disturbances (photopsia, scotomata, cortical blindness, posterior reversible encephalopathy syndrome, retinal vasospasm)
  - Cerebrovascular accident
- Pulmonary oedema

- Features of placental dysfunction
    - Sonographic features of fetal growth restriction or deceleration in fetal growth trajectory associated with abnormal umbilical artery Dopplers or oligohydramnios (in the absence of alternate diagnoses for such changes).
    - The use of angiogenic markers (sFlt-1/PlGF ratio) has been shown to be valuable in 'ruling out' placental dysfunction with good negative predictive value (Recommendation 4.2). There currently remains limited clinical data on the use of angiogenic markers sFlt-1/PlGF ratio or PlGF-based testing in diagnosing preeclampsia (positive predictive value). Therefore, at present, we have not included the use of angiogenic markers in the diagnostic criteria of preeclampsia.

The hypertension and evidence of end organ involvement should return to normal generally within 3 months.

Gestational hypertension

Gestational hypertension is defined by the new onset of hypertension after 20 weeks gestation without any maternal or fetal features of preeclampsia, followed by the return of blood pressure to normal within 3 months post-partum. At first presentation, this diagnosis might include some women (up to 25%) who are developing preeclampsia but have not yet developed organ manifestations. The risk of transition from gestational hypertension to preeclampsia or adverse pregnancy outcome is higher with the earlier onset of gestational hypertension (9). Women with persistent blood pressure elevation beyond 12 weeks post-partum should be assessed for possible underlying chronic hypertension.

Superimposed preeclampsia

Superimposed preeclampsia is defined as features of preeclampsia superimposed on either pre-existing chronic hypertension, or pre-existing renal disease, or both, after 20 weeks of gestation. In women with pre-existing proteinuria, the diagnosis of superimposed preeclampsia is often difficult as the degree of proteinuria often increases during pregnancy.

In such women, substantial increases in proteinuria and hypertension should raise suspicion of preeclampsia and justifies closer surveillance for other maternal systemic features or fetal effects of placental dysfunction. Where available, use of the sFlt-1/PlGF ratio can be used to 'rule out' placental dysfunction related increase in hypertension and proteinuria in these women (Recommendation 4.2).

Chronic hypertension

Chronic hypertension is defined by a blood pressure greater than or equal to 140 mmHg systolic and/or 90mmHg diastolic confirmed before pregnancy or before 20 completed weeks gestation. Chronic hypertension can be due to either essential (idiopathic) hypertension or a secondary cause of hypertension (e.g: primary hyperaldosteronism, pheochromocytoma, obstructive sleep apnoea, renal artery stenosis, Cushing's syndrome). Women may also be diagnosed with chronic hypertension retrospectively, e.g. where women with hypertension in pregnancy remain hypertensive 3 months following birth of her newborn.

White coat hypertension

White coat hypertension refers to raised blood pressure (≥ 140/90mmHg) in the presence of a clinical attendant (clinical blood pressure) with normal blood pressure readings when assessed in a non-clinical setting (ambulatory or home blood pressure monitoring). White coat hypertension in early pregnancy is reported to progress to persistent hypertension after 20 weeks' (gestational hypertension) and 8% to preeclampsia (10).

Masked hypertension

Masked hypertension refers to normal blood pressure readings in a clinical setting with raised blood pressure when measured in a non-clinical setting (ambulatory or home blood pressure monitoring). Outcomes in patients presenting after 20 weeks' appear to equate with gestational hypertension patients (11, 12).

Severe (or acute) hypertension

Severe (or acute) hypertension refers to elevation in blood pressure where the systolic blood pressure is greater than or equal to 160mmHg and or the diastolic blood pressure is greater than or equal to 110mmHg. It should be confirmed on repeated measures. This level of blood pressure has been associated with a greater risk of maternal and fetal adverse outcomes (13).

Investigation and assessment of women with new onset hypertension in pregnancy

Woman presenting with new onset hypertension should be assessed for signs and symptoms of preeclampsia. The assessment should ideally be aimed at identifying the type of HDP present as well as assessing for fetal wellbeing. An initial assessment and management plan that involves either day assessment unit reviews, home blood pressure monitoring or in-patient admission may be determined based on the severity of the clinical features identified. Any concerns regarding fetal well-being or the presence of maternal severe hypertension (≥160/110mmHg), headache, neurological irritability, epigastric pain, chest pain, dyspnoea, or nausea and vomiting should lead to urgent admission and management as these are associated with adverse maternal and obstetric outcomes (14-16).

The following investigations should be performed as part of the initial assessment of new onset hypertension:

- Full blood count (FBC) - Investigations for disseminated intravascular coagulation (DIC) and/or haemolysis (coagulation studies, blood film, lactate dehydrogenase and fibrinogen) should be considered for significant thrombocytopenia or a rapid decline in haemoglobin concentration.
- Electrolytes, urea and creatinine (EUC)

- Liver function tests (LFT)
- Urinary spot protein: creatinine ratio (uPCR) –a dipstick assessment for proteinuria is clinically useful, readily available and easy to perform as an initial screening tool. Where there is clinical suspicion for preeclampsia, a quantitative urine analysis (uPCR) should be performed (Refer to Part 4.1: Urine assessment for proteinuria for more details)
- Angiogenic markers e.g. sFlt-1/PlGF ratio (only after 20 weeks gestation and if locally available in a timely manner) (Refer to Part 4.2: Use of sFlt-1/PlGF ratio for more information)
- Fetal assessment: Ultrasound assessment for fetal growth, amniotic fluid index (AFI) or deepest vertical pocket (DVP)) and umbilical artery Doppler (UAD)(17). Cardiotocography (CTG) assessment may be indicated according to hospital policy and gestation.

Serum uric acid, historically, is tested as part of the initial assessment in women with new onset hypertension in pregnancy. Although it has been associated with adverse maternal and fetal outcomes, the data remains conflicting. Furthermore, maternal serum uric acid concentration has not been shown to be an independent a predictor of adverse maternal or perinatal outcomes (18). Therefore, serum uric acid concentration is not included as part of the recommended initial investigations.

Women with early onset preeclampsia (< 34 weeks gestation) may warrant further investigation for possible underlying associated conditions e.g. systemic lupus erythaematosus, renal disease or antiphospholipid syndrome. The timing of these investigations should be determined by the clinical and biochemical features identified.

Where indicated, transfer of care and timing of transfer should be determined based on gestational age, clinical severity and locally available clinical resources.

Although a very rare disorder, undiagnosed phaeochromocytoma in pregnancy is potentially fatal and may present as preeclampsia. In the presence of very labile or poorly controlled severe hypertension, measurement of plasma free metanephrines/normetanephrines, and 24-hour urinary catecholamines assessment should be considered (19).

Ongoing investigation and assessment of women with a diagnosed hypertensive disorders of pregnancy

Subsequent investigations and management should be based on the ongoing clinical, biochemical and fetal assessment. A systematic assessment of maternal blood pressure (or home readings), symptoms, compliance with medications, clinical examination, laboratory investigations and fetal wellbeing should be undertaken (Table 1.1). Concerning fetal features or the presence of severe maternal hypertension (≥160/110mmHg), headache, neurological irritability, epigastric pain, chest pain, dyspnoea, or nausea and vomiting should lead to urgent admission and in-patient management.

	Diagnostic Category of Hypertensive Disorder of Pregnancy			
Assessment	White Coat HT	Chronic HT	Gestational HT	Preeclampsia
Frequency of maternal review and clinical assessment+	**At least 4 weekly** or more frequent based on clinical indication	**At least 4 weekly** or more frequent based on clinical indication	**At least weekly** or more frequent based on clinical indication	**At least twice weekly** or more frequent based on clinical indication
Proteinuria assessment*	Every time	Every time	Every time	At each assessment **ONLY** if not present at diagnosis~
Biochemistry assessment #	Where there is an abrupt increase in anti-hypertensive requirements or other signs or symptoms of preeclampsia	Where there is an abrupt increase in anti-hypertensive requirements or any other signs or symptoms of preeclampsia	Where there is an abrupt increase in anti-hypertensive requirements or any other signs or symptoms of preeclampsia	At each assessment No evidence to support repeated measurement of angiogenic markers ^
Fetal Ultrasound Assessment	As indicated by clinical assessment	Fetal growth assessment at least monthly	Fetal growth assessment at least monthly	Fetal growth assessment fortnightly AFI/DVP, UAD at least every two weeks Ductus venous Doppler where fetal growth restriction present

Table 1.1: Ongoing assessment of women with HDP. + Where blood pressure is well controlled. * Spot uPCR or initial dipstick urinary assessment with subsequent confirmatory proteinuria quantification. ~Repeated urine assessment is not indicated if clinically significant proteinuria is present at diagnosis (uPCR>30mg/mmol), # Biochemistry assessment includes; FBC,EUC, LFT, sFLT-1/PlGF ratio (where available). ^ Where the diagnosis of preeclampsia is made on clinical grounds, there is no current evidence to support angiogenic marker testing unless there is clinical suspicion of another diagnosis e.g. new presentation of renal disease with hypertension and proteinuria, SLE.

PART 2: Screening for Women at Risk of Preeclampsia

Recommendations

2.1 The use of maternal risk factors (maternal characteristics, medical and obstetric history) to screen all pregnancies for risk of preeclampsia is strongly recommended (Table 2.1). (1A)

2.2 The use of a combined first trimester screen (combined maternal features, biomarkers and sonography) to identify women at risk of developing preeclampsia is conditionally recommended (2B) based on local availability and access to the required resources.

Factors identified as 'High Risk' for developing preeclampsia	
1 or more risk factors	Previous hypertensive disorder during prior pregnancy
	Chronic kidney disease or kidney impairment
	Multi-fetal gestation
	Pre-existing chronic hypertension
	Pre-existing Type 1 or Type 2 diabetes mellitus
	Autoimmune disorders e.g. systemic lupus erythematosus, anti-phospholipid syndrome
Factors identified as 'Moderate Risk' for developing preeclampsia	
2 or more risk factors	Advanced maternal age (>40)
	Obesity (BMI≥35)
	Nulliparity
	Family history of preeclampsia
	Interpregnancy interval of 10 or more years
	Assisted reproduction technologies
	Systolic blood pressure >130mmHg and/or diastolic blood pressure >80

Table 2.1. Clinical factors identified as high or moderate risk in identifying women at risk of developing preeclampsia.

Description of intervention

Given the ability to reduce a woman's risk of preeclampsia (refer to Chapter 3), there has been a growing need to identify women who are at risk of developing preeclampsia and will benefit from preventative measures. Previously, certain clinical factors were identified as a means of identifying women who may develop preeclampsia (20). However, more recently, the NICE and ACOG guidelines, have grouped together clinical risk factors that help identify women at risk of developing preeclampsia **(https://www.nice.org.uk/guidance/qs35/chapter/quality-statement-2-antenatal-assessment-of-pre-eclampsia-risk).**

Multiple risk factors have been identified in the literature, however, these risks vary significantly due to the heterogeneity of the studies and the populations assessed. Table 2.1 summarizes clinical risk factors that help identify women at risk of developing preeclampsia. Where one or more 'high-risk' factors are present or two or more 'moderate-risk 'factors are present in early pregnancy, consideration should be given to ways in which women's risk of preeclampsia can be minimised (Refer to Part 3 for more information).

More recently, combining maternal clinical risk factors with sonographic and serum-based biomarkers have been shown to improve accuracy in identifying women at risk of developing preeclampsia. However, the factors used to predict and identify these women necessitates additional resources and specialised expertise. Many of the non-clinical factors, such as biochemical markers and sonographic expertise to undertake validated and reliable uterine pulsatility index (UtA-PI), may not be available widely. Given this variation in practice, the factors that are available to predict preeclampsia have been presented individually and in various combinations to facilitate clinicians' judgement of the preferred screening tool based on the resources available to them.

We have limited the analysis and discussion below to the prediction of preeclampsia between 11+0-14+1 weeks gestation.

Summary of evidence and rationale for recommendation

A total of 11 studies were examined for this analysis. A combined sample size of 206,232 women were examined for the development of early onset preeclampsia (EOPE) and 265,664 for the development of late onset preeclampsia (LOPE). The studies differ in the definition of EOPE; 2 studies used a cut-off of 32 weeks (21, 22), 5 studies used a cut-off of 34 weeks (23-27) and 1 study used a cut-off of 37 weeks of gestation (28). Given this heterogeneity, we utilised a cut-off of <37 weeks for this analysis.

Maternal clinical risk factor characteristics were assessed as defined by the ACOG or NICE guidelines but mainly by the Fetal Medicine Foundation (FMF) criteria which includes maternal characteristics (age, weight, height, racial origin, smoking, maternal family history and contraception method), medical history (pre-existing chronic hypertension, pre-existing Type 1 or 2 diabetes, systemic lupus erythematosus or antiphospholipid antibody syndrome) and obstetric history (nulliparity, inter-pregnancy interval or previous preeclampsia)(29). Most studies employed standardised protocols to measure the mean arterial pressure (MAP) and UtA-PI and followed the Fetal Medicine Foundation methodology. The serum markers (PAPP-A and PlGF) were measured predominantly by a DELFIA or BRAHMS KRYPTOR analyzer.

The analysis demonstrated that most methods of screening had a high negative prediction value for both preterm preeclampsia (defined as <37 weeks in this analysis) and all preeclampsia (Figures 2.1 and 2.2). Clinical history and maternal characteristics alone (ACOG, NICE and FMF) had differing sensitivities specificities as indicated (Figures 2.1 and 2.2). The addition of UtA-PI and various combinations of serum markers did not adversely affect the reliability, however, it was not possible to compare the different tests. It appears that the addition of ultrasound and biochemical markers modestly improved the performance of the test compared to clinical factors alone (maternal factors and MAP), although the sensitivities vary from 42-92%. The overall quality of evidence was found to be MODERATE.

It is important to appreciate that screening assessments reported in the published literature is undertaken by clinicians that are experts in undertaking the assessment. Additionally, the published studies were difficult to meta-analyse due to heterogeneity in reporting. Ideally, future studies could be reported in a manner that adheres to the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) reporting guidelines (30) and present relevant data on incremental value of the risk prediction.

Based on the analysis conducted, we strongly recommend screening all pregnant women for their risk of developing preeclampsia. The screening tool utilised should be determined based on the locally available resources. We conditionally recommend the use of combined first trimester screening for preeclampsia based on local access to the validated resources and expertise required. It is also important that centres that offer the combined first trimester testing undertake a number of quality assessments to ensure the validity of the measurements and hence assessments.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI
Maternal						
Akolekar 2013	246	5832	322	52484	0.43 (0.39-0.47)	0.90 (0.90-0.90)
Poon 2009	17	833	20	7496	0.46 (0.31-0.62)	0.90 (0.89-0.91)
Sorek 2018	15	104	10	939	0.60 (0 41-0.77)	0 90 (0.88-0.92)
Tan 2018	238	6968	255	53713	0.48 (0.44-0.52)	0.89 (0.89-0.89)
Park 2013	5	300	7	2702	0.42 (0.20-0.68)	0.90 (0.89-0.91)
Maternal + MAP						
Park 2013	7	300	5	2702	0.58 (0.32-0.80)	0.90 (0.89-0.91)
Poon 2009	28	9	833	7496	0.76 (0.60-0.87)	0.90 (0.89-0.91)
Tan 2018	275	7067	218	53614	0.56 (0.52-0.60)	0.88 (0.88-0.88)
Maternal+ UtPI						
Park 2013	9	300	3	2702	0.75 (0.47-0.91)	0.90 (0.89-0.91)
Ian 2018	312	7144	181	53537	0.63 (0.59-0 67)	0.88 (0.88-0.88)
Maternal+ PIGF						
Tan 2018	321	6589	172	54092	0.65 (0.61-0.69)	0.89 (0.89-0.89)
Maternal+ PAPP-A						
Park 2013	6	300	6	2702	0.50 (0.25-0.75)	0.90 (0.89-0.91)
Tan 2018	262	7050	231	53631	0.53 (0.49-0.57)	0.88 (0.88-0.88)
Maternal+ MAP+ UtPI						
Park 2013	11	300	1	2702	0.92 (0.65-0.99)	0.90 (0.89-091)
Poon 2009	33	833	4	7496	0.89 (0.75-0.96)	0.90 (0.89-0.91)
Tan 2018	348	6792	145	53889	0.71 (0.67-0.75)	0.89 (0.89-0 89)
Maternal + MAP+ PIGF						
Tan 2018	338	6266	155	54415	0.69 (0.65-0.73)	0.90 (0.90-0.90)
Maternal + MAP + PAPP-A						
Park 2013	5	300	7	2702	0.42 (0.20-0.68)	0.90 (0.89-0.91)
Tan 2018	289	7014	204	53667	0.59 (0.55-0.63)	0.88 (0.88-0.88)
Maternal + MAP + UtPI + PIGF						
Chaemsaithong 2019	47	1086	26	9776	0.64 (0.53-0.74)	0.90 (0.89-0.91)
Tan 2018	372	6086	121	54595	0.75 (0.71-0.79)	0.90 (0.90-0.90)
Maternal + MAP + UtPI + PAPP-A						
Park 2013	11	300	1	2702	0.92 (0.65-0.99)	0.90 (0.69-0.91)
Parthasarathy 2022	12	34	0	160	1.00 (0.76-1.00)	0.82 (0.76-0.87)
Tan 2018	353	6712	140	53969	0.72 (0.68-0.76)	0.89 (0.89-0.89)
Maternal + MAP+ PIGF + PAPP-A						
Tan 2018	337	6262	156	54419	0.68 (0.64-0.72)	0.90 (0.90-0.90)
Maternal + MAP + UtPI + PIGF + PAPP-A						
Akolekar 2013	435	5572	133	52744	0.77 (0.73-0.80)	0.90 (0.90-0.90)
Skraslad 2014	4	54	1	482	0.80 (0.38-0.96)	0.90 (0.87-0.92)
Tan 2018	375	6093	118	54583	0.76 (0.72-0.80)	0.90 (0.90-0.90)
Zwertbroek 2021	7	84	3	268	0.70 (0.40-0.89)	0.76 (0.71-0.80)
ACOG						
Chaemsaithong 2019	40	2172	33	8690	0.55 (0.44-0.66)	0.80 (0.79-0.81)
O'Gorman 2017	53	3138	6	5578	0.90 (0.80-0.95)	0.64 (0.63-0.65)
NICE						
Chaemsaithong 2019	19	593	54	10269	0.26 (0.17-0.37)	0.95 (0.95-0.95)
O'Gorman 2017	23	872	36	7844	0.39 (0.28-0.52)	0.90 (0.89-0.91)
Tan 2018 a	58	1669	84	14936	0.41 (0.33-0.49)	0.90 (0.90-0.90)

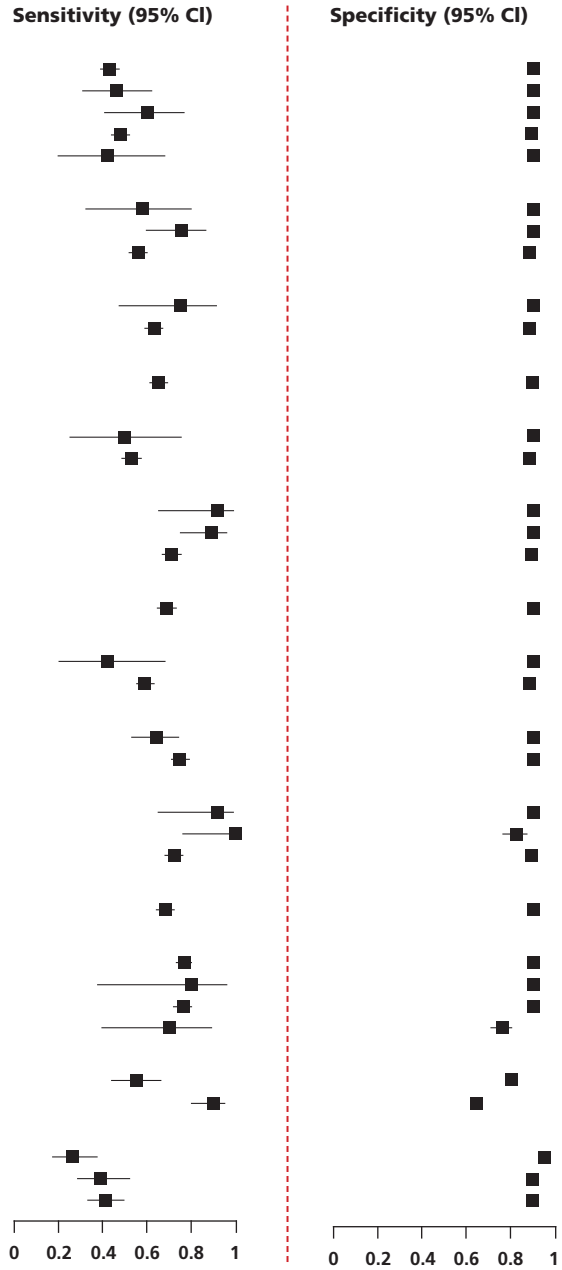


Figure 2.1. Combined first trimester screening sensitivity and specificity in identifying women at risk of early onset preeclampsia (Delivery less than 37 weeks gestation). *Maternal= maternal characteristics as per the FMF.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI
Maternal						
Akolekar 2013	574	5746	852	51712	0.40 (0.37-0.43)	0.90 (0.90-0.90)
Park 2013	20	281	63	2650	0.24 (0.16-0.34)	0.90 (0.89-0.91)
Poon 2009	70	820	95	7381	0.42 (0.35-0.50)	0.90 (0.89-0.91)
Sonek 2018	24	102	22	920	0.52 (0.38-0.66)	0.90 (0.88-0.92)
Tan 2018	708	6498	1062	52906	0.40 (0.38-0.42)	0.89 (0.89-0.89)
Maternal+ MAP						
Park 2013	29	293	54	2638	0.35 (0.26-0.46)	0.90 (0.89-0.91)
Poon 2009	95	820	70	7381	0.58 (0.50-0.65)	0.90 (0.89-0.91)
Tan 2018	822	6520	948	52884	0.46 (0.44-0.48)	0.89 (0.89-0.89)
Maternal+ UtPI						
Park 201	25	281	58	2650	0.30 (0.21-0.41)	0.90 (0.89-0.91)
Tan 2018	814	6642	956	52762	0.46 (0.44-0.48	0.89 (0.89-0.89)
Maternal+ PIGF						
Tan 2018	801	610	969	53295	0.45 (0.43-0.47)	0.90 (0.90-0.90)
Maternal+ PAPP-A						
Park 2013	24	281	59	2650	0.29 (0.20-0.40)	0.90 (0.89-0.91)
Tan 2018	755	6557	1015	52847	0.43 (0.41-0.45)	0.89 (0.89-0.89)
Maternal+ MAP + UtPI						
Park 2013	36	281	47	2650	0.43 (0.33-0.54)	0.90 (0.89-0.91)
Poon 2009	106	820	59	7381	0.64 (0.56-0.71)	0.90 (0.89-0.91)
Tan 2018	918	6222	852	53182	0.52 (0.50-0.54)	0.90 (0.90-0.90)
Maternal+ MAP + PIGF						
Tan 2018	858	5746	912	53658	0.48 (0.46-0.50)	0.90 (0.90-0.90)
Maternal+ MAP + PAPP-A						
Park 2013	29	281	54	2650	0.35 (0.26-0.46)	0.90 (0.89-0.91)
Tan 2018	846	6457	924	52947	0.48 (0.46-0.50)	0.89 (0.89-0.89)
Maternal+ MAP + UtPI + PIGF						
Chaemsaithong 2019	111	1071	113	9640	0.50 (0.44-0.56)	0.90 (0.89-0.91)
Maternal+ MAP + UtPI + PAPP-A						
Tan 2018	923	6142	847	53262	0.52 (0.50-0.54)	0.90 (0.90-0.90)
Maternal+ MAP + PIGF + PAPP-A						
Tan 2018	861	5738	909	53666	0.49 (0.47-0.51)	0.90 (0.90-0.90)
Maternal+ MAP + UtPI + PIGF + PAPP-A						
Akolekar 2013	764	5746	662	51712	0.54 (0.51-0.57)	0.90 (0.90-0.90)
Skrastad 2014	8	52	12	469	0.40 (0.22-0.61)	0.90 (0.87-0.92)
Tan 2018	917	5556	853	53848	0.52 (0.50-0.54)	0.91 (0.91-0.91)
Zwertbroek 2021	15	105	7	235	0.68 (0.47-0.84)	0.69 (0.64-0.74)
AGOG						
Chaemsaithong 2019	99	2160	125	8551	0.44 (0.38-0.51)	0.80 (0.79-0.81)
O'Gorman 2017	213	5480	26	3056	0.89 (0.84-0.92)	0.36 (0.35-0.37)
NICE						
Chaemsaithong 2019	46	567	178	10144	0.21 (0.16-0.27)	0.95 (0.95-0.95)
O'Gorman 2017	84	871	155	7665	0.35 (0.29-0.41	0.90 (0.89-0.91)
Tan 2018 a	144	1583	329	14691	0.30 (0.26-0.34)	0.90 (0.90-0.90)

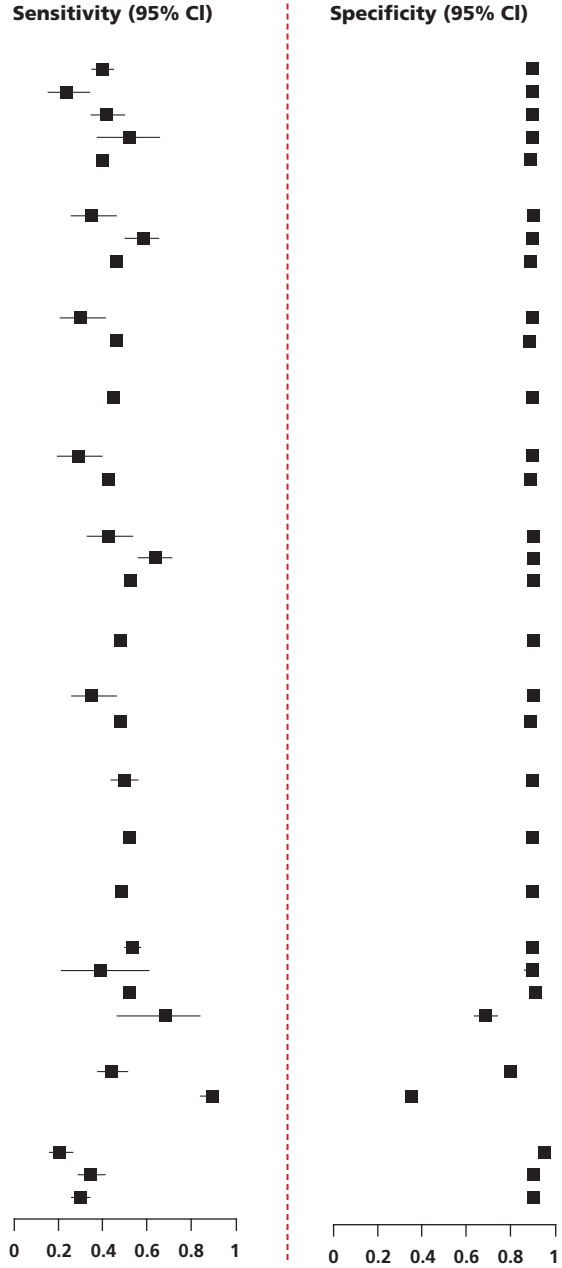


Figure 2.2 Combined first trimester screening sensitivity and specificity in identifying all women at risk of preeclampsia at any gestation.
*Maternal = maternal characteristics as per the FMF.

Cost analysis and accessibility

At the time of this review, combined first trimester screening for preeclampsia is not widely available across Australia and New Zealand but is accessible through some public and private health facilities. It, however, is not currently subsidised by Medicare in Australia. Many of the cost analysis in the literature are difficult to compare due to variations in methods of assessment and assumptions made. However, cost is an important consideration in application of the screening tool and is briefly addressed below.

There have been several cost analyses undertaken both in Australia and internationally. Park *et al* (31) undertook a cost effectiveness analysis of the combined first trimester screening for preeclampsia in comparison to usual care in Australia and demonstrated a reduction in cases of preterm preeclampsia (31 cases) and reduced aggregate economic health service costs (approx. AUD$1.4million). In this study, however, the additional factors for preeclampsia screening were added to an already available universal aneuploidy screening and hence, the marginal cost of the preeclampsia screening was minimal. Similarly, data from Canada demonstrated a theoretical reduction in the number of cases of preeclampsia resulting in a cost saving of C$14.30million, assuming 387,516 births/year (32).

Work from Germany and Switzerland assessed the incremental health care costs and costs per case of preeclampsia averted (33). Mewes *et al* demonstrated that combined first trimester screening for preeclampsia compared to routine care in Switzerland resulted in a cost saving, however in Germany there would be additional health care costs of approximately €14 per woman (33). An analysis comparing the NICE screening criteria to a retrospectively applied FMF algorithm demonstrated that the use of combined first trimester screening for preeclampsia could have resulted in a reduction in 7 preeclampsia cases with a cost saving of £9.06/ pregnancy screened (34). Shmeuli *et al* demonstrated that screening cost effectiveness depends on a number of factors including the population prevalence, although this work included placental protein 13 as an additional serum biomarker (35).

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	Women at a minimum should be screened using clinical information. If testing available women should be screened with a combination of clinical ultrasound and biochemical factors even if they have been identified as high risk.
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	No recommendation made
SOMANZ 2015	No recommendation made

Research opportunities

More data on the following aspects of combined first trimester screening for preeclampsia will be beneficial:

- The role of combined first trimester screening in populations excluded from current studies e.g. women with chronic renal disease
- More data on cost effectiveness of first trimester screening in Australia and New Zealand as this will potentially allow for Medicare Subsidy of this screening tool hence making it more accessible across Australia and New Zealand

PART 3A: Preventative Strategies
(Pharmacological)

3A.1 : Aspirin

Recommendations

3A.1.1 Initiation of aspirin in women at high risk of developing preeclampsia, prior to 16 weeks of gestation, is strongly recommended. (1B)

3A.1.2 The dose of 150mg/day of aspirin is strongly recommended. (1B)

3A.1.3 The use of bedtime aspirin is conditionally recommended. (2C)

3A.1.4 Cessation of aspirin between 34 weeks of gestation and delivery is conditionally recommended. Exact timing of cessation should be based on individualized clinical judgment and informed, shared decision making with the patient. (2B)

3A.1.5 Universal aspirin in low-risk nulliparous women is conditionally recommended against. Informed, shared decision making with patient is recommended where appropriate risk stratification is not possible. (2B)

3A.1.6 Counselling on the use of aspirin in pregnancy is recommended to improve adherence to aspirin in pregnancy (Patient Information Sheet 3A.1). (PP)

Description of intervention

Aspirin was first observed to have a prophylactic role in preventing preeclampsia in 1985, when Beaufils et al used a combination of aspirin (150mg) and dipyridamole (300mg) in the first trimester and demonstrated a reduction in the rate of preeclampsia in the treatment group (36). However, subsequent studies on prophylactic aspirin were contradictory, with equivocal or absence of benefit in preventing preeclampsia, IUGR and preterm delivery (37-39). These studies, however, were confounded by varying doses of aspirin, inconsistent definitions of women who are at high risk of developing preeclampsia and significant heterogeneity in the gestation of aspirin initiation. In the 2000s, aspirin re-emerged as a promising prophylactic agent with studies demonstrating risk reduction of up to 70% when commenced prior to 16 weeks of gestation (40-42). The observed data variation, however, has raised questions on the optimal aspirin dose, gestation of initiation and timing of ingestion (chronotherapy)(36, 43-46).

In more recent times, some studies have argued for the universal use of aspirin in low-risk nulliparous women based on the cost-benefit analysis (47, 48). This, however, is not widely practiced at present.

How the intervention might work

Aspirin is a non-selective, irreversible cyclooxygenase-1 (COX-1) inhibitor. Early studies on the mechanism of aspirin's action in preeclampsia demonstrated an aspirin-induced decrease of TXA2 concentration and mediation of the unbalanced TXA/PGI2 ratio (49, 50). Studies that examined the correlation between TXA2/PGI2 levels and maternal uterine artery pulsatile indexes (PI) demonstrated that aspirin reduced platelet aggregation and inhibited vasoconstriction when an enhanced uterine blood flow was noted (51).

In 1989, Claria et al described an anti-inflammatory role of aspirin through the generation of endogenous 15-epi-Lipoxin A4, better known as aspirin-triggered lipoxins (ATL) (52). In reproductive medicine, ATL has been demonstrated to reverse the inflammatory process observed in preeclampsia and in women at risk of preeclampsia by upregulating IL-10 and nitric oxide (NO) whilst downregulating the generation of TNF -α (53-55). Therefore, aspirin is thought to have both anti-platelet and anti-inflammatory effects on placental development in minimizing the risk of preeclampsia in women who are at high risk.

Summary of evidence, risk of harm and quality of evidence

A total of 38 RCTs with a combined sample size of ~23,000 women in each arm were examined for this analysis (37-39, 41, 45, 49, 50, 56-80).

3A.1.1 Gestation of initiation of aspirin

When commenced prior to 16 weeks of gestation, aspirin was observed to reduce the risk of the following outcomes with no difference in the risk of harm in comparison to placebo (Table 3A.1.1(a):

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	**0.67**	**0.56–0.68**	**MODERATE**
Early onset preeclampsia	**0.29**	**0.12-0.68**	**MODERATE**
Preterm delivery	**0.51**	**0.38-0.68**	**MODERATE**
Small for gestation	**0.52**	**0.37-0.72**	**MODERATE**
Placental abruption	0.87	0.59-1.27	HIGH
Antenatal vaginal spotting or bleeding	1.19	0.76-1.88	HIGH
Antepartum haemorrhage necessitating hospitalisation	0.57	0.17-1.90	HIGH
Post-partum haemorrhage	1.00	0.94-1.07	HIGH
Neonatal intracerebral haemorrhage	2.33	0.34-15.78	MODERATE

Table 3A.1.1(a): Comparison of outcomes based on gestation of initiation of aspirin (<16 weeks)

However, when commenced at or after 16 weeks of gestation, while a small benefit with a lower rate of preterm delivery (risk reduction of 0.73 (CI 0.55-0.98) (evidence with high level of certainty) was observed, there was no benefit with the following outcomes (Table 3A.1.1(b)) :

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.82	0.65–1.03	MODERATE
Early onset preeclampsia	0.82	0.44-1.51	MODERATE
Small for gestation	0.83	0.58-1.18	HIGH

Table 3A.1.1(b): Comparison of outcomes based on gestation of initiation of aspirin (≥ 16 weeks)

3A.1.2 Dose of aspirin

Based on the outcome of the analysis in 3A.1.1, only studies where aspirin was commenced prior to 16 weeks of gestation was used for this analysis. A comparison between aspirin doses <100mg, 100mg and 150mg demonstrated a difference in the rate of preeclampsia, early-onset preeclampsia and preterm delivery, favouring the use of 150mg of aspirin with no difference in the risk of harm (Table 3A.1.2) :

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	**0.72**	**0.54-0.97**	**MODERATE**
Early onset preeclampsia	**0.21**	**0.06-0.71**	**MODERATE**
Preterm delivery	**0.44**	**0.31-0.64**	**HIGH**
Fetal loss (prior to 24 weeks of gestation)	0.64	0.27-1.48	LOW
Placental abruption	0.89	0.49-1.62	LOW
Antenatal vaginal bleeding or spotting	1.02	0.85-1.23	LOW
Antepartum haemorrhage necessitating hospitalisation	0.88	0.71-1.10	HIGH
Postpartum haemorrhage	0.97	0.81-1.17	LOW
Neonatal intracerebral haemorrhage	0.84	0.58-1.21	LOW

Table 3A.1.2: Comparison of outcomes based on dose of aspirin

3A.1.3 Timing of ingestion of aspirin (chronotherapy)

Based on the outcome of the analysis in 3A.1.1, only studies where aspirin was commenced prior to 16 weeks of gestation was used for this analysis. A comparison of the chronotherapy effect of aspirin demonstrated a risk reduction in the following outcomes favouring the use of bedtime aspirin (Table 3A.1.3) :

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Early onset preeclampsia	**0.29**	**0.12-0.68**	**LOW**
Preterm delivery	**0.48**	**0.29-0.77**	**MODERATE**
Small for gestation	**0.43**	**0.26-0.72**	**LOW**

Table 3A.1.3: Comparison of outcomes based on timing of ingestion of aspirin

The use of bedtime aspirin was also incidentally found to be associated with a lower rate of postpartum haemorrhage (0.51 (CI 0.28-0.90)) (evidence with moderate level of certainty), however, the clinical significance of this is unclear.

3A.1.4 Gestation of cessation of aspirin

A comparison between cessation of aspirin at or before 36^{+6} of gestation and at or after 37 weeks of gestation did not demonstrate a difference in the following outcomes (Table 3A.1.4):

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.85	0.67–1.08	LOW
Gestational hypertension	0.89	0.35-2.28	VERY LOW
Preterm delivery	0.73	0.46-1.16	VERY
Small for gestation	0.66	0.42-1.04	LOW
Placental abruption	1.00	0.66-1.52	HIGH
Antepartum haemorrhage	0.98	0.73-1.34	HIGH
Postpartum haemorrhage	1.11	0.99-1.23	HIGH
Neonatal cerebral haemorrhage	0.81	0.99-1.23	MODERATE

Table 3A.1.4: Comparison of outcomes based on gestation of cessation of aspirin

A lower rate of early-onset preeclampsia was observed in the group where aspirin was ceased either at or prior to 36^{+6} weeks of gestation (0.21 (CI 0.06-0.71)) group was observed. However, this is likely related to the cessation of aspirin prior to 36^{+6} weeks gestation in women with early-onset preeclampsia and less likely related to an actual risk reduction.

3A.1.5 Universal aspirin use in low-risk nulliparous women

The use of universal aspirin in low-risk nulliparous women was associated with a small reduction in the rate of preterm delivery when commenced prior to 16 weeks of gestation (risk reduction of 0.88 (CI 0.80-0.97))(evidence with moderate level of certainty), however, it was associated with a moderate increase in the risk of postpartum haemorrhage, 1.32 (CI 1.12-1.54)(evidence with high level of certainty) .

There was no benefit with the use of universal aspirin in low-risk nulliparous women in the following outcomes, irrelevant of the gestation of initiation of aspirin (Table 3A.1.5):

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia (irrelevant of gestation of initiation)	0.88	0.62–1.24	LOW
Preeclampsia (aspirin commenced <16 weeks of gestation)	1.17	0.43-3.15	VERY LOW
Preterm delivery	**0.88**	**0.80-0.97**	**MODERATE**
Small for gestation (irrelevant of gestation of initiation)	0.96	0.91-1.01	MODERATE
Small for gestation (aspirin commenced <16 weeks of gestation	0.96	0.90-1.02	MODERATE
Stillbirth (irrelevant of gestation of initiation)	0.87	0.70-1.07	MODERATE
Stillbirth (aspirin commenced <16 weeks of gestation)	0.85	0.68-1.06	MODERATE
Post-partum haemorrhage	**1.32**	**1.12-1.54**	**HIGH**

Table 3A.1.5: Comparison of outcomes with universal aspirin use in nulliparous women

These studies did not examine the difference between early and late onset preeclampsia.

Rationale for recommendation

3A.1.1 Initiation of aspirin < 16 weeks of gestation

The evidence suggests that the overall moderate benefit of aspirin in reducing the risk of preeclampsia, early-onset preeclampsia, preterm delivery and small for gestational age newborns favours initiation of aspirin prior to 16 weeks of gestation in improving the desired risk reduction. Therefore, based on the evidence of benefit, trivial risk of harm, accessibility of aspirin and implementability, initiation of aspirin <16 weeks of gestation is strongly recommended in women at high risk of developing preeclampsia.

3A.1.2 Dose of 150mg a day

The evidence suggests that the overall large benefit of aspirin in reducing the risk of preeclampsia, early-onset preeclampsia and preterm delivery favours the use of 150mg of aspirin in improving the desired risk reduction. The use of 150mg was not associated with an increased risk of maternal or neonatal harm. Therefore, based on the evidence of benefit, trivial risk of harm and ability to achieve the desired dose, a preferred dose of 150mg of aspirin is strongly recommended.

3A.1.3 Bedtime ingestion of aspirin

The evidence suggests that the overall large benefit of aspirin in reducing the risk of early-onset preeclampsia, preterm delivery and small for gestational age newborns favours the use of bedtime of aspirin in improving the desired risk reduction. However, the quality of data is low with a limited sample size. Therefore, bedtime ingestion of aspirin is conditionally recommended.

3A.1.4 Cessation of aspirin between 34 weeks of gestation to delivery

The overall evidence did not demonstrate a difference in the benefit or harm in comparing the timing of aspirin cessation. Therefore, based on the absence of a difference in harm, the decision on the timing of ceasing aspirin between 34 weeks of gestation and delivery should be individualized based on the women's clinical history, risk of bleeding and through an informed, shared decision-making process with the women.

3A.1.5 Universal aspirin use in nulliparous low-risk women

The overall evidence demonstrates a small benefit in the reduction in rate of preterm term with a moderate increase in the rate of postpartum haemorrhage. The use of universal aspirin in low-risk nulliparous women was not associated with a risk reduction in the rate of preeclampsia. Therefore, on the balance of the risk and benefit, the use of universal aspirin in nulliparous low-risk women is not recommended. Where appropriate risk stratification is not feasible, the decision on the use of aspirin in low-risk nulliparous women should be made through an informed, shared-decision making process with the women

Recommendation in other guidelines

Guideline	Specifics	Recommendation
ISSHP 2022	Gestation of initiation of aspirin	Preferably before 16 weeks of gestation
	Dose of aspirin	100-162mg
	Timing of ingestion	Bedtime
	Gestation of cessation	By 36 weeks of gestation
	Universal aspirin use	No recommendation made
Australian Pregnancy Care Guidelines 2019	Gestation of initiation of aspirin	Early pregnancy (not specified)
	Dose of aspirin	Low dose (not specified)
	Timing of ingestion	No recommendation made
	Gestation of cessation	No recommendation made
	Universal aspirin use	No recommendation made
NICE 2019	Gestation of initiation of aspirin	From 12 weeks of gestation
	Dose of aspirin	75-150mg
	Timing of ingestion	No recommendation made
	Gestation of cessation	No recommendation made
	Universal aspirin use	No recommendation made
SOMANZ 2015	Gestation of initiation of aspirin	Before 20 weeks of gestation
	Dose of aspirin	50-150mg
	Timing of ingestion	No recommendation made
	Gestation of cessation	By 37 weeks of gestation
	Universal aspirin use	No recommendation made

Research priorities

More research and data on the following aspects on the use of aspirin in pregnancy remains unclear and warrants further studies:

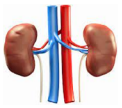
- More information on the use of pre-conception aspirin and very early initiation of aspirin (prior to 8 weeks of gestation) is required in understanding the optimal time to initiate aspirin, <16 weeks of gestation
- Randomized control studies that directly compare the benefit and risk of complications between 100mg and 150mg of aspirin will be beneficial in strengthening the understanding the optimal dose of aspirin for high-risk pregnant women
- Randomized control studies that examine the timing of cessation of aspirin will be beneficial in better guiding clinicians and health care providers in determining the optimal time of aspirin cessation
- More information on the adherence, acceptability, and risk of harm of universal aspirin use in low-risk nulliparous women is required prior to confident recommendation for its use. More information on the local cost-effectiveness and acceptability to low-risk women and health care provided is also required prior to implementation of this practice in Australia and New Zealand

ASPIRIN IN PREGNANCY

Preeclampsia is a common pregnancy related condition that can be dangerous to the mother's and baby's wellbeing.
You may be at risk of preeclampsia if you have any of the following risk factors :


High blood pressure

Diabetes


Kidney Disease


Autoimmune disorder


Previous preeclampsia

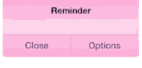

High risk on first trimester screening

However, your risk of preeclampsia can be reduced by 60-70% with the optimal use of aspirin


Start aspirin **before 16 weeks** of pregnancy

Take **150mg** daily (Either ½ of 300mg or 1 & ½ of non-coated 100mg aspirin)


Take aspirin everyday at **bedtime** until your doctor advices you to stop aspirin



Don't forget to take aspirin as it doesn't work if you miss even 10% of doses. **Use a reminder** to help you

Treatment with aspirin should not replace your antenatal care with your health care provider. Please discuss any concerns you may have with your health care provider.

SOMANZ

CLICK HERE FOR A PDF COPY

Patient information sheet 3A.1 : Use of aspirin in pregnancy

3A.2 : Oral Calcium supplementation

Recommendations

3A.2.1 The use of supplemental calcium is strongly recommended in pregnant women with low dietary calcium intake (<1g/day) for the prevention of preeclampsia, preterm delivery, and gestational hypertension. (1C)

3A.2.2 Assess dietary calcium intake prior to recommending oral calcium supplementation (Flowchart 3A.1). (PP)

3A.2.3 Consider assessing serum corrected calcium prior to commencement of calcium oral supplementation (to ensure the absence of underlying hypercalcaemia). (PP)

Description of intervention

The use of calcium supplement, either in the form of calcium carbonate, citrate, lactate or gluconate in the prevention of preeclampsia has been studied over the years (81).

The World Health Organization (WHO) conducted a randomised control trial (RCT) of calcium supplementation among low calcium intake pregnant women from 2001 to 2003 (82). Results from this trial showed that although 1.5 g calcium/day supplement did not prevent preeclampsia, it reduced its severity, maternal morbidity, and neonatal mortality (82).

In more recent times, a systematic review (Cochrane 2018) found that high-dose calcium supplementation (> 1 g/day) reduces the risk of preeclampsia and preterm birth, particularly for women with low calcium diet with no difference in overall maternal and fetal mortality, and morbidity (81).

How the intervention might work

The exact mechanism by which calcium prevents preeclampsia remains largely unknown.

It is hypothesized that low calcium intake potentially stimulates either parathyroid hormone or renin release, which consequently, results in elevated blood pressure through an increase in vascular smooth muscle intracellular calcium and vasoconstriction (83-86). It is also hypothesized that, through the proposed mechanism, supplementary calcium intake affects uteroplacental blood flow by lowering the resistance index in uterine and umbilical arteries (87).

Summary of evidence

A total of 17 RCTs, that were examined for this analysis (82, 84, 88-102). The use of high-dose calcium (>1g/day) was found to reduce the risk of preeclampsia (RR 0.40, CI 0.24-0.67), gestational hypertension (RR 0.53, CI 0.36-0.79) and preterm , in women with low dietary calcium intake (<1g/day) (Table 3A.2.1):

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	**0.40**	**0.24-0.67**	**LOW**
Gestational hypertension	**0.53**	**0.36-0.79**	**LOW**
Preterm birth	**0.85**	**0.73-0.99**	**HIGH**
Maternal mortality	0.17	0.02-1.39	VERY LOW
Eclampsia	0.67	0.37-1.22	LOW
Placental abruption	0.89	0.50-1.56	LOW
Stillbirth	0.92	0.73-1.18	MODERATE
Small for gestational age	0.98	0.87-1.11	MODERATE

Table 3A.2.1 : Comparison of outcome between calcium and placebo in women with low dietary calcium intake (<1g/day)

There was no evidence to suggest benefit with the use of high-dose supplemental calcium in women with adequate dietary calcium intake (≥ 1g/day)(Table 3A.2.2):

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.62	0.32-1.20	LOW
Gestational hypertension	0.88	0.77-1.00	HIGH
Preterm birth	0.59	0.26-1.34	LOW
Eclampsia	1.00	0.25-3.99	LOW
Placental abruption	0.81	0.39-1.68	LOW
Stillbirth	0.80	0.42-1.54	MODERATE
Small for gestational age	0.87	0.60-1.28	MODERATE

Table 3A.2.2 : Comparison of outcome between calcium and placebo in women with adequate dietary calcium intake (≥1g/day)

Only 1 RCT that compared the use of high-dose supplementary calcium (>1g/day) to low-dose supplementary calcium (≤1g/day) was identified (80). The analysis of this single study demonstrated a preeclampsia risk reduction of 0.42 (CI 0.18-0.96), favouring low-dose calcium (≤1g/day), however the study was identified to have evidence of very low level of certainty.

Rationale for recommendation

The evidence suggests a benefit in the risk reduction of preeclampsia, gestational hypertension and preterm delivery with the use of high-dose supplemental calcium intake in women with low dietary calcium intake (<1g/day). The risk of harm with increased risk of HELLP syndrome and bone mineralisation remains largely unclear and requires further studies.

Given the need to determine women's dietary calcium intake in assessing the need for oral calcium supplementation, we propose the use of a dietary calcium calculator in ascertaining women's daily dietary calcium intake (Link below or Flowchart 3A.2):

Guide to daily dietary calcium intake assessment

Instructions: Enter the number of servings per day in the green column of the relevant foods to calculate the calcium intake of nominated foods

- Data suggests approx. 250mg calcium is consumed daily from generally dietary intake
- Recommended daily intake for women of childbearing age is 1,000mg
- Average daily calcium intake in women of childbearing age in Australia 666.4mg/day
- https://www.abs.gov.au/statistics/health/health-conditions-and-risks/australian-health-survey-nutrition-supplements/latest-release

		Calcium Calculator		
Food	**Serving Size**	**Calcium (mg) per serving/day**	**Servings/day (n)**	**Food Total**
Milk	200ml	240		0
Soy Milk	200ml	26		0
Soy Milk (enriched)	200ml	240		0
Almond Milk	200ml	90		0
Natural Yoghurt	150g	207		0
Hard Cheese (e.g. Cheddar)	30g (1 slice)	240		0
Feta Cheese	60g	270		0
Tofu	120g	126		0
Almonds	30g	75		0
Sardines (canned, oil)	60g	240		0
			Total Calcium Intake (mg)	0

Calcium content taken from Healthy Bones Australia

CLICK HERE FOR A PDF COPY **3A.2 : Flow chart Guide to daily dietary calcium intake assessment**

CLICK HERE FOR CALCIUM CALUCULATOR

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	For women with dietary intake of calcium (<900 mg/day), oral calcium supplementation of at least 500 mg/d is recommended
Australian Pregnancy care guidelines 2019	Advise women at high risk of developing pre-eclampsia that calcium supplementation is beneficial if dietary intake is low
NICE 2019	Use of calcium not discussed
SOMANZ 2015	Calcium supplementation (1.5g/day) should be offered to women with moderate to high risk of preeclampsia, particularly those with low dietary calcium intake

Research opportunities

More research and data on the following aspects on the use of calcium in pregnancy remains unclear and warrants further studies:

- More studies with specific data on the maternal and fetal effects of supplemental calcium in pregnancy and lactation is required to provide reassurance that on the antenatal use of supplemental calcium.
- More data on the use of low-dose supplementary calcium (<1day) compared to high-dose supplementary calcium (>1g/day) is required as the current data does not allow for confident evidence-based comparison.
- The appropriate gestation to initiate and cease calcium supplementation remains unclear and warrants further studies.

3A.3 Omega-3 long-chain polyunsaturated fatty acids (LCPUFA) supplementation

Recommendations

3A.3 The use of oral omega-3 LCPUFA supplementation for the prevention of preeclampsia, is recommended against until more data is available. (2B)

Description of intervention

Increased intake of omega-3 long-chain polyunsaturated fatty acids (LCPUFA) (e.g., docosahexaenoic acid (DHA); eicosapentaenoic acid (EPA)) in pregnancy and lactation, is thought to influence fetal growth and development, reduce childhood allergies, decrease maternal depression and anxiety and in more recent times, thought to reduce the risk of preeclampsia (103-106).

Major dietary sources of omega-3 LCPUFA are fish and seafood, therefore, the concentration of dietary omega-3 LCPUFA consumption vary worldwide, depending on local dietary customs. Given this, there has been a recent increase in the practice of oral omega-3 supplementation in pregnancy.

How the intervention might work

Dietary omega-3 LCPUFA is converted to its biologically active derivatives EPA and DHA. These fatty acids are precursors to a range of compounds that are known to minimise and help resolve inflammatory responses and oxidative stress (107). Pregnancy outcomes with an inflammatory component, such as preterm birth and preeclampsia, are thought to be reduced by increasing omega-3 LCPUFA concentrations, either through maternal diet or omega-3 supplementation (108). Omega-3 fatty acids, particularly DHA, is thought to reduce placental oxidative stress by increasing the levels of resolvins and protectins (109). Additionally, women with elevated circulating sFlt-1 were found to have lower serum DHA concentration (110). However, clinical studies to date have not demonstrated a significant association between omega-3 LCPUFA supplementation and a reduction in the risk of preeclampsia (108).

Summary of evidence, risk of harm and quality of evidence

A total of 7 RCTs with a combined sample size of ~2,100 women in each arm were examined (111-114). The prescription of oral omega-3 supplementation had a varied concentration of DHA (616mg - 1,080mg) and EPA (120mg - 3,000mg) across 5 studies. The concentration of DHA and EPA were not specified in 2 studies. Studies that examined the use of dietary omega-3 or oral omega-3 with vitamin C,E and/or D co-supplementation were excluded. None of the studies examined baseline maternal serum DHA and EPA concentration.

There was no difference in the following outcomes of interest (Table 3A.3.1)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.91	0.68-1.22	MODERATE
Early preterm delivery (<34 weeks)	0.71	0.50-1.01	MODERATE
Preterm delivery	0.93	0.80-1.08	MODERATE
Gestational hypertension	1.12	0.91-1.38	MODERATE
Small for gestation	0.97	0.73-1.29	LOW
Stillbirth	0.94	0.52-1.70	LOW
Antenatal vaginal spotting or bleeding	1.01	0.69-1.58	MODERATE

Table 3A.3.1 : Comparison of outcomes with the use of oral omega-3 and placebo

There was, however, a difference in the rate of patient-reported adverse maternal outcomes RR 1.87 (CI 1.50 - 2.38) (moderate), particularly with the reported rate of unpleasant taste of oral omega-3 capsule RR 5.99 (CI 2.72-13.21) (moderate) and rate of belching or burping RR3.57 (CI 2.55-5.01)(moderate) with the use of omega-3 capsules.

Rationale for recommendation

There remains lack of certainty on the efficacy and optimal dose of oral omega-3 supplementation in the prevention of preeclampsia. Based on which, we suggest a conditional recommendation against the use of omega-3 for prevention of preeclampsia until more data on its efficacy and safety is available. This recommendation is not applicable to the general use of omega-3 replacement in pregnancy to minimize the risk of childhood asthma and allergies or reduce the risk of preterm birth.

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Do not recommend the use of fish oil for prevention of hypertensive disorders of pregnancy
SOMANZ 2015	No recommendation made

Research opportunities

More data on the follow aspects of the use of omega-3 LCPUFA is required:

- Efficacy of oral omega-3 supplementation in preventing preeclampsia in women with low dietary DHA and EPA intake
- A comparison of efficacy and cost between oral omega-3 supplementation and high dietary omega-3 intake in preventing preeclampsia

3A.4 Oral garlic supplementation

Recommendations

3A.4 The use of oral garlic supplementation, specifically for the prevention of preeclampsia, is recommended against until more data is available. (2D)

Description of intervention

Garlic (*Allium sativum*) is part of the Allium family and has been widely used in many cultures for both medicinal and culinary purposes. Garlic›s main active ingredient is allicin, a strong-smelling sulphide.

Meta-analyses of studies involving non-pregnant participants have demonstrated a reduction in systolic and diastolic blood pressure along with a reduction in serum triglycerides with the use of oral supplemental garlic for more than 8 weeks (115-117). However, a more recent meta-analysis contradicted the effect of oral supplemental garlic on blood pressure (118).

Given the potential effect of oral supplemental garlic on blood pressure, its influence in high-risk pregnant women has been of interest, however, data on its clinical benefit remains sparse.

How the intervention might work

In vitro and animal studies have proposed an anti-inflammatory and antiplatelet effect of garlic on blood pressure regulation, however, the pharmacokinetic and pharmacodynamic studies in humans, especially in pregnant women remains significantly sparse (119-122).

Summary of evidence, risk of harm and quality of evidence

A total of 2 RCTs with a combined sample size of 103 women in each arm were examined for this analysis. Both studies prescribed a garlic capsule (800mg/day) for 8 weeks in the third trimester in women who were at risk of preeclampsia (123, 124).

There was no difference in the rate of preeclampsia, gestational hypertension and difference in both systolic and diastolic blood pressure with the use of oral garlic supplementation. Women in the oral garlic supplementation group were noted to have reported a higher rate of intolerance of odour of oral garlic supplementation (Table 3A.4.1)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.78	0.31-1.93	VERY LOW
Gestational hypertension	0.50	0.25-1.00	VERY LOW
Maternal side effect : intolerant of odour	**8.50**	**2.07-34.88**	**VERY LOW**
Maternal side effect :Nausea	4.00	0.89-17.91	VERY LOW

Table 3A.4.1 : Comparison of outcomes between garlic and placebo

Neither study reported on fetal outcomes and gestation of delivery.

Rationale for recommendation

There is currently inadequate data to support the use of oral supplemental garlic in the prevention of preeclampsia. More data on the bioavailability, risk of harm, side effects and clinical efficacy in high-risk pregnant women is required.

Recommendations in other guidelines

Guideline	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Do not recommend the use of garlic for prevention of hypertensive disorders of pregnancy
SOMANZ 2015	No recommendation made

Research priorities

More research and data on the following aspects on the use of oral garlic supplementation in pregnancy remains unclear and warrants further studies:

- Bioavailability of oral garlic supplementation, especially in the capsule formulary
- Clinically efficacy of oral garlic supplementation in reducing the risk of preeclampsia and preterm delivery in high-risk pregnant women
- Risk of harm to fetus with the antenatal use of oral garlic supplementation

3A.5 Antioxidants (Vitamin C and E)

Recommendation

3A.5 The use of oral Vitamin C and E supplementation, specifically for the prevention of preeclampsia, is recommended against until more data is available. (2B)

Description of intervention

Antioxidants refers to substances that delays or inhibits oxidation of a substrate when present in low concentrations compared to that of an oxidisable substrate (125). Antioxidants protect proteins and enzymes from oxidation and destruction by free radicals and help to maintain cellular membrane integrity. Antioxidants can be categorised as either free radical scavengers or cellular and extracellular enzymes that inhibit peroxidase reactions involved in the production of free radicals (125).

The Heart Protection Study which examined the use of antioxidants vitamins C, E and beta-carotene in 20,536 non-pregnant adults for five years demonstrated improved blood pressure and metabolic profile without an increase in the risk of side-effects or harm (126, 127). However, a systematic review of vitamin E supplementation in a combined sample size of 135,967 men and non-pregnant women demonstrated an increase in all-cause mortality in individuals supplemented with 400 or more IU vitamin E per day for at least one year (128).

Oxidative stress, with an imbalance in the reactive oxygen species (ROS), has been proposed to play a role in the pathophysiology of placental dysfunction and preeclampsia (129, 130). Given this, there remains an ongoing interest on the use of antioxidants as a prophylactic strategy in high-risk women, however, data on its efficacy and importantly, safety in pregnancy, remains largely unclear. For the purpose of this review, only the commonly studied Vitamin C (1g/day) and Vitamin E (400 IU/day) were examined. Antioxidants such as selenium, curcumin and lycopene were not examined due to the limited human data.

How the intervention might work

Vitamin C functions as a first-line antioxidant by scavenging ROS and nitrogen species (131, 132). Plasma ascorbate reserves decrease gradually throughout normal pregnancy but in women with preeclampsia, the reserves are thought to further decrease by 20% - 50% compared to normal pregnancy (133, 134). A study which examined the effect of oral Vitamin C (1g/day) and E (400 IU/day) supplements in high-risk pregnant women demonstrated a reduction in markers of endothelial dysfunction (plasminogen activator inhibitor ratio, PAI-I/PAI-2) and a decrease in the incidence of preeclampsia along with an improvement in markers suggestive of oxidative stress (135, 136), therefore, proposing an antioxidative role in reducing the risk of endothelial and placental dysfunction.

Plasma vitamin E concentrations is thought to increase during normal gestation due to the increase in circulating lipoproteins, the transporters of vitamin E (133). Plasma vitamin E concentrations are either unchanged or increased in women with preeclampsia, however, a proposed synergistic effect of Vitamin C and E is though to enhance the antioxidative property of Vitamin C and E in combination (133, 134, 137).

Summary of evidence, risk of harm and quality of evidence

A total of 11 RCTs with a combined sample size of ~8,800 participants in each arm were examined in this analysis (136, 138-147). Only studies that examined the use of Vitamin C (1g/day) and Vitamin E (400 IU/day) were included in this analysis.

There were no statistically significant differences in the rate of preeclampsia, eclampsia, small for gestational weight newborns, maternal and perinatal mortality or stillbirths between the use of Vitamin C and E and placebo (Table 3A.5.1).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.97	0.86-1.08	MODERATE
Eclampsia	1.74	0.71-4.28	MODERATE
Small for gestational age	0.93	0.81-1.07	MODERATE
Perinatal mortality	0.98	0.74-1.31	HIGH
Stillbirth	0.98	0.68-1.43	HIGH
Maternal death	0.62	0.14-2.74	MODERATE
Gestational hypertension	1.14	0.99-1.32	HIGH
Neonatal ICU admission	0.99	0.90-1.08	HIGH
Maternal bleeding (including placental abruption, antepartum and postpartum haemorrhage)	0.94	0.74-1.20	HIGH
Neonatal intraventricular haemorrhage	0.72	0.39-1.31	MODERATE
Preterm birth	1.00	0.91-1.09	MODERATE

Table 3A.5.1: Comparison of outcomes between the use of antioxidants (Vitamin C and E) vs placebo

Rationale for recommendation

Based on the absence of difference in benefit and given the lack of data on side effect profile, the use of antioxidants for the purpose of prevention of preeclampsia is currently recommended against. More data on the maternal and fetal side effect and safety profile is required to make a safe recommendation on its use.

Recommendation by other guidelines

Guidelines	Recommendation
ISSHP 2022	Use of Vitamin C and E are not recommended
Australian Pregnancy Care Guidelines 2019	Advise women that vitamins C and E are not of benefit in preventing pre-eclampsia.
NICE 2019	Do not recommend the use of Vitamin C and E solely for the purpose of preventing hypertensive disorders of pregnancy
SOMANZ 2015	Prophylactic antioxidant therapy with vitamins C and E is not recommended

Research priorities

More research and data on the following aspects on the use of oral antioxidants (Vitamin C and E) supplementation in pregnancy remains unclear and warrants further studies:

- More data on the pharmacokinetics, pharmacodynamics and optimal dose of oral supplemental Vitamin C and E in pregnancy is required
- More data on the maternal side effect profile (gastrointestinal symptoms, renal calculi) will be beneficial in understanding the risk of harm of supplemental oral Vitamin C and E in pregnancy, especially in higher doses.

3A.6 : Oral Magnesium

Recommendation

3A.6 There is inadequate data to recommend for the use or against the use of oral magnesium supplementation specifically for the prevention of preeclampsia. More data on the safety profile is required. (2C)

Description of intervention

Magnesium is an essential mineral that plays an important role in modulating vasomotor tone and cardiac excitability.

A physiology study demonstrated a reduction in both ionised and total plasma serum magnesium concentration after 18 weeks of gestation (148). An early retrospective study, reported an observed association between oral magnesium supplementation during pregnancy and a reduction in the risk of fetal growth retardation and preeclampsia (149). A subsequent cross-sectional study of increased dietary magnesium intake demonstrated that higher dietary magnesium intake was associated with increased birthweight (150). However, subsequent RCTs have demonstrated variable outcomes with significant heterogeneity in the study population, use of co-supplementation with Vitamin D, C or aspirin and variation in the type of oral magnesium replacement.

How the intervention might work

In a study on magnesium responsive genes, pregnant women were observed to have a higher expression of TRPM6 – a gene that upregulates renal and intestinal uptake of magnesium towards the end of the first and third trimesters, proposing a state of increased demand of magnesium in pregnancy. A pilot study with a small sample size proposed that oral magnesium replacement in the second trimester was associated with lower systolic and diastolic blood pressure along with lower expression of TRPM6 (151).

However, there remains a lack in data to demonstrate a pharmacotherapeutic effect of oral magnesium replacement in addressing the proposed altered magnesium homeostasis in pregnancy. Therefore, the mechanism of action of oral magnesium replacement in prevention of preeclampsia remains largely unknown.

Summary of evidence, risk of harm and quality of evidence

A total of 6 RCTs with a combined sample size of ~1,200 participants in each arm were examined in this analysis (152-157). The studies examined one of four types of oral magnesium supplements: magnesium oxide 500mg/day (D'Almeida *et al*), Magnesium aspartate 365mg/day (Sibai *et al*, Spatling *et al*) Magnesium gluconate 4g/day (Martin *et al*), Magnesium citrate 300mg/day (Araujo *et al*, Bullarbo *et al*). A sub-analysis for difference between the various preparation of oral magnesium replacement was also conducted. Studies where magnesium was co-supplemented with either aspirin, calcium or an additional mineral supplement were excluded to minimize heterogeneity.

There were no statistically significant difference in the rate of preeclampsia, eclampsia, small for gestational weight newborns, maternal and perinatal mortality or stillbirths between the use of oral magnesium replacement (all preparations) and placebo (Table 3A.6.1).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.99	0.71-1.37	MODERATE
Eclampsia	0.14	0.01-2.70	VERY LOW
Small for gestational age	0.90	0.60-1.35	MODERATE
Stillbirth	0.35	0.01-8.46	LOW
Maternal death	3.11	0.13-76.13	VERY LOW
Gestational hypertension	1.49	0.82-2.72	MODERATE
Neonatal ICU admission	0.88	0.51-1.52	LOW
Preterm birth	1.00	0.74-1.35	LOW
Fetal loss	1.44	0.46-4.54	LOW

Table 3A.6.1: Comparison of outcomes between oral magnesium (all preparations) and placebo

Where comparison between the preparations of magnesium was feasible, no statistically significant difference in the outcome between preparation of magnesium was identified (Table 3A.6.2)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia			
Magnesium aspartate	0.94	0.61-1.43	MODERATE
Magnesium oxide	0.40	0.08-1.97	VERY LOW
Magnesium citrate	1.18	0.69-2.02	MODERATE
Neonatal ICU admission			
Magnesium aspartate	0.76	0.41-1.40	LOW
Magnesium citrate	1.38	0.59-3.25	MODERATE
Preterm birth			
Magnesium aspartate	0.72	0.36-1.43	LOW
Magnesium citrate	1.04	0.68-1.59	MODERATE
Magnesium gluconate	1.21	0.80-1.83	LOW

Table 3A.6.2: Subanalysis of various preparations of oral magnesium supplement

Incidentally, a lower rate of antepartum haemorrhage with a risk reduction of 0.38 (CI 0.16-0.90) (based on evidence with very low certainty) and placental abruption with a risk reduction of 0.44 (CI 0.21-0.96) (based on evidence of high level of certainty) were observed. The significance and pathophysiology of this findings is unclear.

Rationale for recommendation

While a lower rate of antepartum and placental abruption was noted, a confident recommendation for routine oral magnesium supplementation for the prevention of preeclampsia can't be made based on the lack of adequate data to safety, side effect profile and lack of benefit in the key outcomes of interest.

Recommendations by other guidelines

Guideline	Recommendation
ISSHP 2022	Insufficient information at this stage to recommend for or against
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Do not recommend the use of oral magnesium solely for the purpose of preventing hypertensive disorders of pregnancy
SOMANZ 2015	No recommendation made

Research priorities

More research and data on the following aspects on the use of oral magnesium supplementation in pregnancy remains unclear and warrants further studies:

- More data on the pharmacokinetics, pharmacodynamics and optimal dose and preparation of oral magnesium supplementation is required
- More data on the side effect profile and risk of harm (to mother and fetus) is required
- More data on the relationship between oral magnesium supplementation in women with adequate dietary magnesium intake and women with a deficiency in their dietary magnesium intake will be beneficial

3A.7: Progesterone

Recommendation

3A.7 The use of progesterone replacement, specifically for the prevention of preeclampsia, is recommended against until more data is available. (2B)

Description of intervention

Progesterone is a hormone which plays an essential role in reproduction, both in the regulation of the menstrual cycle, and in the maintenance of pregnancy.

A number of progesterone derivatives are now commercially available. Vaginal progesterone is often used for the prevention of preterm birth in women with shortened cervix and intramuscular progesterone, in the form of 17 alpha-hydroxyprogesterone caproate, is often used to prevent preterm delivery in women with a history of spontaneous preterm delivery (RANZCOG 2010).

Some studies have proposed an additional benefit in minimizing the risk of preeclampsia, however, the use of progesterone specifically for reducing the risk of preeclampsia is not widely practiced at the time of publication.

How the intervention might work

During pregnancy, progesterone stimulates the growth and differentiation of endometrium to allow implantation, immunological tolerance of the fetus, and inhibits uterine contractions (158, 159). Progesterone has also been observed to influence vascular adaptations of normal pregnancy by decreasing endothelial vasoconstrictors and inducing vasodilatation in addition to a possible immunomodulatory role (158-163).

Robson et al proposed that maternal progesterone insufficiency played a role in the pathophysiology of preeclampsia in 1937(164). Subsequently, the hypothesis that progesterone reduced the risk of preeclampsia was tested by Dalton et al in the 1950s and 1960s (165-167).

More recently, progesterone has been shown to increase the expression of HLA-G protein in placental cytotrophoblast cells, which supports the hypothesis that progesterone may reduce the risk of preeclampsia (168, 169).

Summary of evidence, risk of harm and quality of evidence

A total of 3 RCTs with a combined sample size of ~ 650 participants in each arm were examined for this analysis (170-172). All 3 RCTs enrolled women who were at risk of per-term delivery where two studies enrolled primigravids with twin gestation and one study examined women who were actively working in the air force. There was heterogeneity in the prescription of progesterone in all three studies. Hauth et al utilized 17 alpha-hydroxyprogesterone caproate 1,000 mg IM weekly from 16-20 weeks of gestation to 36 weeks gestation and Rouse et al utilized 17 alpha-hydroxyprogesterone caproate 250 mg IM injections weekly from 16-20 weeks of gestation. However, in the STOPPIT study, vaginal progesterone gel was used at 90 mg daily from 24 weeks for 10 weeks.

There was no statistically significant difference in the outcomes examined (Table 3A.7.1).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	1.31	0.99-1.71	MODERATE
Small for gestational age	0.82	0.19-3.57	VERY LOW
Gestational hypertension	0.92	0.42-2.01	VERY LOW
Neonatal ICU admission	1.06	0.88-1.25	HIGH
Preterm birth < 37 weeks	1.01	0.93-1.09	HIGH
Preterm birth < 34 weeks	1.28	0.91-1.79	HIGH
Preterm birth < 32 weeks	1.16	0.82-1.66	HIGH
Preterm birth < 28 weeks	1.32	0.75-2.32	MODERATE
Congenital malformation (patent ductus arteriosus)	0.60	0.34-1.05	HIGH
Any major congenital malformation *	1.06	0.34-3.31	LOW
Any maternal side effects #	1.02	0.91-1.15	HIGH

Table 3A.7.1: Comparison of outcomes between progesterone replacement and placebo

Rationale for recommendation

Data on the efficacy and safety of progesterone replacement, specifically for the prevention of prevention of preeclampsia, remains sparse. This analysis consists of three studies with significant heterogeneity in the prescription of progesterone replacement and a study population of women who were at risk of preterm delivery (two studies with primigravids with twin pregnancy and one study with women who were actively in the air force).

Recommendation by other guidelines

Guideline	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Do not recommend the use of progesterone solely for the purpose of preventing hypertensive disorders of pregnancy
SOMANZ 2015	No recommendation made

Research priorities

More research and data on the following aspects on the use of progesterone replacement, specifically for the prevention of preeclampsia, remains unclear and warrants further studies:

- Efficacy of progesterone replacement in preventing preeclampsia in women who at high risk of developing preeclampsia
- Optimal route of progesterone replacement specifically for the prevention of preeclampsia
- Maternal and fetal safety and side effect profile on progesterone replacement in women at risk of preeclampsia, especially the influence on maternal blood pressure

*** Breakdown of malformation not provided in the study | # Includes injection site reaction, urticaria, nausea, fatigue, dizziness, headaches**

3A.8 : Statins

Recommendation

3A.8 The use of statins, specifically for the prevention of preeclampsia, is recommended against until more data is available. (2B)

Description of intervention

Statins are HMG-CoA reductase inhibitors and have been traditionally used for lowering low-density lipoprotein (LDL)-cholesterol to reduce cardiovascular risk. In pregnancy, statin is hypothesized to improve endothelial function and reduce inflammatory cytokines by reducing C-reactive protein concentrations, inhibiting proinflammatory transcription factors, and blunting the T-helper cell immune response through its non-cholesterol pleiotropic effects (173, 174).

The only statin that has been studied in pregnancy is the hydrophilic statin, pravastatin, which is thought to have less transmission through the placenta and therefore, less potential to affect cholesterol biosynthesis and adversely affect the developing fetus (175). However more data is required to ensure the safety of pravastatin in pregnancy.

How the intervention might work

Many of the proposed vascular effects of statins appear to involve restoring or improving endothelial function through regulation of the angiogenic balance of sFlt-1 and PLGF, increasing the bioavailability of nitric oxide, reducing oxidative stress, and inhibiting inflammatory responses (176-181).

HUVEC studies along with placental and human studies on the effect of pravastatin in subjects with established preeclampsia have demonstrated a decrease in anti-angiogenic protein sFlt-1 and an increase of sEng which appeared to be directly mediated through HMG-CoA reductase inhibition (176, 177). Statins also appeared to significantly reduce the expression of adhesive molecules such as VCAM-1 and endothelin-1 (ET-1) on endothelial cells and therefore enhancing endothelial cells migration and invasion (176-178, 182, 183).

Given this, there have been interest on the effect of pravastatin in women with established preeclampsia and the effect of pravastatin as a prophylactic intervention in women at risk of preeclampsia. However, given the current paucity in human data, the use of statins is not clinically utilised for prevention or treatment of preeclampsia at the time of publication.

Summary of evidence, risk of harm and quality of evidence

A total of 4 RCTs with a combined sample size of ~1,200 women at high risk of preeclampsia in each arm (total of 2,400 women) were assessed in this analysis (180, 184). Studies that examined the effect of pravastatin in women with established preeclampsia, on human placental tissue and HUVEC studies were excluded for this analysis. All four studies consisted of significant heterogeneity in dose of pravastatin, gestation of initiation and control used (Table 3A.8.1) Given the significant heterogeneity in these studies, data from all 4 studies studies were examined individually.

Study	Sample size	Intervention	Control	Gestation of initiation
Constantine *et al* 2016	20	Pravastatin 10mg	Placebo	12-16 weeks until delivery
Dobert *et al* 2021	1,120	Pravastatin 20mg	Placebo	35-37 weeks until delivery
Constantine *et al* 2021	20	Pravastatin 20mg	Placebo	12-16 weeks until delivery
Akbar *et al* 2021	163	Pravastatin 20 mg + Aspirin 80mg + Calcium 1g	Aspirin 80mg + Calcium 1g	14-20 weeks until delivery

Table 3A.8.1: Characteristics of studies examined

In the first study, where pravastatin was prescribed in the first trimester at 10mg daily until delivery, there was no statistically significant difference in the following outcomes of interest (Table 3A.8.2)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.11	0.01-1.83	MODERATE
Gestational hypertension	1.00	0.07-13.87	VERY LOW
Preterm birth	0.20	0.03-1.42	MODERATE
Neonatal NICU admission	0.33	0.04-2.69	MODERATE
Fetal			
Polydactyly	3.00	0.14-65.90	VERY LOW
Ventriculomegaly	3.00	0.14-65.90	VERY LOW
Hypospadias	0.33	0.02-7.32	MODERATE
Coarctation of aorta	0.33	0.02-7.32	MODERATE
Maternal			
Muscle cramps or pain (normal creatinine kinase level)	0.25	0.03-1.86	MODERATE
Headache and/or dizziness	1.00	0.42-2.40	MODERATE
Nausea and/or vomiting	2.00	0.21-18.69	LOW

Table 3A.8.2 Outcomes from Constantine *et al* (2016)

Similarly, in the second study, where pravastatin was prescribed in the third trimester at 20mg daily until delivery, there was no statistically significant difference in the following outcomes of interest (Table 3A.8.3)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	1.07	0.80-1.44	HIGH
Gestational hypertension	1.10	0.85-1.43	HIGH
Neonatal NICU admission	0.62	0.28-1.35	MODERATE
Small for gestational age	1.01	0.80-1.26	HIGH
Placental abruption	0.49	0.04-5.38	MODERATE
Composite outcome of all neonatal morbidity*	0.53	0.23-1.24	HIGH
Fetal			
Cleft palate	2.97	0.12-72.81	VERY LOW
Ventricular septal defect	2.97	0.12-72.81	VERY LOW
Hypospadias	0.20	0.01-4.12	MODERATE
Talipes equinovarous Unilateral	0.33	0.01-8.09	LOW
Maternal			
Muscle cramps or pain (normal creatinine kinase level)	0.85	0.29-2.51	MODERATE
Headache and/or dizziness	1.15	0.78-1.68	HIGH
Nausea and/or vomiting	1.30	0.79-2.13	MODERATE
All other self-reported side effects#			

Table 3A.8.3 Outcomes from Dobert *et al*

The third RCT (Costantine *et al* 2021) examined the use of 20mg of Pravastatin from 12-16 weeks of gestation until delivery. The outcomes of this study are as summarized in Table 3A.8.4.

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.40	0.10-1.60	MODERATE
Neonatal NICU admission	0.67	0.27-1.66	MODERATE
Fetal			
Cleft palate	0.20	0.01-3.78	LOW
Maternal			
Muscle cramps or pain (normal creatinine kinase level)	3.00	0.14-65.90	VERY LOW
Headache and/or dizziness	1.67	0.54-5.17	LOW
Nausea and/or vomiting	0.33	0.02-7.32	VERY LOW

Table 3A.8.4 : Outcomes from *Costantine* et al (2021)

The fourth RCT (Akbar *et al*) examined the use of Pravastatin 20mg daily in conjunction with aspirin (80mg) and calcium (1,000mg). Interventions were commenced before 20 weeks of gestation. This study demonstrated a lower rate of preterm preeclampsia and SGA newborn with the use of pravastatin in addition to aspirin and calcium (Table 3A.8.5). There were, however, no difference in other outcomes examined. Maternal side effects were not examined in this study.

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.75	0.51-1.11	LOW
Preterm preeclampsia (<37 weeks)	0.52	0.27-0.97	LOW
Small for gestational age	0.56	0.17-1.86	LOW
Stillbirth	0.25	0.03-2.17	VERY LOW

Table 3A.8.5: Outcomes from Akbar *et al*

* Respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, sepsis

\# Abdominal and/or pelvic pain, dyspepsia and/or heartburn, nasal bleeding, skin rash, pruritus, diarrhoea, constipation, peripheral oedema, shortness of breath, visual disturbance, palpitations, paraesthesia, fatigue or weakness, sweating, dry mouth, sleep disturbance

Rationale for recommendation

There remains a significant lack of data on the safety and side effect profile of statins, specifically pravastatin in pregnancy. Given this and the lack of evidence to suggest benefit, the use of statins for the prevention of preeclampsia is recommended against until more data is available.

Recommendations made by other guidelines

Guideline	Recommendation
ISSHP 2022	There is insufficient information at this stage to recommend for or against
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	No recommendation made
SOMANZ 2015	No recommendation made

Research priorities

More research and data on the following aspects on the use of statins in pregnancy remains unclear and warrants further studies:

- More human data on the efficacy and safety is required, especially in establishing an appropriate dose and safety profile with the use of statin from first trimester to delivery. A large RCT with a target sample size of 1,150 high-risk women is currently underway (https://clinicaltrials.gov/ct2/show/NCT03944512

3A.9 : Low molecular weight heparin

Recommendation

3A.9.1 The use of low molecular weight heparin (LMWH) in addition to aspirin in women without a history of APLS or thrombophilia is conditionally recommended against. The decision to use LMWH (at prophylactic dose) in addition to aspirin should be individualised based on the woman's clinical and obstetric history and through shared- decision making. (2C)

3A.9.2 The use of low molecular weight heparin (LMWH) alone (without aspirin) in women without a history of thrombophilia or APLS is not recommended due to inadequate data at present. The decision to use LMWH in women with contraindications to aspirin may be considered but should be individualised based on the patient's clinical and obstetric history and through a shared, informed decision-making process. (2D)

Description of intervention

Unfractionated heparin (UFH) or low molecular weight heparin (LMWH) are anticoagulants that are often prescribed either for the prevention or treatment of thromboembolism in pregnancy. UFH is often administered through continuous intravenous infusions, whereas LMWH is administered by subcutaneous injections, hence, making LMWH the preferred choice of heparin for long term therapy. Heparins do not cross the placenta and are considered safe for the fetus (185, 186) however, from a maternal point of view, long term use of heparin can be associated heparin-induced thrombocytopenia, increased risk of bleeding and osteoporosis (187).

The use of LMWH in high-risk women was first observed in women with a history of antiphospholipid syndrome (APLS) or hereditary thrombophilia where maternal vascular thrombosis plays a strong role in the pathophysiology of placental dysfunction (188). The efficacy of LMWH in high-risk women without a history of APLS or hereditary thrombophilia, however, remains unclear with conflicting data.

How the intervention might work

In addition to its well-established anticoagulant effects, heparin is also thought to have anti-inflammatory activities that could potentially influence complement activation, modulate inflammatory placental biomarkers, inhibit placental apoptosis and stimulating placenta proliferation (189, 190). In a woman with APLS, heparin has been shown to prevent pregnancy complications by blocking the APL activation of the complement cascade (191). Additionally, LMWH has also been shown to improve circulating maternal levels of the pro-angiogenic protein, placental growth factor (PlGF) and relaxin (192). The mechanism of action in women without APLS, however, remains unclear.

Summary of evidence, risk of harm and quality of evidence

A total of 6 RCTs with a combined sample size of ~530 participants in each arm were examined for the use of LMWH in addition to aspirin (193-197) and a total of 2 RCTs with a combined sample size of ~70 participants in each arm were examined for the use of LMWH alone (without aspirin) in preventing preeclampsia (198, 199). Studies that examined the use of LMWH in women with antiphospholipid syndrome, thrombophilia and specifically for recurrent miscarriages were excluded from this analysis.

3A.9.1 Use of LMWH in addition to aspirin compared to aspirin alone for prevention of preeclampsia

Of the 6 RCTs examined, 5 RCTs examined the use of enoxaparin (40-60mg/day) (193-197) and 1 RCT (with a sample size of 55 women in each arm) examined the use of dalteparin (5,000 IU/day)(200).

There was no difference in most outcomes of interest with the use of LMWH in combination with aspirin against the use of aspirin alone, except for early onset preeclampsia, where the use of dalteparin was associated with a RR of 0.13 (CI 0.02 -0.97). However, this was based on a single RCT with a small sample size, a wide confidence interval and very low certainty of evidence (200).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.64	0.37-1.10	MODERATE
Early onset preeclampsia	**0.13**	**0.02-0.97**	**VERY LOW**
Gestational hypertension	0.67	0.32-1.38	LOW
Eclampsia	0.03	0.01-8.10	VERY LOW
Small for gestational age	0.78	0.57-1.06	LOW
Preterm birth	0.80	0.52-1.24	LOW
Stillbirth	0.45	0.16-1.29	LOW
Maternal intracerebral haemorrhage	0.31	0.01-7.55	VERY LOW
Maternal ICU admission	0.31	0.01-7.55	VERY LOW
Neonatal ICU admission	0.94	0.67-1.31	MODERATE
Maternal antepartum bleeding (placental abruption and antepartum haemorrhage)	1.39	0.79-2.44	LOW
Post-partum haemorrhage	0.99	0.69-1.42	MODERATE
Neonatal intraventricular haemorrhage	0.24	0.03-2.16	VERY LOW

Table 3A.9.1 : Outcomes with the use of LMWH in combination with aspirin vs aspirin alone

3A.9.2 Use of LMWH alone in comparison to placebo in preventing preeclampsia

Of the 2 RCTs examined, 1 RCT examined the use of enoxaparin (40mg/day) with a sample size of 30 participants in each arm and1 RCT examined the use of dalteparin (5,000 IU/day) with a sample size of ~40 participants in each arm.

A lower rate in the following outcomes was observed with the use of LMWH compared to placebo (Table 3A.9.2).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	**0.53**	**0.31-0.91**	**VERY LOW**
Early onset preeclampsia	**0.12**	**0.02-0.91**	**VERY LOW**
Small for gestational age	**0.47**	**0.28-0.79**	**VERY LOW**

Table 3A.9.2 : Outcomes with LMWH alone vs placebo

However, the findings above are based largely on a single study with a small sample size and very low certainty of evidence. There was no difference in the rate of placental abruption and stillbirth.

Rationale for recommendation

The use of LMWH alone compared to placebo demonstrated a large reduction in preeclampsia, early onset preeclampsia and small of gestational weight newborns in women with no history of thrombophilia. This, however, was based on 2 RCTs with a small sample size and with very low certainty of evidence. Additionally, the RCTs did not report on significant maternal and fetal adverse outcomes, particularly the risk of bleeding.

Given the presence of alternative effective preventative interventions (aspirin and calcium), we recommend using aspirin and calcium (where appropriate) as the prophylactic interventions of choice. The use of LMWH alone (without aspirin) in women without a history of thrombophilia or APLS can be considered if a contraindication to aspirin is present. The decision to use LMWH (at a prophylactic dose) should be individualised based on the patient's clinical and obstetric history and through a shared, informed decision-making process. LMWH should not replace the use of aspirin in women without contraindications to aspirin.

There is inadequate evidence to support the use of LMWH in addition to aspirin for the prevention of preeclampsia in women without a history of thrombophilia or APLS. Therefore, the use of LMWH in addition to aspirin for the prevention of preeclampsia in women without a history of thrombophilia or APLS is conditionally recommended against. The decision to use LMWH in addition to aspirin should be individualised based on the patient's clinical and obstetric history and through shared- decision making.

Recommendation by other guidelines

Guidelines	Recommendation
ISSHP 2022	Not recommended
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Recommended against the use of LMWH
SOMANZ 2015	Not recommended

3A.10 : Nitric Oxide

Recommendations

3A.10 The use of nitric oxide (either in donor or precursor forms) for the prevention of preeclampsia is recommended against until more data is available. (2D)

Description of intervention

Nitric oxide use can be either in the form of nitric oxide donors or nitric oxide prescursors. Nitric oxide donors, such as, glyceryl trinitrate (GTN), isosorbide mononitrate (ISMN), isosorbide dinitrate, S-nitroglutathione and sodium nitroprusside refers to agents that can be converted by the body into nitric oxide. These agents are often administered either orally, sublingually, skin patches, or intravenously. Common side-effects include headache, flushing, postural hypotension, and local irritation with patches. Nitric oxide donors are not commonly used in pregnancy, and therefore, has minimal data on potential maternal and fetal adverse effects.

L-arginine is an amino acid that is also known as a nitric oxide precursor. It can be administered orally, either as tablets or solutions, or intravenously. Known side-effects include diarrhoea. Similar to nitric oxide precursors, L-arginine is not commonly used in pregnancy and safety data remains sparse.

How the intervention might work

Nitric oxide promotes vasodilatation and reduces the effect of vasoconstrictors (201-205). Additionally, it also inhibits platelet aggregation and adhesion to vascular endothelial surfaces, modifies the expression of inflammatory cytokines, and inhibits interactions between immune and endothelial cells (206, 207).

In pregnancy, nitric oxide is thought to play a role in physiological vasodilatation, decreased responsiveness to vasopressors and increased uteroplacental blood flow (208). Some studies have demonstrated decreased nitric oxide concentration in the serum and urine of women with preeclampsia (209, 210), however, it remains unclear if this is due to increased degradation of nitric oxide or reduced production. Increased degradation of nitric oxide may result from the oxidative stress which occurs in preeclampsia (211, 212).

In animal studies, chronic inhibition of nitric oxide synthesis resulted in the development of hypertension, proteinuria, thrombocytopenia, reduced plasma volume and intrauterine growth restriction in pregnant rats (213). In humans, in vitro inhibition of nitric oxide synthesis in blood vessels resulted in vasoconstriction, but less so in blood vessels from women with preeclampsia, suggesting possible basal deficiency of nitric oxide in preeclampsia (214).

Some studies have demonstrated that administration of nitric oxide donors is associated with a reduction in uterine artery resistance in women with preeclampsia (215, 216). Although this observation has not been confirmed in all reports, it has led some to suggest that nitric oxide may have a role in prevention and treatment of preeclampsia. Others have highlighted concerns that such dilatation of the uterine vessels may not be appropriate in all cases of preeclampsia and may theoretically result in a relative underfill of the uterine circulation, further compromising blood supply to the placenta (217). Given the uncertainties, there remains a significant paucity in evidence for the use of nitric oxide, both in the donor and precursor form, for prevention and treatment of preeclampsia.

Summary of evidence, risk of harm and quality of evidence

A total of 5 RCTs with a total sample size of ~ 170 women in each arm were examined for this analysis (218-220). Studies that examined the use of nitric oxide for the treatment of established preeclampsia and studies which examined the use of nitric oxide with co-supplementation (with aspirin or micronutrients) were excluded.

There was significant heterogeneity in the type of nitric oxide (donor/precursor) and duration of nitric oxide therapy in all 5 studies:

- Abdel Razik *et al* 2016 utilized 20mg of isosorbid mononitrate tablet applied vaginally from 24 weeks of gestation until delivery
- Camarena Pulido *et al* 2016 utilized oral L-arginine (dose not specified) from 20 weeks of gestation until delivery
- Lees *et al* 2018 utilized 5mg topical GTN patch for 15 hours daily from 24-26 weeks of gestation until delivery
- Picciolo *et al* 2000 utilized 5mg topical GTN patch for 14-16 hours day from 16 weeks of gestation until 38 weeks of gestation
- Ponmozhi *et al* 2019 utilized 20mg of oral isosorbid mononitrate from 12-16 weeks of gestation until delivery

There was no difference in the following outcomes with the use of nitric oxide:

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.60	0.23-1.55	VERY LOW
Any hypertensive disorders of pregnancy (not specified)	1.17	0.60-2.27	MODERATE
Small for gestation	0.58	0.25-1.42	LOW
NICU admission	0.75	0.34-1.65	LOW
Stillbirth	0.50	0.05-5.34	VERY LOW
Headaches	1.90	0.36-9.97	VERY LOW
Skin rash	0.90	0.26-3.12	LOW
Gastrointestinal symptoms	1.81	0.90-3.66	LOW

Table3A.10.1 : Outcomes of nitric oxide vs placebo

There was an observed difference in the rate of preterm delivery RR 0.29 (CI 0.13-0.64) (MODERATE). However, this finding was largely driven by 1 study (with a sample size weight of 48.9% out of 4 studies) with a sample size of 20 women in each arm.

Rationale for recommendation

Most outcomes examined did not demonstrate a difference with the use of nitric oxide, except for the rate of preterm delivery which demonstrated a RR of 0.26. However, all 5 RCTs examined in this analysis had significant heterogeneity with the type and duration of nitric oxide. The difference in the rate of preterm delivery was largely driven by 1 study with a sample size of 20 women in each arm.

There remains a significant paucity in data to demonstrate a benefit with the use of nitric oxide. We therefore propose a recommendation against the use of nitric oxide for the prevention of preeclampsia until more data is available.

This recommendation is not applicable to cardiovascular indications for the use of nitric oxide donors (I.e. : GTN).

Recommendation made in other guidelines

Guidelines	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Do not use nitric oxide to prevent hypertensive disorders during pregnancy
SOMANZ 2015	No recommendation made

Research opportunities

More data on the following aspects of antenatal nitric oxide is required prior to further use of nitric oxide in pregnancy:

- Fetal safety
- Risk of significant hypotension and placental perfusion, particularly with the use of long-acting topical GTN patch

3A.11 Metformin

Recommendations

3A.13 The use of oral metformin, specifically for the prevention of preeclampsia is recommended against until more data is available. (2C)

Description of intervention

Metformin is a biguanide that prevents gluconeogenesis in the liver and increases the sensitivity of the peripheral tissue to insulin. Metformin is safe in pregnancy and currently is used to treat gestational diabetes mellitus.

Meta-analyses that compared the use of metformin against the use of insulin in managing gestational diabetes demonstrated the added effect of metformin with lower maternal weight gain and gestational hypertension (221-223). However, the efficacy of metformin in reducing the risk of preeclampsia in women at high risk of developing preeclampsia, especially in comparison to aspirin, has not been adequately examined.

How the intervention might work

Whilst the mechanism of action remains largely unclear, an in-vitro study demonstrated that metformin reduced the production of sFlt-1 and soluble endoglin in a dose-dependent manner by endothelial cells, villous trophoblast, and villous explants (224). The study also suggested that metformin regulates these antiangiogenic factors at the level of the mitochondria. Metformin was also found to decrease the expression of vascular cell adhesion molecule, which has been also thought to contribute towards the pathophysiology of preeclampsia. Based on which, there has a been a growing interest in understanding the potential role of metformin in preventing and treating preeclampsia.

Summary of evidence, risk of harm and quality of evidence

A total of 3 RCTs with a total sample size of ~ 420 women in each arm were examined in this analysis. All three studies examined the use of metformin (2,500 - 3,000mg daily) from 12-16 weeks of gestation until delivery in non-diabetic obese women (BMI of 30 or greater)(225-227). Studies that examined the use of metformin in women with established type 2 diabetes, gestational diabetes or women who were on metformin preconception for PCOS were excluded.

There was no difference with the following outcomes with the use of metformin:

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	0.45	0.13-1.61	VERY LOW
Gestational hypertension	1.24	0.76-1.21	MODERATE
Small for gestation	0.97	0.49-1.91	LOW
Preterm birth	0.94	0.56-1.56	LOW
Stillbirth	1.99	0.61-6.55	LOW
Fetal congenital defect	2.94	0.31-28.03	VERY LOW
Congenital hyperinsulinism	2.94	0.12-71.76	VERY LOW
Maternal acute fatty liver	2.94	0.12-71.76	VERY LOW
Maternal pancreatitis	2.94	0.12-71.76	VERY LOW
Cessation of metformin due to side effects	1.21	0.60-1.44	MODERATE

Table 3A.11.1 : Comparison of outcomes between metformin and placebo

There was a statistically significant difference in the rate of NICU admission, favouring metformin, with a RR of 0.62 (0.39-0.97) (moderate), however, the clinical significance of this, in the absence of a difference in the rate of preterm delivery and rate of small of gestational age, is unclear. Additionally, there was a difference in the rate of patient reported GI symptoms (nausea/vomiting/diarrhoea) RR 1.48 (1.08-2.04)(moderate).

Rationale for recommendation

The analysis of the 3 selected RCTs demonstrated a moderate reduction in the rate of NICU admission in women who were prescribed metformin. The clinical significance of this finding, particularly in the absence of a difference in the rate of preeclampsia, small for gestational age newborn and preterm delivery, is unclear. There was also an associated in increased risk of maternal GI symptoms of nausea, vomiting and diarrhoea in women who were prescribed metformin.

It is also important to note that the women recruited into all 3 studies were non-diabetic obese women and not specifically women who were risk stratified as high risk for preeclampsia based on the current clinical guidelines.

On the balance of all the above, we propose a recommendation against the use of metformin until more data, specifically in women who are risk stratified as high-risk for developing preeclampsia is available.

The recommendation from this analysis is not applicable to the use of metformin in women with PCOS and for the purpose of glycaemic control in women with diabetes and gestational diabetes.

Recommendation in other guidelines

Guidelines	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	No recommendation made
SOMANZ 2015	No recommendation made

Research opportunities

More data on the use of metformin specifically in women who are risk stratified as high risk for developing preeclampsia would be beneficial. A RCT that examines the use of metformin in combination with aspirin vs aspirin alone in women at risk of developing preeclampsia is currently underway : https://clinicaltrials.gov/ct2/show/NCT04855513.

3A.12: Oral Vitamin D supplementation

Recommendations

3A.12 The use of oral Vitamin D supplementation for the prevention of preeclampsia, is recommended against until more data is available. (2B)

Description of intervention

Vitamin D deficiency has been found to be associated with an increased risk of preeclampsia, preterm birth and gestational diabetes (228-230). However, data on the use of oral vitamin D supplementation, specifically in preventing preeclampsia and preterm delivery, remains inconsistent (231, 232).

There also remains significant inconsistencies with the recommended threshold for oral vitamin D supplementation in pregnancy. The Royal College of Obstetricians and Gynaecologists recommends 400 IU/d (10 µg/d) of oral vitamin D supplementation in all pregnant women (RCOG 2014). However, for high-risk women (dark skin, reduced exposure to sunlight, or those who are socially excluded or obese), at least 1,000 IU/d (25 µg/d) of oral vitamin D is recommended. Additionally, for women at high-risk of preeclampsia, the RCOG recommends at least 800 IU/d (20 µg/d) oral vitamin D in combination with calcium. However, the recent US Dietary Guidelines does not recommend universal vitamin D supplementation during pregnancy and recommends supplementation specifically for those with limited sun exposure (DGA 2015). The WHO supplementation guidelines in pregnancy also does not recommend universal vitamin D supplementation as part of routine antenatal care (WHO 2012) and recommends supplementation only in women with vitamin D deficiency, which is in alignment with the American Congress of Obstetricians and Gynaecologists guidelines (ACOG 2015).

Very high dose vitamin D supplementation (> 10,000 IU/d or 250 µg/d) has been demonstrated to lead to hypercalcaemia and hypercalciuria with the associated risk of nephrocalcinosis in the non-pregnant population (233-235). However, the use of very high dose Vitamin D has not been examined in pregnant women.

How the intervention might work

The active form of vitamin D, 1,25-dihydroxyvitamin D3, has been demonstrated to adjust the transcription and function of genes associated with normal implantation, placental invasion, and angiogenesis [12]. Therefore, maternal vitamin D deficiency is thought to negatively influence placentation through an increase in inflammatory reaction [14]. Vitamin D deficiency is also thought to increase the risk of hypertension through reduced anti-inflammatory effect on the vascular endothelium [15]. However, the direct effect of vitamin D replacement on placental development and angiogenesis, especially in women with vitamin D deficiency, has not been adequately examined.

Summary of evidence, risk of harm and quality of evidence

A total of 3 RCTs with 176 women in the intervention and 127 women in the placebo arm (1 study with a 2:1 randomisation) were examined. All three studies had significant heterogeneity in the prescription of vitamin D:

- Sasan *et al* prescribed 50,000 IU of vitamin D3 every 2 weeks, however, excluded women with vitamin D deficiency in their study.
- Sablok *et al* prescribed vitamin D3 based on serum vitamin D level at recruitment; single dose of 60,000 IU for vitamin D replete women (>50), 120,000 IU of vitamin D3 at 20 and 24 weeks of gestation for women with insufficiency serum vitamin D (25-50) and 120,000 IU of vitamin D at 20,24,28 and 32 weeks of gestation for women with vitamin D deficiency (<25). However, a sub-analysis of outcomes based on the various level of vitamin D deficiency was not conducted in the study.
- Nagshineh *et al* prescribed 600IU daily from the first trimester until delivery, however, women with vitamin D deficiency were excluded.
- For the purpose of this analysis, studies that included concurrent use of aspirin and/or other vitamins and minerals were excluded.
- A statistically significant difference in the following outcomes were observed:

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	**0.47**	**0.26-0.86**	**MODERATE**
Preterm delivery	**0.32**	**0.17-0.60**	**MODERATE**
Small for gestation	**0.43**	**0.19-0.98**	**LOW**

Table 3A.12.1 Comparison of outcomes between oral vitamin D supplementation and placebo

Rationale for recommendation

The studies appropriate for this analysis consisted of a small sample size with significant heterogeneity in the prescription of vitamin D. Outcomes on side effects and adverse outcomes were not reported on. Based on the lack of adequate information on efficacy based on baseline maternal serum vitamin D level, optimal dose and side effects, we propose a conditional recommendation against the use of vitamin D for the prevention of preeclampsia until more data is available. This recommendation is not applicable to antenatal vitamin D replacement in women with vitamin D deficiency.

Recommendation in other guidelines

Guidelines	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	No recommendation made
SOMANZ 2015	No recommendation made

Research opportunities

More data on the follow aspects of the use of vitamin D in the prevention of preeclampsia is required:

- Efficacy of oral vitamin D supplementation in preventing preeclampsia specifically in women with vitamin D deficiency
- Optimal dose of oral vitamin D in preventing preeclampsia

3A.13: Proton pump inhibitors

Recommendations

3A.13 The use of proton pump inhibitors for prevention of preeclampsia is recommended against until more data is available. (PP)

Description of intervention

Proton pump inhibitors (PPIs) are commonly used to treat gastroesophageal reflux and has been shown to be relatively safe in pregnancy with no associated risk of major congenital malformation (236, 237). A systematic review of population-based studies, however, reported an associated increase in the incidence of childhood asthma (238). At the time of publication, PPIs, especially omeprazole and esomeprazole, are commonly prescribed in managing gastroesophageal reflux symptoms.

How the intervention might work

Preclinical studies on placental explant tissue from women diagnosed with preeclampsia and human umbilical vein endothelial cells (HUVEC) demonstrated that PPIs reduced secretion of sFlt-1 from primary placental cells, placental tissue, and primary endothelial cells from both normotensive and preeclamptic patient samples (239). In a mouse model of preeclampsia, PPIs were shown to reduce vascular endothelial dysfunction and reduce blood pressure (239). Clinical studies which examined the role of esomeprazole reversing endothelial dysfunction and clinical features of preeclampsia in women with established preeclampsia did not demonstrate a difference in circulating angiogenic markers or a difference in duration of pregnancy (240). A RCT on the therapeutic effect of PPI in managing preeclampsia is underway at the time of publication (ESOPE trial (NCT03213639).

Based on the preclinical studies, there have been additional interest in examining for a potential prophylactic role of PPIs in the prevention of preeclampsia.

Summary of evidence, risk of harm and quality of evidence

At time of publication, there have been no published studies on the prophylactic role of PPIs in women at risk of preeclampsia .

Two population-based registry data studies of pregnant women who were prescribed PPIs antenatally demonstrated conflicting data with one study suggesting an increase in the risk of preeclampsia, while the second study did not demonstrate a difference in obstetric outcomes (241, 242). These studies, however, contained significant heterogeneity in the type, dose, and duration of PPIs for treatment of gastroesophageal symptoms. Additionally, the study population in these studies were not specific to women who were at risk of developing preeclampsia.

Rationale for recommendation

We recommend against the use of proton pump inhibitors for the purpose of preventing preeclampsia until more data, specific to women at high risk of developing preeclampsia, is available.

This recommendation is not applicable to women who require proton pump inhibitors for other indications in pregnancy.

Recommendation in other guidelines

Guidelines	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	No recommendation made
SOMANZ 2015	No recommendation made

Research priorities

More research and data on the clinical efficacy of PPI on the prevention of preeclampsia in women at high-risk of preeclampsia is required. At the time of publication, a RCT examining the prophylactic effect of esomeprazole, co-administered with aspirin, is underway (https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12618001755224).

3A.14: Clopidogrel

Recommendations

3A.14 The use of clopidogrel for prevention of preeclampsia is recommended against until human data is available. (PP)

Description of intervention

Clopidogrel is an adenosine diphosphate (ADP) receptor inhibitor and prevents platelet aggregation by selectively and irreversibly binding the platelet surface receptor P2Y12.

How the intervention might work

Human umbilical vein endothelial cell (HUVEC) studies have demonstrated potential upregulation in anti-oxidant defences with a decrease in sFlt1/sEng secretion. Therefore, suggesting a possible role in improving placentation and consequently, reducing the risk of preeclampsia (243).

Summary of evidence, risk of harm and quality of evidence

At the time of publication, there have been no human studies on the use of clopidogrel, specifically, for the prevention of preeclampsia.

Rationale for recommendation

We recommend against the use of clopidogrel for the purpose of preventing preeclampsia given the absence of human studies.

This recommendation is not applicable to women who require clopidogrel in pregnancy for cardiovascular indications.

Recommendations in other guidelines

Guidelines	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	No recommendation made
SOMANZ 2015	No recommendation made

Research priorities

More research and data on the following aspects on the use of clopidogrel, specifically for the prevention of preeclampsia, remains unclear and warrants further studies:

- Efficacy of clopidogrel on the obstetric outcomes in women who are at risk of developing preeclampsia
- Maternal and fetal safety and side effect profile of clopidogrel in pregnancy

PART 3B: Prevention of preeclampsia
(non-pharmacological intervention)

3B.1 : Exercise

Recommendation

3B.1 Moderate intensity exercise, in the form of aerobic, stretching and/or muscle resistance exercises, for a total of 2.5-5 hours a week, as recommended as part of routine pregnancy wellbeing has the added benefit of reducing the risk of hypertensive disorders of pregnancy. Adherence to the current recommended exercise regimen for general pregnancy wellbeing is encouraged. (Patient information sheet 3B.1). (2D)

Description of intervention

The term 'aerobic exercise' refers to energetic exercise that results in a rise in oxygen consumption (to around 40% to 80% of maximum), and heart rate (to around 50% to 90% of maximum). This level of activity is necessary for at least 10 minutes on at least two days per week to produce a 'training effect' of increasing or maintaining fitness in non-pregnant people. Non-aerobic exercise, such as stretching, yoga and muscle resistance refers to exercise that improves strength of muscles and flexibility. Current guidelines recommend that all pregnant women (not specific to women at risk of preeclampsia), in the absence of contraindications should aim for 3 to 4 days (total of 150 to 300 minutes) of moderate intensity aerobic and/or anaerobic exercise per week on non-consecutive days (RANZCOG 2020, Australian Pregnancy Care Guidelines 2020).

Case-control studies have suggested that recreational exercise may be associated with a reduction in the risk of preeclampsia and gestational hypertension (244). These studies largely evaluated the effects of exercise before conception and during the first half of pregnancy for primiparous women but have not been examined specifically in women at high risk of developing preeclampsia.

How the intervention might work

Exercise in pregnancy is thought to enhance placental growth and vascularity, reduce oxidative stress and correction of vascular endothelial dysfunction, particularly with aerobic exercise (245-247). Regular exercise is also associated with an increase in plasma volume and cardiac output, decrease in inflammatory cytokines and insulin resistance (248, 249). However, the effect of exercise specifically in women with chronic hypertension and/or women at high risk of developing preeclampsia has not been adequately examined.

Summary of evidence, risk of harm and quality of evidence

A total of 10 RCTs with a combined sample size of 1,640 in the intervention arm and 1,770 in the control arm (1 study with a 1:2 randomisation) were examined (250-258). Women in the intervention arm were prescribed exercises (either aerobic, stretching, yoga or muscle resistance) for 50-60 minutes a day for three times a week. This is in keeping with the standard recommendation for exercise in pregnancy (for general pregnancy wellbeing) (Australian Pregnancy Care Guidelines 2019 and RANZCOG). Women in the control arm were not provided prescribed exercise to meet the standard recommended exercise threshold.

Nine of the ten studies recruited low-risk women except for 1 study which specifically recruited women at high-risk of developing preeclampsia. Women who adhered to the prescribed exercise to meet the standard recommendation for exercise in pregnancy were found to have a low rate of preeclampsia, gestational hypertension and maternal weight gain in pregnancy (Table 3B.1.1).

Outcome	Risk Ratio/Mean difference	Confidence interval	Quality of evidence
Preeclampsia	**0.63**	**0.44-0.63**	**LOW**
Gestational hypertension	**0.39**	**0.19-0.80**	**LOW**
Maternal weight gain in pregnancy	**-0.96**	**-1.47 to –0.44**	**VERY LOW**
Preterm delivery	0.74	0.41-1.32	VERY LOW
Small for gestational age	0.79	0.56-1.10	VERY LOW
NICU admission	0.87	0.44-1.74	VERY LOW

Table 3B.1.1: Comparison of outcomes between prescribed exercise and without prescribed exercise

Rationale for recommendation

The exercise regimen prescribed in the studies examined are in keeping with the standard recommendation for exercise in pregnancy (as part of routine antenatal care).

We, therefore, propose that the standard recommendation for exercise in pregnancy, cumulative of 2.5-5 hours of moderate intensity aerobic, stretching and/or muscle resistance exercises, has the added benefit of reducing the risk of hypertensive disorders of pregnancy (Patient information sheet 3B.1). This, however, has not been adequately examined specifically in women who are at high risk of developing preeclampsia.

This recommendation is not applicable to women with a BMI of >30 or with other medical comorbidities (diabetes or gestational diabetes) who may require a varied duration/intensity of exercise in pregnancy.

Recommendation in other guidelines

Guidelines	Recommendation
ISSHP 2022	Unless there are contraindications, all women should exercise in pregnancy to reduce the likelihood of gestational hypertension and preeclampsia.
Australian Pregnancy Care Guidelines 2019	Advise women that usual physical activity during pregnancy has health benefits and is safe.
NICE 2019	Give the same advice on rest, exercise and work to women with chronic hypertension or at risk of hypertensive disorders during pregnancy as healthy pregnant women.
SOMANZ 2015	No recommendation made

Research priorities

Benefit of increased physical activity, specifically in women at high risk of developing preeclampsia and in women with pre-existing chronic hypertension will be beneficial.

Pregnant women should get at least 2.5-5 hours of moderate-intensity activities every week. This can be in the form of aerobic, stretching or muscle resistance exercises.

Exercise in pregnancy has been shown to reduce medical complications in pregnancy, including hypertension (high blood pressure) and excessive weight gain in pregnancy.

Exercising in pregnancy

Pregnant women should get at least **2.5-5 hours of moderate-intensity activities every week.**
This can be in the form of aerobic, stretching or muscle resistance exercises.
Exercise in pregnancy has been shown to reduce medical complications in pregnancy, including hypertension (high blood pressure) and excessive weight gain in pregnancy.

Aerobic exercises

Aerobic exercises involve continuous activities that use large muscle groups and elevates the heart rate and breathing. Some examples of aerobic exercises include:

Brisk walking | Stationary cycling | Swimming

Stretching exercises

Slow and controlled stretches (i.e.: yoga) can be incorporated as part of warm up or exercise routine

Muscle resistance exercises

Strengthening exercises should be performed twice per week, on non-consecutive days, covering the main muscle groups of the body. Resistance can be provided by light weights, body weight or elasticised resistance-bands.

Aim to perform 1 to 2 sets of 12 to 15 repetitions for each exercise. These strengthening exercises should be performed with slow and steady movements and proper breathing technique (i.e.: exhale on exertion).

Avoid heavy weight-lifting and activities that involve straining or holding the breath. Exercises should not be performed lying flat on the back after the first trimester and walking lunges are best avoided to prevent injury to the pelvic connective tissue.

If you are new to exercise, start out slowly and gradually increase your activity. Begin with as little as 5 minutes a day. Add 5 minutes each week until you can stay active for 30 minutes a day.

Warning signs to stop physical activity

If you experience chest pain, persistent shortness of breath, severe headache, persistent dizziness, painful uterine contractions, or vaginal bleeding during physical activity, be sure to stop and seek immediate medical attention.

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Patient information sheet 3B.1 : Exercise in pregnancy (PDF)

3B.2: Dietary salt restriction

Recommendations

3B.2 Dietary salt restriction, for prevention of preeclampsia, is recommended against given the lack of evidence of benefit. (2D)

Description of intervention

Historically, a low-salt diet was often recommended as treatment for oedema in both pregnant and non-pregnant people. Early study demonstrated that dietary salt restriction restricting could potential prevent and also treat preeclampsia (Green 1989). However, subsequent studies have suggested the possibility of salt loading in treating preeclampsia (259, 260). These contradictory hypotheses have led to uncertainty with the role of sodium in preventing and managing preeclampsia (261).

In most parts of the world, women are no longer advised by clinicians to alter their salt intake during pregnancy.

This analysis was aimed at examining the current data on the dietary sodium restriction (~20mmol/day) in preventing preeclampsia.

Summary of evidence, risk of harm and quality of evidence

A total of 3 RCTs with a combined sample size of ~ 200 women in each arm were examined in this analysis (262-264). All three studies restricted dietary salt intake to ~20 mmol/day from 14 weeks of gestation to delivery in women with a history of preeclampsia. Women in the control arm had a regular diet. Studies that examined dietary salt restriction in managing established preeclampsia were excluded for the purpose of this analysis.

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Preeclampsia	1.00	0.45-2.05	VERY LOW
Gestational hypertension	0.97	0.94-1.94	LOW
Preterm delivery	1.08	0.46-2.56	VERY LOW
Small for gestational age	1.64	0.96-2.81	VERY LOW

Table 3B.2.1: Comparison of outcomes between dietary salt restriction and without dietary salt restriction

Rationale for recommendation

There was no statistically significant difference in the outcomes of interest, however, this is based on a relatively small sample size with inadequate assessment of potential adverse effects. We, therefore, propose a recommendation against dietary salt intake restriction for the prevention of preeclampsia until more data is available.

Recommendation by other guidelines

Guidelines	Recommendation
ISSHP 2022	No recommendations made
Australian Pregnancy Care Guidelines 2019	Reducing salt intake is unlikely to reduce the risk of pre-eclampsia (Duley 2011). However, avoiding foods with added salt has other health benefits
NICE 2019	Do not recommend salt restriction during pregnancy solely to prevent gestational hypertension or pre-eclampsia.
SOMANZ 2015	No recommendation made

Research priorities

More data on the effect of dietary salt intake, specifically in women at high risk of developing preeclampsia and in women with pre-existing chronic hypertension will be beneficial.

PART 4: Diagnosis of Preeclampsia

4.1 : Urine assessment for proteinuria

Recommendations

4.1.1 Urine dipstick can be used for initial screening; however, dipstick alone is inadequate to diagnose proteinuria in pregnancy. A confirmatory quantifying method of urine protein assessment (i.e., urine protein to creatinine ratio) should be used in women with clinical suspicion of preeclampsia. (2B)

4.1.2 Urine protein to creatinine ratio (uPCR) with a cut off ≥30mg/mmol can be used to diagnose proteinuria in pregnancy. (1B)

4.1.3 Urine albumin to creatinine ratio (uACR) with a cut off ≥8mg/mmol can be used as an alternative if urine protein to creatinine ratio (uPCR) is not available to diagnose proteinuria in pregnancy. (2B)

4.1.4 Cut-off for abnormal urinary protein excretion in multi-gestational pregnancy remains unclear and therefore urine PCR, ACR and 24-hour urine assessment should be interpreted with caution. (PP)

4.1.5 Repeated urinary protein assessment in women with proteinuria from established preeclampsia (in the absence of other indications) is not recommended. There is inadequate data to determine the severity of preeclampsia or timing of delivery based on urine protein assessment. (PP)

Description of intervention

Reliable detection of significant proteinuria in women with new-onset hypertension in pregnancy is important in differentiating hypertensive disorders of pregnancy. Current practise in assessing for proteinuria involves initial screening (semi quantitative assessment) with a urine dipstick and subsequent confirmation and quantification through either spot urine protein to creatinine ratio (cut off ≥30mg/mmol) or 24-hour urine collection (≥300mg/24 hours).

While urine dipsticks are cheap and easy to use, interpretation of the dipstick testing is highly subjective and is therefore often not accurate in confirming or excluding significant proteinuria (≥300mg/24 hours)(265). This has been shown to improve slightly with automated dipstick testing but even then, more than half the patients with significant proteinuria are likely to be missed (266).

Although generally considered the "gold standard" for diagnosis of proteinuria in both preeclampsia and kidney disease (in the general population), 24-hour urine protein excretion assessment is often inaccurate due to collection errors (267). Given this, spot urinary protein:creatinine ratio (uPCR) or urinary albumin:creatinine ratio (uACR) assessments have emerged as preferred alternatives.

In defining abnormal proteinuria in pregnancy, current data recommends a cut-off of ≥300mg/24 hours for 24-hour urine collection, ≥30 mg/mmol for spot uPCR and ≥8 mg/mmol for uACR (NICE Guidelines 2019). These values, however, are often higher in women with multi-gestational pregnancies due to the physiologically increased renal hyperfiltration in pregnancy. At present, there remains a lack of certainly on the appropriate cut-off to define abnormal urinary protein excretion in women with multi-gestational pregnancy.

Summary of evidence and rationale for recommendation

Two prospective studies with a combined sample size of 427 women with suspected preeclampsia (clinical features of preeclampsia) were reviewed to examine for the sensitivity and specificity of urine dipstick analysis (≥1+) compared to 24 hour urine collection (≥ 300mg/24 hours) in identifying proteinuria in pregnancy (268, 269). The diagnostic accuracy found in these two studies varied (Figure 4.1.1) (moderate certainty of evidence).

A total of 13 prospective studies with a combined sample size of 3,619 women with suspected preeclampsia were reviewed to examine for the sensitivity and specificity of spot uPCR (cut-off of ≥30mg/mmol) compared to 24 hour urine collection (cut-off of ≥300mg/24 hrs) to quantify proteinuria for the purpose of diagnosing preeclampsia (270-282). The analysis demonstrated a pooled sensitivity and specificity of 0.89 (CI 0.84-0.93) and 0.90 (CI 0.78-0.96) respectively (moderate certainty of evidence) (Figure 4.1.1).

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Protein-creatinine ratio						
Amin 2014	70	11	8	13	0.90 (0.81-0.95)	0.54 (0.35-0.72)
Berthet 2020	134	4	17	61	0.89 (0.83-0.93)	0.94 (0.85-0.98)
Bhatti 2018	69	20	37	350	0.65 (0.56-0.73)	0.95 (0.92-0.97)
Cade 2012	98	6	5	12	0.95 (0.89-0.98)	0.67 (0.44-0.84)
Durnwald 2003	156	35	12	17	0.93 (0.88-0.96)	0.33 (0.22-0.47)
Kyle 2008	12	4	1	133	0.92 (0.66-0.99)	0.97 (0.93-0.99)
Lamontagne 2014	35	1	8	47	0.81 (0.67-0.90)	0.98 (0.89-1.00)
Leanos-Miranda 2007	277	8	5	637	0.98 (0.96-0.99)	0.99 (0.98-1.00)
Rizk 2007	35	7	16	25	0.69 (0.55-0.80)	0.78 (0.61-0.89)
Saudan 1997	56	3	4	37	0.93 (0.84-0.97)	0.92 (0.79-0.97)
Sethuram 2011	25	0	5	2	0.83 (0.66-0.92)	1.00 (0.34-1 .00)
Waugh 2017	441	182	34	302	0.93 (0.90-0.95)	0.62 (0.58-0.66)
Wilkinson 2013	47	2	9	74	0.84 (0.72-0.91)	0.97 (0.90-0.99)
Dipsticku rinalysis						
Brown 1995	60	98	10	62	0.86 (0.76-0.92)	0.39 (0.32-0.47)
Waugh 2001	31	1	107	58	0.22 (0.16-0.30)	0.98 (0.91-1.00)
Albuminin-creatininera tio						
Kyle 2008	13	5	0	132	1.00 (0.77-1.00)	0.96 (0.91-0.98)

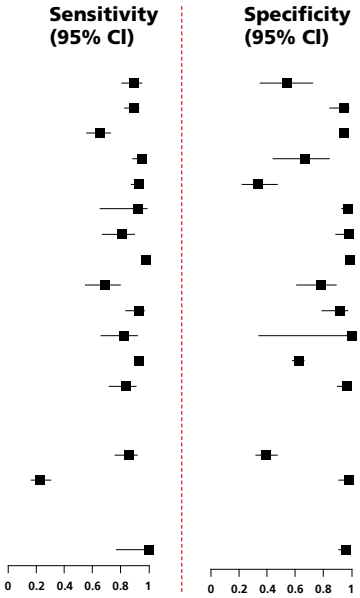


Figure 4.1.1. Forest plots assessing the accuracy of various means of assessing proteinuria where the gold standard was 24hr urinary protein excretion. TP- True positives, FP-false positives, FN- False negatives, TN- True negatives.

One prospective study with a sample size of 150 women with suspected preeclampsia was reviewed to examine for the sensitivity and specificity of spot uACR (cut-off of ≥8 mg/mmol) compared to 24 hour urine collection (cut-off of ≥300mg/24 hrs) to quantify proteinuria for the purpose of diagnosing preeclampsia (274). Urine ACR (cut-off of ≥8mg/mmol) was found to have high sensitivity (1.00, CI 0.75-1.00) and specificity (0.96, CI 0.91-0.98) with a positive predictive value of 72% (MODERATE certainty of evidence) however this is based on a single study with a relatively small sample size.

Where the gold standard for urinary protein assessment is spot urinary protein assessment (uPCR) only one study assessing the diagnostic accuracy of urinary dipstick was analysed (Figure 4.1.2)(266).

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Urinatysls>= 1+						
Phelan 2004	115	128	24	236	0.83 (0.76-0.88)	0.65 (0.60-0.70)
Urinalysis >=2+						
Phelan 2004	74	27	24	378	0.76 (0.67-0.83)	0.93 (0.90-0.95)

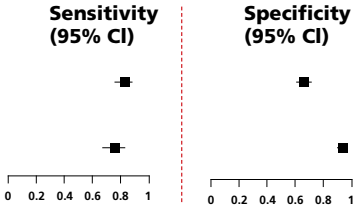


Figure 4.1.2. Forest plots assessing the accuracy of various means of assessing proteinuria where the gold standard was spot urinary protein:creatinine ratio. TP- True positives, FP-false positives, FN- False negatives, TN- True negatives.

Studies with asymptomatic women (routine screening) and the use of variable or non-specified cut offs were excluded from this analysis.

There is inadequate data to suggest the need for repeated testing of uPCR once proteinuria from preeclampsia is established. There is also inadequate data to reliably assess severity of preeclampsia or timing of delivery based on urine protein assessment.

Recommendation by other guidelines

Guidelines	Recommendation
ISSHP 2022	Quantitative proteinuria testing for pre-eclampsia should be performed as part of the work-up for women suspected of having pre- eclampsia or at high-risk of developing it. Proteinuria should be defined as ≥30 mg/mmol urinary protein: creatinine ratio (PrCr) in a spot (random) urine sample, or albumin: creatinine ratio (ACR) ≥ 8 mg/mmol, or ≥ 0.3 g/d in a complete 24-hour urine collection, or ≥ 2 + by urinary dipstick if confirmatory testing is not available
Australian Pregnancy Care Guidelines 2019	For point-of-care testing, use an automated analyser if available, as visual inspection of a urinary dipstick is the least accurate method to detect true proteinuria. Repeat testing for proteinuria is of little or no benefit in predicting pre-eclampsia and should be confined to women with other risk factors such as existing or newly diagnosed high blood pressure and new or pre-existing kidney disease
NICE 2019	If dipstick screening is positive (1+ or more), use albumin:creatinine ratio or protein:creatinine ratio to quantify proteinuria in pregnant women Do not routinely use 24-hour urine collection to quantify proteinuria in pregnant women.
SOMANZ 2015	Dipstick testing is simple, cheap and an appropriate screening test but spot urine PCR is recommended for confirmation or exclusion of proteinuria when preeclampsia is suspected

Research opportunities

More data on the appropriate cut-off for abnormal urinary protein excretion in multi-gestational pregnancy is required.

4.2 Use of sFlt-1/PlGF ratio

Recommendations

4.2.1 The sFlt-1/PlGF ratio should be used as an adjunct to clinical assessment. The use of the ratio should not replace clinical assessment and management decisions should not be made based on the ratio alone (Flowsheet 4.2). (PP)

4.2.2 Utility of sFlt-1/PlGF (≤38) in ruling out preeclampsia within 1- 4 weeks of testing in women with clinical suspicion of preeclampsia is conditionally recommended where a clinically validated ratio assessment is available in a timely manner. (2D)

4.2.3 The use of the sFlt-1/PlGF ratio in diagnosing preeclampsia, determining fetal outcomes, severity of disease, timing of delivery and its used in routine screening in asymptomatic women is not recommended until more data is available to support its use in these settings. (2D)

Description of intervention

Many of the clinical and biochemical features of preeclampsia overlap with abnormalities in women with new or pre-existing medical issues e.g. chronic hypertension, chronic kidney disease, chronic liver disease systemic lupus erythematosus (SLE). This leads to a clinical conundrum in identifying women with preeclampsia in these high-risk women.

Circulating angiogenic factors have received considerable attention, particularly the anti-angiogenic factor, soluble fms-like tyrosine kinase 1 (sFlt-1) and the pro-angiogenic factor, placental growth factor (PlGF). These molecules can be measured in plasma and serum on automated platforms and can be reported as a ratio. Both these molecules are largely produced in the placenta and are circulating markers of placental health. The PRediction of short-term Outcome in preGNant wOmen with Suspected preeclampsla Study (PROGNOSIS) study demonstrated that the use of a maternal plasma sFlt-1/PlGF ratio with a cut-off of ≤ 38 ruled out preeclampsia within 1 week (negative predictive value [NPV] 99.3%) or 4 weeks (NPV 94.3%) in women with a singleton pregnancy who were suspected to have preeclampsia after 20 weeks of gestation (283). The study also demonstrated that ratio values above 38 were not helpful in ruling in preeclampsia within 4 weeks (positive predictive value [PPV] > 36%). Similar results were reported in 764 pregnant women in Asia at gestational week 20–37. The Preeclampsia Open Study, which was based on the aforementioned studies, showed the ratio test influenced clinical decision making towards appropriate hospitalization in a considerable proportion of women with suspected preeclampsia, therefore, potentially demonstrating a benefit in minimizing inpatient management of women with suspected preeclampsia and allowing for outpatient management where clinically appropriate (284). The use of the ratio in diagnosing preeclampsia, predicting fetal growth restriction, fetal outcomes and timing of delivery, however, remains unclear with limited data. The appropriate use of the ratio in these settings is likely to become more evident in the near future.

Summary of evidence and rationale for recommendation

A total of 9 studies were examined for the sub-analysis below (283, 285-292). Studies with multi-gestational pregnancies and studies which did not utilize the clinically validated ROCHE COBAS assay for sFlt-1/PlGF analysis were excluded. Studies with no pre-defined cut off (for the purpose of the sub analysis below) were also excluded. The figures (4.2.1-3) below demonstrate the diagnostic test accuracy (DTA) assessment conducted based on the three clinical scenarios listed . A combined meta-analysis of the studies was not feasible given the number of studies within each sub-analysis.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Asymptomatic testing - sFlt-1/PlGF ratio (cut-off 38)								
Dragan Wright 2017	10	530	2	11224	0.83 (0.55-0.95)	0.95 (0.95-0.95)		
Dragan 2017	11	554	3	11737	0.79 (0.53-0.93)	0.95 (0.95-0.95)		
Symptomatic testing - sFlt-1 /PlGF ratio (cut-off 38)								
Bian 2019	26	119	8	547	0.76 (0.59-0.87)	0.82 (0.79-0.85)		
Cailon 2018	3	11	0	53	1.00 (0.44-1.00)	0.83 (0.72-0.90)		
Cerdiera 2019	23	33	1	129	0.96 (0.80-0.99)	0.80 (0.73-0.85)		
Zeisler 2016	42	209	7	792	0.86 (0.74-0.93)	0.79 (0.76-0.81)		

Figure 4.2.1: Forest plot demonstrating the utility of the sFlt-1/PlGF ratio (cut off >38) in predicting preeclampsia within 1 week of testing in asymptomatic women and symptomatic women.TP-True positives, FP- False positives, FN- False negatives, TN- True negatives

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Asymptomatic testing - sFlt1/PlGF ratio (cut-off 38)								
Dragan Wright 2017	53	487	15	11211	0.78 (0.67-0.86)	0.96 (0.96-0.96)		
Dragan 2017	59	506	18	11722	0.77 (0.66-0.85)	0.96 (0.96-0.96)		
Symptomatic testing - sFlt/PlGF ratio (cut-off 38)								
Bian 2019	44	101	27	528	0.62 (0.50-0.72)	0.84 (0.81-0.87)		
Cailon 2018	2	9	0	53	1.00 (0.34-1.00)	0.85 (0.74-0.92)		
Zeisler 2016	97	168	41	744	0.70 (0.62-0.77)	0.82 (0.79-0.84)		

Figure 4.2.2 : Forest plot demonstrating the utility of the sFlt-1/PlGF ratio (cut off >38) in predicting preeclampsia within 4 weeks of testing in asymptomatic women and symptomatic women. TP-True positives, FP- False positives, FN- False negatives, TN- True negatives

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
sFlt-1/PlGF ratio (>=85) in diagnosing/confirming PE						
Saleh 2016	56	3	6	42	0.90 (0.80-0.95)	0.93 (0.82-0.98)
Tardif 2018	2	4	6	55	0.25 (0.07-0.59)	0.93 (0.84-0.97)
sFlt-1/PlGF ratio (>85) in predicting PE with severe features						
Rana 2018	41	28	25	308	0.62 (0.50-0.73)	0.92 (0.89-0.94)
sFlt-1/PlGF ratio (>85) in predicting indicated delivery						
Rana 2018	88	40	54	220	0.62 (0.54-0.70)	0.85 (0.80-0.89)
sFlt-1/PlGF ratio (>85) in predicting adverse fetal outcome						
Saleh 2016	56	3	6	42	0.90 (0.80-0.95)	0.93 (0.82-0.98)

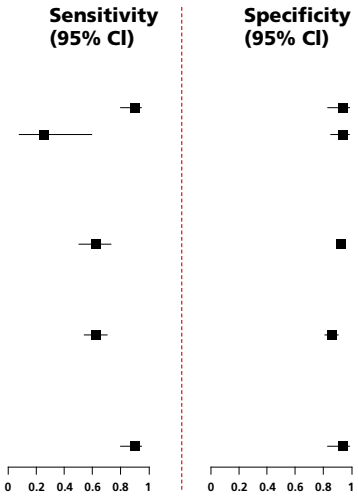


Table 4.2.3: Forest plot demonstrating the utility of the sFlt-1/PlGF ratio (cut off >85) in the diagnosis of preeclampsia. TP-True positives, FP- False positives, FN- False negatives, TN- True negatives

Clinical scenario	Number of studies	Combined sample size	Quality of evidence
Predicting preeclampsia			
4.2.1 Utility of sFlt-1/PlGF (≤ 38) **in ruling out** preeclampsia within 1- 4 weeks of testing in women where there is a **clinical suspicion of preeclampsia**	4	1,650	VERY LOW
4.2.2 Utility of **asymptomatic third trimester** sFlt-1/PlGF ratio (≤38) in **ruling out** preeclampsia within 1-4 weeks of testing	2	24,071	VERY LOW
Diagnosing preeclampsia			
4.2.3 Utility of sFlt-1/PlGF (>85) in **diagnosing preeclampsia**	2	185	VERY LOW
4.2.4 Utility of sFlt-1/PlGF (>85) in **predicting indicated delivery** within 2 weeks of testing	1	187	VERY LOW
4.2.5 Utility of sFlt-1/PlGF (>85) in **predicting adverse fetal outcomes**	1	109	VERY LOW

Table 4.2.1 : Summary of quality of evidence

Based on the data presented, we recommend the use of the sFlt-1/PlGF ratio with a cut-off of ≤38 in ruling out preeclampsia in women with features to suggest clinical suspicion of preeclampsia (Chapter 1). There remains inadequate data to support the use of the ratio in the setting below:

- Multigestation pregnancies
- Diagnosis of preeclampsia
- Determining disease severity
- Determining fetal outcomes
- Determining timing of delivery
- Routine asymptomatic screening

Cost analysis and accessibility

At the time of this review, analysis of the sFlt1/PlGF ratio costs AUD$ 82.00 per test and is not subsidised by Medicare in Australia. The cost of testing is often covered by the patient and occasionally, by the hospital, if a financial arrangement between the hospital and in-house pathology service is in place.

At present, access to this biomarker testing is not widely available throughout Australia. Results can be obtained within 4-6 hours in centres with local testing capability and 24-36 hours in centres where offsite testing is required.

To date, there have not been cost-analysis studies specific to Australia. However, various international cost analysis studies have demonstrated that the use of the sFlt-1/PlGF ratio as an adjunct to clinical indicators reduces inpatient care and its associated cost. A US-based cost analysis study by Khosla *et al* demonstrated that the use of the sFlt1/PlGF ratio in women with suspected preeclampsia reduced admission by 34-49% with a cost saving of ~USD $1,050 (AUD$1,513) per patient (293). Similarly, a Japanese based cost analysis study by Ohkuchi *et al* (294) and a German based study by Schlembach *et al* (295) demonstrated a reduction in hospitalisation with a cost saving of ~ 16 373 JPY (AUD$180) and € 361 (AUD$ 532) per patient respectively.

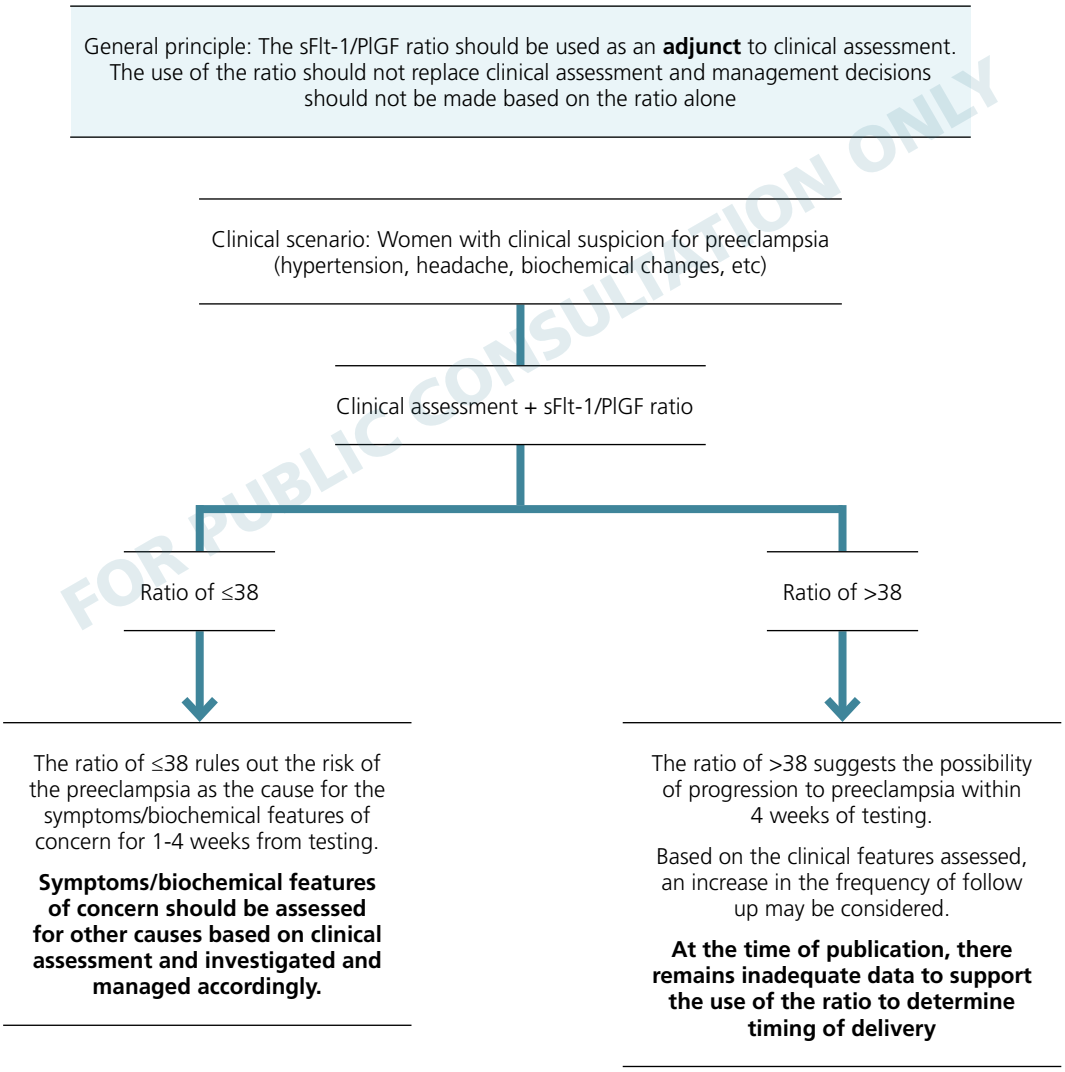
Recommendation by other guidelines

Guidelines	Recommendation
ISSHP 2022	sFlt-1/PlGF imbalance in itself is not an indication for delivery
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Not recommended for routine use
SOMANZ 2015	No recommendation made

Research opportunities

More data on the following aspects of the use of the sFlt-1/PlGF biomarker ratio is required:

- Clinical utility of the ratio in predicting adverse fetal outcome and timing of delivery
- Data on the clinical utility of the ratio in Australia and New Zealand
- Cost saving analysis in Australia and New Zealand



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Flowsheet 4:2: Proposed clinical utility of sFlt-1/PlGF ratio

4.3 Use of PlGF biomarker assessment

Recommendations

4.3.1 More data on the clinical application of PlGF-based testing in predicting preeclampsia in women with clinical suspicion of preeclampsia are required prior to clinical implementation of PlGF-based testing in Australia and New Zealand. (PP)

4.3.2 Use of the PlGF value (alone) from the sFlt-1/PlGF ratio assay (ROCHE COBAS) for the use of PlGF-based testing has not been clinically validated and is not recommended. (PP)

Description of intervention

Circulating angiogenic factors have received considerable attention, particularly the anti-angiogenic factor, soluble fms-like tyrosine kinase 1 (sFlt-1) and the pro-angiogenic factor, placental growth factor (PlGF). Some of the currently used clinically validated angiogenic biomarker assays quantify sFlt-1 and PlGF presenting the results as a ratio (Recommendation 4.2), however, more recently, a PlGF-based testing has been proposed as a potential alternative angiogenic biomarker in aiding with the diagnostic and management of women with clinical suspicion of preeclampsia (296).

PlGF is thought to induce nonbranching angiogenesis leading to a low-resistance placental vascular network. In a healthy pregnancy, PlGF increases with progressing gestation, with concentrations peaking at 26 to 30 weeks and declining towards term (297). In preeclampsia, a decrease in the circulating PlGF concentration has been found to contribute towards the observed angiogenic imbalance that is implicated in the clinical features of preeclampsia (297, 298). Based on this understanding of the pathophysiology of preeclampsia, the National Institute for Health and Care Excellence (NICE, UK) has released specific diagnostics guidance relating to PlGF-based testing and has recommended the potential use of two PlGF-based tests (DELFIA Xpress PLGF 1-2-3 or Triage PLGF test) with standard clinical assessment to help decide on care (to help rule in or rule out preeclampsia) in women with suspected preterm (between 20 weeks and 36 weeks and 6 days of pregnancy) preeclampsia (NICE Guidelines 2022).

Summary of evidence and rationale for recommendation

A total of three studies, 2 prospective cohort studies and 1 RCT were reviewed for this analysis (296, 298, 299).

The first prospective cohort study by Chappell *et al* (PELICAN 2013) examined the use of Triage PlGF (Alere™) in 625 women (596 women with singleton pregnancies and 29 with multi-gestational pregnancies) 20 to 40+6 weeks of gestational with clinical suspicion of preeclampsia in predicting the risk of preterm delivery and risk of delivery within 14 days of testing. Data was presented based on a PlGF value of <100 pg/ml or at <5th centile for gestation (296).

The second prospective cohort study by Barton *et al* (PETRA 2019) examined the use of Triage PlGF (Alere™) in 753 women (680 women with singleton pregnancies and 73 with multi-gestational pregnancies) < 35 weeks of gestation with clinical suspicion of preeclampsia in predicting the onset of preeclampsia and risk of delivery within 14 days of testing. Data was presented based on PlGF value of <100pg/ml (298).

The single RCT to date by Duhig *et al* (PARROTT 2019) examined the clinical application of PlGF based testing (Alere™) in women with singleton pregnancies with clinical suspicion of preeclampsia between 20 – 36+6 weeks of gestation (299).

All three studies were partly funded by Alere, the manufacturers of the utilised PlGF-based testing kits. This was factored into the risk of bias assessment of these studies.

Given the heterogeneity of these studies, the key outcomes are presented separately in Tables 4.3.1 and 4.3.2. Both prospective cohort studies demonstrated a modest positive predictive value at 0.44 and 0.68 respectively in predicting preeclampsia and delivery within 14 days of testing with a cut off of <100pg/ml. The negative predictive value, however, was good at 0.98 and 0.90 respectively. The single RCT examined demonstrated shorter duration to diagnosis of preeclampsia (in mean days) 1.9 vs 4.1 (RR -2.20, CI -2.94 to -1.46) and less outpatient visits (in mean frequency) 6.14 vs 9.44 (RR -3.30, CI -3.39 to-3.21) in the group where the outcome of PlGF-based testing (with a cut off of <100pg/ml) was used in the clinical management of women with clinical suspicion of preeclampsia. There was no difference in the gestation of delivery, rate of preterm delivery or rate of planned delivery.

Study	Sample size	Clinical use of PlGF-based testing	Predictive value	Sensitivity (CI)	Specificity (CI)	Quality of evidence
Chappell *et al*	625	Cut off of <100pg/ml in predicting preeclampsia requiring delivery within 14 days of testing	PPV 0.44 (0.36-0.52) NPV 0.98 (0.93-1.00)	0.96 (0.89-0.99)	0.56 (0.49-0.63)	LOW
		Cut off of <100pg/ml in predicting preterm delivery (<37 weeks)	PPV 0.36 (0.26-0.44) NPV 0.94 (0.80-0.99)	0.95 (0.83-0.99)	0.32 (0.22-0.42)	LOW
		Cut off of <5th centile for gestation in predicting preeclampsia requiring delivery within 14 days of testing when tested at <35 weeks of gestation	PPV 0.43 (0.36-0.51) NPV 0.98 (0.93-1.00)	0.96 (0.89-0.99)	0.55 (0.48-0.61)	LOW
		Cut of off <5th centile for gestation in predicting preeclampsia requiring delivery within 14 days of testing when tested at 35 to 36+5weeks of gestation	PPV 0.65 (0.53-0.76) NPV 0.69 (0.57-0.80)	0.70 (0.58-0.81)	0.64 (0.52-0.75)	LOW
		Cut of off <5th centile for gestation in predicting preeclampsia requiring delivery within 14 days of testing when tested at ≥37 weeks of gestation	PPV 0.65 (0.53-0.75) NPV 0.70 (0.62-0.78)	0.57 (0.46-0.78)	0.77 (0.68-0.84)	LOW
Barton *et al*	753	Cut off of <100pg/ml in predicting preeclampsia and delivery within 14 days of testing	PPV 0.68 (CI N/A) NPV 0.90 (CI N/A)	0.92 (CI N/A)	0.63 (CI N/A)	LOW
		Cut off of <100pg/ml in predicting preterm delivery (37 weeks)	PPV 0.93 (CI N/A) NPV 0.64 (CI N/A)	0.82 (CI N/A)	0.85 (CI N/A)	LOW

Table 4.3.1 : Key outcomes from the two prospective cohort studies examined

Outcome	Risk Ratio/Mean Difference	Confidence interval	Quality of evidence
Time to diagnosis of preeclampsia	**-2.20**	**-2.94 to -1.46**	**LOW**
Composite maternal outcome *	0.78	0.44-1.39	LOW
Planned delivery	1.04	0.94-1.16	MODERATE
Preterm delivery	1.09	0.93-1.27	MODERATE
Mean outpatient visits	**-3.30**	**-3.39 to -3.21**	**MODERATE**
Composite perinatal outcome **	0.96	0.74-1.24	MODERATE
Gestation age of delivery	-0.20	-0.57 to 0.17	LOW
NICU admission	1.04	0.87-1.24	LOW

Table 4.3.2 : Key outcome from single RCT examined

Based on the limitations and heterogeneity with the current data, more randomised controlled studies on the clinical application of PlGF-based testing are required prior to clinical implementation of PlGF-based testing in Australia and New Zealand.

Cost analysis and accessibility

At the time of this review, PlGF-based testing is not available in Australia or New Zealand.

In the United Kingdom, the Triage PlGF kit costs £1,000 for 25 tests (£40 per test). Based on this, it is estimated to cost approximately AUD$68 and NZ$77 per test. The cost per test used in the economic model (incorporating additional cost components such as machine costs, reagents, service charges, training and staff costs) was £49.58 per test (~AUD$84.33 and NZ$95.64 respectively)(NICE Guidelines 2022).

A cost analysis study in the UK estimated a cost saving of £149 per patient with the use of PlGF-based testing (~ AUD$253.99 and NZ$287.40)(300)

Recommendation by other guidelines

Guideline	Recommendation
ISSHP 2022	Where angiogenic marker testing is available, the lack of angiogenic imbalance, as assessed by normal PlGF (≥ 5th centile for gestational age) suggests that there is no uteroplacental dysfunction
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2022 (updated)	The Triage PLGF Test (<100pg/ml) can be used at the point of care and in the laboratory. The test is used with other clinical information to help diagnose preterm pre-eclampsia, and as an aid in the prognosis of birth, in women who are between 20 weeks and 35 weeks pregnant with signs and symptoms of preeclampsia.
SOMANZ 2015	No recommendation made

Research opportunities

More data on the following aspects of the use of the PlGF-based testing are required:

- Data on the use of PlGF-based testing in multi-gestational pregnancies compared to singleton pregnancies
- Acceptable cut off of PlGF-based testing : <5th centile for gestational age vs <100pg/ml
- Australian and New Zealand based data on the use of PlGF-based testing

* Combined incidence of seizure, CVA, acute kidney injury, pulmonary oedema, intubation

** Combined incidence of any grade of intraventricular haemorrhage, seizure, retinopathy of prematurity, respiratory distress symptom, bronchopulmonary dysplasia, necrotising enterocolitis

PART 5: Management of Chronic Hypertension and Gestational Hypertension

5.1 Blood pressure target in women with chronic or gestational hypertension

Recommendation

5.1 Women with gestational or chronic hypertension should have blood pressure control to a target of ≤135/85mmHg. (1C)

Description of intervention

Blood pressure control in women with pre-existing chronic hypertension or gestational hypertension have been found to correlate with maternal and fetal outcomes (301).

This analysis examined the difference in outcomes between tight blood pressure control (≤135/85mmHg) against less tight blood pressure control (>135/85mmHg) in women with non-preeclamptic hypertension. Women with multi-gestational pregnancy, underlying renal disease and established preeclampsia were excluded from this analysis.

Summary of evidence, risk of harm and quality of evidence

A total of 4 RCTs with a combined sample size of ~1,810 participants in each arm were examined in this analysis (302-305).

Women with tight blood pressure control (≤135/85mmHg) were found to have a lower rate of severe hypertension (>160/110mmHg)(RR 0.71, CI 0.58-0.86), preeclampsia (RR 0.85, CI 0.75-0.95) and preterm delivery (RR 0.88, CI 0.78-0.99)(Table 5.1.1).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Severe hypertension (>160/110mmHg)	**0.71**	**0.58-0.86**	**LOW**
Preeclampsia	**0.85**	**0.75-0.95**	**MODERATE**
Preterm birth	**0.88**	**0.78-0.99**	**MODERATE**
Eclampsia	1.00	0.14-7.07	VERY LOW
Placental abruption	1.01	0.44-2.31	LOW
Maternal ICU admission	0.75	0.35-1.57	LOW
Maternal pulmonary oedema	0.42	0.17-1.04	LOW
Maternal TIA/Stroke	3.03	0.12-74.21	VERY LOW
Maternal death	0.50	0.05-5.47	VERY LOW
Small for gestational age	0.97	0.75-1.26	LOW
Neonatal mortality	2.21	0.50-9.86	VERY LOW
Admission into NICU	0.96	0.83-1.12	MODERATE

Table 5.1.1: Comparison of outcomes between tight and less tight control of blood pressure in women with gestational or chronic hypertension

Rationale for recommendation

Tight blood pressure control (≤135/85mmHg) in women with chronic or gestational hypertension is associated with a lower rate preeclampsia, severe hypertension (≥160/110mmHg) and preterm delivery. This recommendation, however, is not applicable to women with established preeclampsia or in women where individualised blood pressure target maybe required.

Recommendation by other guidelines

Guideline	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Aim for a target blood pressure of 135/85 mmHg
SOMANZ 2015	Aim for levels between 130-140 mmHg systolic and 80-90 mmHg diastolic during pregnancy

Research priorities

- More data on the acceptable lower limits of blood pressure in women with chronic and gestational hypertension is required to minimise the risks associated with iatrogenic hypotension.
- Mora data on the acceptable blood pressure limits in women with secondary causes of hypertension, multi-gestational pregnancy and underlying renal disease is required.

5.2 Use of home BP monitoring (HBPM) in monitoring women with stable chronic or gestational hypertension

Recommendation

5.2.1 Where appropriate, home blood pressure monitoring (HBPM) with the use of a validated blood pressure device can be utilised in women with chronic or gestational hypertension The use of HBPM, however, should not replace the minimum recommend frequency of antenatal review according to the woman's parity and stage of pregnancy. (1B)

5.2.2 Compliance and technique with home blood pressure monitoring (Patient information sheet 5.2.1 and 5.2.2) should be reassessed at each review to ensure ongoing suitability. (PP)

Description of intervention

Women with chronic or gestational hypertension in pregnancy attend increased (~2-4 weekly) outpatient service, either through a clinic or day assessment unit review, for blood pressure monitoring. However, increased outpatient monitoring can be a source of stress and cost for these women in addition to the impact on service implications for healthcare providers.

In recent times, particularly during the COVID-19 pandemic lockdowns, there was increased use of home blood-pressure monitoring (HBPM). Women with chronic or gestational hypertension were often required to monitor and record their blood pressure readings using a validated machine (Table 5.2.1) with instructions from a healthcare professional. Despite its increased clinical utility in recent times, there remains a paucity of data on the use of HBPM in pregnancy. It has also been noted that 30% of pregnant women monitor their own blood pressure with a wide range of devices without informing their healthcare provider, not all of which have been validated in pregnancy. This, therefore, highlights the need for a systematic and evidence based process where women can be provided with guidance on blood pressure measurement techniques and the necessary action based on appropriate blood pressure thresholds.

Validated *	Preferred**	
Microlife BP 3BTO-A	Andon iHealth Track	Omron M400 Intelli IT (HEM-7155T-D)
Microlife WatchBP Home S	Omron Evolv (HEM-7600T-E)	Omron M500 Intelli IT (HEM-7361T-D)
Microlife WatchBP Home	Omron BP760N (HEM-7320-Z)	Omron M6 Comfort (HEM-7321-E)
Microlife WatchBP Home A	Omron M3 Comfort (HEM-7155-ALRU)	Omron M6 Comfort (HEM-7360-E)
Microlife WatchBP Home A BT	Omron X3 Comfort (HEM-7155-EO)	Omron X6 Comfort (HEM-7360-EO)
Omron M7 (HEM-780-E)	Omron M3 Comfort (HEM-7155-E)	Omron X7 Smart (HEM-7361T-ESL)
Omron MIT	Omron M3 Comfort (HEM-7134-E)	Omron M7 Inteli IT (HEM-7361T-EBK)
Omron MIT Elite	Omron X4 Smart (HEM-7155T-ESL)	Omron M7 Intelli IT (HEM-7322T-E)
	Omron M4 Intelli IT (HEM-7155T-ALRU)	Omron M7 Intelli IT (HEM-7361T-ALRU)
	Omron M4 Intelli IT (HEM-7155T-EBK)	Withings BPM Connect
	Omron M400 Comfort (HEM-7155-D)	Withings BPM Connect Pro

Table 5.2.1 : List of validated and preferred home blood pressure monitoring *devices*
(Source : High Blood Pressure Research Council of Australia (HBPRCA))

Summary of evidence, risk of harm and quality of evidence

A total of 4 RCTs with a sample size of ~ 1,740 women in each arm home blood pressure monitoring vs increased regular antenatal reviews were examined. Women with established preeclampsia were excluded from recruitment into these studies (306-309). Women in all three studies were provided with a validated blood pressure measuring device (Table 5.2.1) and were trained on blood pressure measuring techniques. They were required to measure their blood pressure readings 2-3 times a day (with 3 consecutive readings each time) approximately every alternate day for the duration of the study. Women were provided with the option of recording their readings in a logbook or into an electronic application. Women were also provided with an instruction sheet on the required actions for blood pressure reading above a set threshold was reached.

A comparison between HBPM and regular care demonstrated a lower number of antenatal visits (-2.9 (CI -3.86 to -1.94)) with an increase in frequency of blood pressure monitoring (in weeks) (3.10 (CI 2.09-4.11)) (Table 5.2.2) in the HBPM group. There was no difference in other outcomes of interest (Table 5.2.2).

* Validated devices: have passed established validation procedures that have been checked and approved by the STRIDE BP Scientific Advisory Board.

** Preferred devices: are upper-arm cuff devices with at least one STRIDE BP approved validation study, which was published within the last 10 years and used a recent protocol (AAMI/ESH/ISO 2018; ANSI/AAMI/ISO 2013 or 2009; ESH-IP 2010).Preferred devices for home use should also allow automated storage of multiple readings, or mobile phone, PC or internet link connectivity enabling data transfer.

Outcome	Risk Ratio/Mean Difference	Confidence interval	Quality of evidence
Number of antenatal visits	**-2.9**	**-3.86 to -1.94**	**LOW**
Frequency of blood pressure monitoring (weeks)	**3.10**	**2.09-4.11**	**LOW**
Preeclampsia	1.16	0.96-1.40	MODERATE
Composite adverse maternal outcomes*	0.74	0.51-1.06	MODERATE
Maternal ICU admission	1.54	0.06-37.25	VERY LOW
Preterm delivery	1.15	0.37-3.55	LOW
Need of intravenous antihypertensives prior to delivery	5.66	0.32-100.43	VERY LOW
Clinically confirmed severe hypertension (>160/110)	1.15	0.95-1.39	MODERATE
Time to diagnosis of clinically confirmed severe hypertension (in minutes)	-1.90	-4.51 to 0.71	VERY LOW
Emergency delivery (for hypertension)	1.07	0.90-1.28	MODERATE
Antihypertensive use at 34 weeks of gestation	0.79	0.57-1.10	MODERATE
Admission into NICU	1.01	0.87-1.18	MODERATE
Stillbirth	1.49	0.51-4.36	LOW

5.2.2 : Comparison of outcomes between home blood pressure monitoring vs increased outpatient antenatal reviews

Rationale for recommendation

The current evidence suggests that HBPM with a validated device (Table 5.2.1) can be a safe alternative in monitoring blood pressure in women with chronic or gestational hypertension. This recommendation is not applicable to women with established preeclampsia and in women who may not be suitable for HBPM. The use of HBPM should not replace the minimum recommend frequency of antenatal review according to the woman's parity and stage of pregnancy . Compliance and technique with home blood pressure monitoring (Patient information sheet 5.2.1 and 5.2.2) should be reassessed at each review to ensure ongoing suitability.

Recommendation by other guidelines

Guideline	Recommendation
ISSHP 2022	Once BP is found to be elevated in a clinical setting (i.e., clinic/office, obstetrical day unit, or hospital inpatient), in the absence of pre-eclampsia, 'out-of-office' BP monitoring is advised.
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	No recommendation made
SOMANZ 2015	No recommendation made

Research priorities

More Australian and New Zealand data on the utility and safety of home blood pressure monitoring is required.

How to measure your blood pressure at home

- Remember to rest for 5-10 minutes before you start measuring your blood pressure
- Measure your blood pressure in a quiet and relaxed environment with minimal distractions
- Avoid talking while measuring your blood pressure readings
- Use the techniques in the picture when measuring your blood pressure
- Take 2-3 readings, about 2 minutes apart as instructed by your doctor
- Record your readings in a logbook with the date and time you measured your blood pressure or enter your readings into the app provided by your doctor
- Refer to the instruction sheet from your doctor for the appropriate action for your blood pressure reading

Adapted from the American Medical Association for SOMANZ's Hypertension in Pregnancy Guideline

CLICK HERE FOR A PDF COPY

Patient information sheet 5.3.1 : Instructions on home blood pressure monitoring (PDF)

* Combined maternal outcomes of death, TIA/CVA, acute kidney injury, pulmonary oedema, ICU admission

HOME BLOOD PRESSURE LOG

SOMANZ
SOCIETY OF OBSTETRIC MEDICINE OF AUSTRALIA AND NEW ZEALAND

- Always measure your blood pressure with an accurate machine- speak to your doctor to check your machines is OK.
- Sit in a relaxed position with the cuff at heart level
- Always measure the blood pressure at least twice.
- Discard the first reading and write down the second and/or the third reading

My doctor has asked me to check my blood pressure_____ times a day /week

Date	Time	Systolic Blood Pressure (Top number)	Diastolic Blood Pressure (Bottom number)	Notes
E.g., 7/10/22	9:36am	128	75	

My doctor has asked me to _____ if the systolic blood pressure is more than _____

My doctor has asked me to _____ if the diastolic blood pressure is more than _____

CLICK HERE FOR A PDF COPY

Patient information sheet 5.2.2 :
Sample home blood pressure log (PDF)

5.3 : Antihypertensives for the management of stable hypertension (chronic, gestational hypertension and stable non-severe preeclampsia)

Recommendation

5.3.1 Oral agents labetalol, methyldopa and/or nifedipine can be used in managing stable hypertension in pregnancy (gestational hypertension, chronic hypertension, non-severe hypertension in preeclampsia). The choice of agent should be individualised based on women's clinical history and through a shared informed decision-making process (Flow chart 5.3). (2C)

5.3.2 In addition to the agents above, oral hydralazine can also be used in managing stable hypertension in pregnancy. (PP)

This recommendation is also applicable to the management of stable non-severe hypertension in women with preeclampsia (Recommendation 6.1)

Description of intervention

A wide variety of medications have been advocated for lowering blood pressure in pregnant women with hypertension, and each antihypertensive has different potential side-effects and adverse events.

In this analysis, agents from three commonly used drug-groups; beta-blockers, centrally acting alpha-2-agonist and calcium channel blockers were examined.

Summary of evidence, risk of harm and quality of evidence

A total of 23 RCTs were examined in reviewing the antihypertensives used in the management of stable hypertension in pregnancy. A summary of the examined studies is provided in Table 5.3.1. Given the heterogeneity in the antihypertensives used, sub-analyses based on the drug-group of antihypertensives were done:

- 15 RCTs compared the use of beta blockers (2 x atenolol, 2 x oxprenolol, 1 propranolol, 1 x metoprolol, 9 x labetalol) to methyldopa (310-324)
- 6 RCTs compared the use of calcium channel blockers (2x immediate release nifedipine, 2 x controlled release nifedipine, 1x nimodipine) to methyldopa (325-330)
- 2 RCTs compared the use of calcium channel blockers (1x immediate release nifedipine, 1 x control release nifedipine) to beta blockers (labetalol) (331, 332)
- 2 RCTs used Hydralazine as a second line agent when blood pressure targets were not adequately achieved

Study	Intervention	Comparator	Sample size	Note
Fidler *et al* 1983	Oxprenolol 80mg twice a day up to 320mg twice a day	Methyldopa 250mg three times a day up to 1,000mg three times a day	100	Hydralazine added to both groups if BP inadequately controlled
Gallery *et al* 1985	Oxprenolol 40mg twice a day up to 320mg twice a day	Methyldopa 250mg twice a day up to 1,000mg three times a day	183	Hydralazine added to both groups if BP inadequately controlled
Livingstone *et al* 1983	Propranolol 30mg daily up to 160mg daily (in divided doses)	Methyldopa 500mg daily up to 1,000mg daily (in divided doses)	28	
Oumachigui *et al* 1992	Metoprolol 50mg twice a day up to 150mg daily (in divided doses)	Methyldopa 250mg three times a day up to 2,000mg daily (in divided doses)	30	
Voto *et al* 1985	Atenolol 50mg daily up to 250mg daily	Methyldopa 750mg daily up to 2,000mg daily (in divided doses)	60	
Thorley *et al* 1984	Atenolol 100mg daily (in divided doses)	Methyldopa 750mg daily (in divided doses)	60	
Plouin *et al* 1987	Labetalol 200mg twice a day up to 600mg twice a day	Methyldopa 250mg twice a day up to 750mg twice a day	188	
Srivastava *et al* 2013	Labetalol 100mg three times a day	Methyldopa three times a day	180	
Subhedar *et al* 2013	Labetalol 100mg three times a day, doubled every 48 hours until BP controlled	Methyldopa 250mg three times a day, doubled every 48 hours until BP controlled	180	
Lamming *et al* 1980	Labetalol 400mg daily up to 800mg daily (in divided doses)	Methyldopa 750mg daily up to 1,500mg daily (in divided doses)	26	
Lardoux *et al* 1988	Labetalol 400mg daily up to 1,200mg daily (in divided doses)	Methyldopa 500mg daily up to 1,500mg daily (in divided doses)	42	
Magee *et al* 2016	Labetalol. Dose titration not specified	Methyldopa. Dose titration not specified	481	
Molvi *et al* 2012	Labetalol 100mg twice a day up to 2,500 daily (in divided doses)	Methyldopa 250mg twice a day up to 2,000mg daily (in divided doses)	149	

Continued over >

Study	Intervention	Comparator	Sample size	Note
Rezk *et al* 2020	Labetalol 100-300mg daily (in divided doses)	Methyldopa 1,000-2,000g daily (in divided doses)	324	
Sibai *et al* 1990	Labetalol 300mg daily up to 2,400mg daily (in divided doses)	Methyldopa 750mg daily up to 4,000mg daily (in divided doses)	200	
Borghi *et al* 2000	Control-release nifedipine 30mg daily up to 60mg daily	Methyldopa 500mg daily up to 1,000mg daily (in divided doses)	20	
Eloff *et al* 1993	Control-release nifedipine 30mg daily	Methyldopa 750mg daily	26	Dose adjustment not detailed
Salama *et al* 2019	Immediate-release nifedipine 20-40mg daily (in divided doses)	Methyldopa 1,000-2,000mg daily (in divided doses)	326	
Aparna *et al* 2013	Immediate-release nifedipine 10mg four times a day	Methyldopa 250mg three times a day	100	
Banerjee *et al* 2002	Nimodipine 30mg four times a day	Methyldopa 250mg four times a day	110	
Jannet *et al* 1994	Nicardipine 20mg three times a day	Metoprolol controlled-release 200mg daily	100	
Webster *et al* 2017	Controlled-release nifedipine 10mg twice a day up to 40mg twice a day	Labetalol 100mg twice a day to up 600mg three times a day	114	
Babbar *et al* 2013	Immediate-release nifedipine 10mg twice a day	Labetalol 100mg twice a day	160	Dose adjustment not detailed

Table 5.3.1: Summary of studies examined

Oral beta blocker versus oral methyldopa

A total of 15 RCTs with a combined sample size of 2,228 women were examined in this analysis. There was no difference in the outcomes examined (Table 5.3.2).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Severe hypertension (>160/110)	1.08	0.82-1.42	MODERATE
Preeclampsia	1.01	0.77-1.32	MODERATE
Small for gestational age newborn	1.17	0.67-2.01	VERY LOW
Preterm delivery	1.24	0.97-1.58	MODERATE
Need for additional antihypertensives	1.03	0.56-1.91	MODERATE
Antenatal hospitalisation for BP control	0.69	0.44-1.08	MODERATE
Placental abruption	1.30	0.60-2.79	LOW
Maternal side effects	0.22	0.02-2.09	LOW
Admission into NICU	1.10	0.70-1.73	MODERATE
Neonatal hypoglycaemia	1.10	0.60-2.00	LOW
Neonatal bradycardia	3.00	0.12-72.18	VERY LOW
Neonatal jaundice	1.62	0.91-2.90	MODERATE

5.3.2: Comparison of outcomes between oral beta blockers and methyldopa

Oral calcium channel blocker versus oral methyldopa

A total of 6 RCTs with a combined sample size of 682 women were examined in this analysis. There was no difference in the outcomes examined (Table 5.3.3).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Severe hypertension (>160/110)	0.66	0.25-1.73	LOW
Preeclampsia	0.91	0.58-1.43	MODERATE
Small for gestational age newborn	0.83	0.35-2.00	LOW
Preterm delivery	1.08	0.68-1.72	MODERATE
Need for additional antihypertensives	0.62	0.30-1.28	LOW
Antenatal hospitalisation for BP control	1.10	0.72-1.70	MODERATE
Placental abruption	1.25	0.55-2.80	LOW
Admission into NICU	1.22	0.79-1.89	MODERATE

Table 5.3.3 : Comparison of outcomes between oral calcium channel blockers and methyldopa

Oral calcium channel blockers versus oral labetalol

A total of 2 RCTs with a combined sample size of 274 women were examined in this analysis. There was no difference in the outcomes examined (Table 5.3.4).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Severe hypertension (>160/110)	2.14	0.96-4.80	VERY LOW
Preeclampsia	0.91	0.49-1.69	LOW
Small for gestational age newborn	0.96	0.55-1.68	LOW
Preterm delivery	0.62	0.34-1.15	MODERATE
Need for additional antihypertensives	1.17	0.76-1.80	MODERATE
Placental abruption	0.35	0.01-8.30	VERY LOW
Maternal side effects	1.39	0.85-2.28	LOW
Admission into NICU	0.90	0.50-1.62	LOW
Neonatal hypoglycaemia	0.76	0.29-2.05	LOW

Table 5.3.4 : Comparison of outcomes between oral calcium channel blockers and oral labetalol

Rationale for recommendation

The current data suggests a lack of difference in the outcomes between the agents examined. Intravenous IV hydralazine is often used in managing acute hypertension (Recommendation 6.2), however, oral hydralazine can also be used as a second line agent in managing hypertension in pregnancy (310, 311)

Given this, the choice of agent should be individualised based on the woman's clinical history and should be done through a shared informed decision-making process (Flow chart 5.3).

Recommendation by other guidelines

Guideline	Recommendation
ISSHP 2022	Non-severe hypertension should be treated with the first line agents, methyldopa, labetalol, nifedipine
Australian Pregnancy Care Guidelines 2019	No recommendations made
NICE 2019	Consider labetalol to treat hypertension in pregnant women. Consider nifedipine for women in whom labetalol is not suitable, or methyldopa if both labetalol and nifedipine are not suitable. Base the choice on any pre-existing treatment, side-effect profiles, risks (including fetal effects) and the woman's preference.
SOMANZ 2015	In terms of lowering blood pressure in preeclampsia, a number of drugs have demonstrated safety and efficacy. First line drugs include methyldopa, labetalol and oxprenolol. Second line agents are hydralazine, nifedipine and prazosin. These same agents may be used for treating gestational or chronic hypertension.

Research priorities

More data on other commonly used agents such as hydralazine and clonidine would be beneficial.

Clinical correlation between antihypertensive agents and angiogenic/inflammatory biomarkers would be useful in understanding the influence of antihypertensives on placental development in the first trimester.

Target BP ≤ 135/85

↓

	Antihypertensives	Class of agent	Dose (Start from low dose and titrate as required)	Caution
FIRST LINE^†	Oral Methyldopa	Alpha blocker	250-750mg three to four times a day	Avoid in women with a history of depression, anxiety or postpartum depression
	*Oral Clonidine	Alpha blocker	75-300 micrograms three to four times a day	Risk of rebound hypertension with sudden withdrawal
	Oral Labetalol	Beta blocker	100-400mg three to four times a day	Avoid in women with a history of asthma or chronic airway limitation
	Oral Nifedipine SR	Calcium channel blocker	20-60mg (slow release) twice a day	Avoid in women with aortic stenosis, may cause peripheral oedema
	*Oral Nifedipine IR	Calcium channel blocker	10-30mg (immediate release) three times a day	Avoid in women with aortic stenosis, may cause peripheral oedema
	Oral Hydralazine	Vasodilator	12.5-50mg three to four times a day	May cause headache, tachycardia if given as first line (without concurrent alpha, beta or calcium blockade)

↓

SECOND & THIRD LINE	Consider adding a second or third agent from another class (Second line agent can be initiated prior to reaching the maximum dose of the first line agent)

SR= slow release, IR= immediate release

* Access and supply may be limited in certain parts of Australia and New Zealand

^ Choice of agent should be individualised based on women's medical history and through an informed shared decision-making process

† Oxprenolol is no longer accessible in Australia and New Zealand. Where it remains available, a dose of 20-60mg three times a day can be used. Oxprenolol should be avoided in women with a history of asthma or chronic airway limitation

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Flowchart 5.3 : Management of chronic, gestational and non-severe hypertension preeclampsia (PDF)

5.4 Timing of birth in women with chronic hypertension or gestational hypertension

Recommendation

5.4 There remains inadequate data to suggest the need for planned birth between 36 and 37^{+6} weeks of gestation in women with gestational or chronic hypertension. The decision on the timing of birth should be individualised based on the patient's clinical and obstetric history and through a shared, informed decision-making process. (2D)

Recommendation on timing of delivery in women with established preeclampsia is discussed separately (Recommendation 6.3)

Description of intervention

Planned birth, either in the form of induction of vaginal birth or planned caesarean section is occasionally proposed in women with chronic hypertension or gestational hypertension to minimise the risk of escalation of hypertension or transition to preeclampsia.

This analysis was aimed at examining the evidence on the benefit and risk with planned delivery between 36-37^{+6} weeks in women with stable chronic hypertension or gestational hypertension.

Summary of evidence, risk of harm and quality of evidence

A total of 2 RCTs with a combined samples size of ~350 women in each arm examined the maternal and fetal outcome with planned delivery between 36-37^{+6} weeks of gestation in women with stable chronic or gestational hypertension (333, 334).

A total of 2 retrospective studies with a combined sample size of 4,814 women in the expectant management group were compared to 661 women who had planned birth prior to 38 weeks of gestation (335, 336).

Analysis of all 4 studies excluded women with established preeclampsia, unstable or poorly controlled hypertension and women who had other maternal or fetal indications for planned birth.

Planned birth between 36-37^{+6} weeks in women with stable chronic or gestational hypertension was associated with a higher rate of composite fetal outcomes (combined incidence of small for gestational age, NICU admission and perinatal mortality) (Table 5.4.1) however, this was based on data from a single RCT (sample size of 76 women) with very low certainty of evidence. There was no statistically significant difference with other key outcomes of interest (Table 5.4.1).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Composite fetal outcomes*	1.50	1.06-2.11	VERY LOW
Preeclampsia	0.92	0.49-1.76	VERY LOW
Severe Hypertension (>160/110)	1.67	0.43-6.49	VERY LOW
Placental abruption	1.00	0.22-4.65	VERY LOW
Small for gestational age	2.11	0.73-6.16	VERY LOW
Admission to NICU	1.96	0.98-3.94	LOW

Table 5.4.1: Comparison of outcomes between expectant management and planned delivery between 36-37^{+6} weeks

Based on the data from 2 retrospective studies, planned birth before 38 weeks in women with stable chronic or gestational hypertension was associated with a lower rate of preeclampsia with a RR of 0.01 (CI 0.00- 0.15) (very low certainty). This, however, was based on data from two retrospective studies with very low certainty of evidence.

Rationale for recommendation

There remains significant paucity of data on the benefit and risk of planned birth between 36-37^{+6} weeks in women with stable chronic or gestational chronic hypertension.

Therefore, the decision on the timing of birth, if indicated, should be individualised based on the patient's clinical and obstetric history and through a shared, informed decision-making process.

The recommendation above is not applicable to women with established preeclampsia or to women who require induction of labour for other medical or fetal indications.

Appropriate maternal and fetal surveillance should be undertaken to ensure that there are no new maternal or fetal indications to recommend earlier birth.

Recommendation by other guidelines

Guideline	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Do not offer planned early birth before 37 weeks to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment, unless there are other medical indications.
SOMANZ 2015	A team approach, involving obstetrician, midwife, neonatologist, anaesthetist, and physician provides the best chance of achieving a successful outcome for mother and baby

Research priorities

More RCT data on maternal and fetal outcomes are required in examining the appropriate timing of birth in women with stable chronic or gestational hypertension.

* Combined incidence of small of gestational age, NICU admission and perinatal mortality

5.5 Utility of ABPM in pregnancy

Recommendations

5.5.1 Ambulatory blood pressure should be considered to exclude white coat hypertension in women with isolated hypertension in pregnancy (in the absence of an established diagnosis of preeclampsia, chronic hypertension, or gestational hypertension). (PP)

5.5.2 Where there are poor pregnancy outcomes in current or previous pregnancies that could not be explained by other factors, we suggest an ABPM in the post-partum period to assess for masked hypertension. (PP)

Description of intervention

Ambulatory blood pressure monitoring (ABPM) has an established role in the diagnosis and management of hypertension in the non-pregnant population, however, the role of ABPM in pregnancy remains unclear (337). The physiological changes that occur in pregnancy alters thresholds of normal blood pressure in pregnancy and have in part, contributed to the ambiguity of blood pressure variations in pregnancy. Given the observed physiological changes, several publications have explored and proposed various normal ABPM cutoffs through differing stages of pregnancy (338, 339).

ABPM plays a pivotal role in the identification of women with white coat hypertension (WCH) and masked hypertension (MH). However, underdiagnosis of WCH and MH due to underutilisation of ABPM in pregnancy remains a major barrier in identifying the true effect of these diagnoses on pregnancy outcomes. Additionally, availability and access to validated and accurate ABPM machines are added barriers that contribute towards underutilisation of ABPM in pregnancy in identifying women with WCH and MH (340). The ABPM monitors that are currently validated for use in pregnancy are as listed in Table 5.5.1.

Summary of evidence and rationale for recommendation

At the time of this review, there remains a paucity in randomised controlled trials to assess for obstetric outcomes in women with WCH and MH. As such, a total of 11 observational cohort studies were examined in assessing the obstetric outcomes in women with WCH and MH in comparison to normotensive pregnant women.

Monitor	Validation Protocol	Population
Spacelabs 90207	BHS, AAMI, Other	Pregnancy with and without hypertension
Welch Allyn QuietTrak	BHS, AAMI	Pregnancy with and without hypertension*
BP Lab	ESH, BHS	Pregnancy with and without hypertension

Table 5.5.1 : Validated Ambulatory Blood Pressure Monitors.

This analysis was aimed at examining the obstetric outcomes in with women with WCH and MH in understanding the value of ABPM assessment in pregnancy.

White Coat Hypertension versus Normotension

Three studies (341-343) compared women with WCH to normotensive pregnant women. Women with WCH were diagnosed based on a normal ABPM following an elevated blood pressure reading in the clinic. Pregnant women with WCH were not found to have significantly different outcomes in comparison to normotensive women (Table 5.5.2). It is, however, important to note that there was significant heterogeneity in the gestation at which these women underwent ABPM assessment. The majority on the women in these studies underwent the ABPM assessment in the third trimester.

Outcome	Risk Ratio/Mean Difference	Confidence interval	Quality of evidence
Preeclampsia	0.6	0.26-1.42	VERY LOW
Gestational Hypertension	0.57	0.19-1.70	LOW
Small for gestational Age	0.64	0.09-4.62	VERY LOW
Neonatal Weight (g)	65.34g lower	252.9g lower- 122.2g higher	VERY LOW
Caesarean Section	0.08	0.00-1.63	VERY LOW
Preterm Delivery	1.07	0.06-17.56	VERY LOW
Weeks at Delivery (weeks)	MD 1.15 higher	1.14 lower- 3.44 higher	VERY LOW
Neonatal Death	0.4	0.02-6.58	VERY LOW

Table 5.5.2 : Pregnancy related outcomes of women with white coat hypertension compared to women that are normotensive. MD- Mean difference.

* Performance different in women with preeclampsia compared to pregnancy alone (BHS: D/D, AAMI: F/F)

Masked Hypertension versus Normotension

Three studies (342-344) compared obstetric outcomes between normotensive pregnant women to women who were found to have MH (normal clinic readings but elevated ABPM). Women diagnosed with MH were found to have a higher rate of preeclampsia, small for gestational age newborn, higher caesarean section rate and shorter gestation (Table 5.5.3). It is however important to note that there was significant heterogeneity in the gestation at which the women in the study underwent the ABPM assessment.

Outcome	Risk Ratio/Mean Difference	Confidence interval	Quality of evidence
Preeclampsia	**2.99**	**1.72-5.22**	**VERY LOW**
Small for gestational Age	**3.20**	**1.43-7.20**	**VERY LOW**
Neonatal Weight (g)	**374.6g lower**	**641g lower- 108.2g lower**	**VERY LOW**
Caesarean Section	**2.06**	**1.36-3.14**	**VERY LOW**
Preterm Delivery	2.64	0.95-7.34	VERY LOW
Weeks at Delivery (weeks)	**MD 0.8 lower**	**1.4 lower- 0.19 lower**	**VERY LOW**

Table 5.5.3: Pregnancy related outcomes of women with masked hypertension compared to women that are normotensive. MD- Mean difference.

True Hypertension versus White Coat Hypertension

Five (341, 343-346) studies compared obstetric outcomes in women with true chronic hypertension to women with WCH. Women with WCH were found to have a lower risk of preeclampsia, gestational hypertension, small for gestational age newborn, preterm delivery and greater gestational age at delivery (Table 5.5.4). It is again important to note that there was marked heterogeneity in the gestation at which the ABPM assessment was undertaken.

Outcome	Risk Ratio/Mean Difference	Confidence interval	Quality of evidence
Preeclampsia	**0.24**	**0.12-0.50**	**VERY LOW**
Gestational Hypertension	**0.36**	**0.15-0.86**	**VERY LOW**
Small for gestational Age	**0.46**	**0.23-0.90**	**VERY LOW**
Neonatal Weight (g)	298.7g higher	39.3g lower- 636.7g higher	VERY LOW
Caesarean Section	0.85	0.64-1.12	VERY LOW
Preterm Delivery	**0.45**	**0.26-0.8**	**VERY LOW**
Weeks at Delivery (weeks)	**MD 1.15 higher**	**0.37 higher – 1.93 higher**	**VERY LOW**
Neonatal Death	0.41	0.02-6.30	LOW

Table 5.5.4: Pregnancy related outcomes of women who are truly hypertensive compared to women with white coat hypertension. MD- Mean difference.

Rationale for recommendations

Obstetric outcomes in women with WCH and MH appear to differ from normotensive women. At present, there remains limited data on the appropriate timing of ABPM assessment and the appropriate interventions in managing these women in pregnancy. However, based on the current known knowledge, we recommend utilising ABPM to rule out WCH in women with isolated hypertension in pregnancy (in the absence of an established diagnosis of preeclampsia, chronic hypertension or white coat hypertension). We also recommend screening for MH in the post-partum period in women with unexplained poor obstetric outcomes in their pregnancy.

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	HBPM or ABPM if possible, should be used to exclude WCH
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	No recommendation made
SOMANZ 2015	No recommendation made

Research opportunities

More data on homogenised normal cut off values for ABPM assessment (based on obstetric outcomes) will help improve the clinical utility of ABPM in pregnancy.

More RCT based data in understanding the incidence of masked and white coat hypertension and their effects on pregnancy outcomes will be beneficial.

PART 6: Management of Preeclampsia

Part 6.1 : Please refer to Recommendation 5.3 for the mamagement of stable (non-severe) hypertension in pregnancy

6.2 : Management of acute hypertension (≥160/110 mmHg) in preeclampsia

Recommendations

6.2.1 Short acting agents such as IV hydralazine, IV labetalol, oral immediate release (IR) nifedipine or IV diazoxide should be used in managing acute hypertension (Flow chart 6.2). The choice of short acting antihypertensive should be based on the unit's access and familiarity with agent of choice. (2C)

6.2.2 Acute (severe) hypertension should be treated to a target of <160/110 mmHg. (PP)

Refer to recommendation 6.7 and Flowchart 6.7 for recommendations on the use of magnesium sulphate where indicated as part of management of acute (severe) hypertension

Description of intervention

Acute (severe) hypertension in pregnancy is defined as sustained blood pressure of ≥160/110mHg. Persistent severe hypertension in pregnancy is associated with poor maternal and fetal outcomes which include haemorrhagic stroke, maternal death, eclampsia and placental abruption.

Short acting agents, in both intravenous and oral forms are often used in managing severe hypertension in pregnancy due to their rapid onset of action. This analysis examined the difference between the commonly used drugs, IV labetalol, IV hydralazine, IV diazoxide, oral immediate release (IR) nifedipine, oral labetalol and oral methyldopa, in this setting.

Summary of evidence, risk of harm and quality of evidence

A total of 23 RCTs were reviewed to examine the antihypertensives used to manage acute (severe) hypertension. A summary of the antihypertensives examined in these studies are provided in Table 6.2.1. Sub analyses were conducted based on the group of antihypertensives:

- RCTs compared IV labetalol to IV hydralazine with a combined sample size of 269 women
- 7 RCTs compared IV labetalol to oral immediate release (IR) nifedipine with a combined sample size of 731 women
- 1 RCT compared IV labetalol to IV diazoxide with a sample size of 90 women
- 7 RCTs compared IV hydralazine to oral IR nifedipine with a sample size of 434 women
- 1 RCT compared IV hydralazine to IV diazoxide with a sample size of 97 women
- 2 RCTs compared oral labetalol to oral methyldopa with a combined sample size of 668 women

Study	Intervention	Comparator	Sample size	Target BP
Vigil de Gracia *et al* 2006	IV labetalol 20mg followed by escalating doses of 40 mg, and 80 mg followed by 80 mg every 20 minutes to a maximum of 300mg	IV hydralazine 5mg every 20 minutes to a maximum of 25mg	200	<160/100
Mabie *et al* 1987	IV labetalol 20mg followed by escalating doses of 40 mg, and 80 mg followed by 80 mg every 10 minutes to a maximum of 300mg	IV hydralazine 5mg every 10 minutes maximum of 25mg	19	DBP <100
Ashe *et al* 1987	IV labetalol infusion 200 mg in 200 mL 5% dextrose at 20 mg/hr. Increased every 20 min by 20 mg/hr until DBP 90-100 mmHg, or maximum dose of 160 mg/hr. Then continued for 1 hr.	IV hydralazine 25 mg in 200 mL saline at 3.7 mg/hr. Increased every 20 min by 3.7 mg/hr until DBP 90-100 mmHg, or maximum dose of 15 mg/hr. Then continued for 1 hr.	20	DBP 90-100
Harper *et al* 1991	IV labetalol 100mg single dose	IV hydralazine 10mg single dose	30	Not specified
Raheem *et al* 2012	IV labetalol 20mg followed by escalating doses of 40 mg, and 80 mg followed by 80 mg every 15 minutes to a maximum of 300mg	Oral nifedipine (IR) 10 mg repeated every 15 minutes up to 5 doses	50	≤ 150/100
Wasim *et al* 2020	IV labetalol 20mg followed by escalating doses of 40 mg, and 80 mg followed by 80 mg every 15 minutes to a maximum of 300mg	Oral nifedipine (IR) 10 mg repeated every 15 minutes up to 5 doses	204	≤150/100
Shi *et al* 2016	IV labetalol 20mg followed by escalating doses of 40 mg, and 80 mg followed by 80 mg ever 15 minutes to a maximum of 300mg	Oral nifedipine (IR) 10 mg repeated every 15 minutes up to 5 doses	147	≤ 150/100
Shekhar *et al* 2013	IV labetalol 20mg followed by escalating doses of 40 mg, and 80 mg followed by 80 mg every 15 minutes to a maximum of 300mg	Oral nifedipine (IR) 10 mg repeated every 15 minutes up to 5 doses	60	≤ 150/100
Zulfeen *et al* 2019	IV labetalol 20mg followed by escalating doses of 40 mg, and 80 mg followed by 80 mg every 15 minutes to a maximum of 300mg	Oral nifedipine (IR) 10 mg initially followed by repeated doses of 20 mg every 15 min (total 5 doses to a maximum of 90 mg	120	≤150/100

Continued over >

Study	Intervention	Comparator	Sample size	Target BP
Vermillion *et al* 1999	IV labetalol 20mg followed by escalating doses of 40 mg, and 80 mg followed by 80 mg every 15 minutes to a maximum of 300mg	Oral nifedipine (IR) 10 mg initially followed by repeated doses of 20 mg every 15 min (total 5 doses)	50	<160/100
Satya Laksmi *et al* 2012	IV labetalol 20 mg followed by 40 mg 30 minutes later then two more doses of 80 mg every 30 minutes up to a maximum of 220 mg	Oral nifedipine (IR) 10 mg initially followed by 10 mg every 30 minutes up to a maximum of 50 mg	100	25% reduction of mean arterial BP
Michael *et al* 1986	IV labetalol infusion 200 mg in 200 mL 5% dextrose IV at 0.5 mg/kg/hr to a maximum of 3 mg/kg/hr, to maintain DBP at 85-90 mmHg. Continued until 24 hrs after delivery	IV diazoxide 75 mg IV, repeated every 30 min until BP controlled. Continued until 24 hrs after delivery	90	DBP 85-90
Aali *et al* 2002	IV hydralazine 5-10 mg, repeated until DBP 90-100 mmHg	8 mg sublingual repeated until DBP 90-100 mmHg	126	DBP 90-100
Razaei *et al* 2011	IV hydralazine 5 mg, repeated in 10 mg doses, up to maximum of 5 injections in intervals of 20 min	Oral nifedipine (IR) 10 mg initially followed by repeated doses of 20 mg every 20 min (total 5 doses)	50	150/90-100
Seabe *et al* 1989	IV hydralazine 6.25 mg in 10 mL water IV over 5-10 mins. Repeated after 30 mins if no response	Oral nifedipine (IR) 10 mg. Repeated after 30 mins if no response	33	Not specified
Martins-Consta *et al* 1992	IV hydralazine 5 or 10mg	Oral nifedipine (IR) 10 or 20mg	37	DBP ≤100
De Souza *et al* 1994	IV hydralazine 20mg	10mg sublingual nifedipine	50	DBP ≤110 Dose titration not provided
Sharma *et al* 2017	IV hydralazine 5 mg followed by 10 mg every 20 minutes for a total of 4 doses	Oral nifedipine (IR) 10 mg each every 20 minutes to a maximum of 4 dose	60	<150/100
Adebeyo *et al* 2020	IV hydralazine 10 mg every 30 min up to 5 doses	Oral nifedipine (IR) 20mg every 30 min up to 5 doses	78	SBP 140–150 DBP 90–100
Hennessy *et al* 2007	IV hydralazine 5 mg boluses every 20 min for up to 3 doses, to a maximum dose of 15 mg	IV diazoxide 15 mg boluses every 3 mins until the BP reached target or until 300 mg was given (20 x 15 mg mini-bolus doses) within a 1-hr period	124	<140/90 (<150/100 in women with features of fetal compromise)
Moore *et al* 1982	Oral labetalol 100 mg up to 4 doses.	Oral methyldopa 250mg up to 4 doses	72	Not specified
Easterling *et al* 2019	Oral labetalol 200mg each hour maximum of 600mg	Oral methyldopa single dose of 1,000mg	596	SBP 120-150 DBP 70-100

6.2.1: Summary of studies examined

IV labetalol versus IV hydralazine

A total of 4 RCTs with a combined sample size of 269 women were examined in this sub-analysis (347-350). There was no difference in the outcomes examined between both intravenous agents (Table 6.2.2)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Persistently elevated blood pressure ≥160/110mmHg	1.57	0.66-3.74	LOW
Fetal or neonatal death	0.75	0.17-3.21	LOW
Maternal hypotension	0.20	0.01-4.11	LOW
Any maternal side effects	0.78	0.49-1.23	MODERATE
Placental abruption	0.50	0.05-5.43	VERY LOW
Fetal heart rate deceleration	0.80	0.13-4.95	LOW
Neonatal hypoglycaemia	1.14	0.19-6.94	VERY LOW
Admission into NICU	0.99	0.66-1.49	MODERATE

Table 6.2.2: Comparison of outcomes between IV labetalol and IV hydralazine

IV labetalol versus IV diazoxide

One RCT with a sample size of 90 women compared the use of IV labetalol to IV diazoxide. A higher rate of hypotension was noted with diazoxide (RR 0.06, CI 0.00-0.99), however, this was based on a small sample size with low certainty of evidence (Table 6.3.3)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Persistently elevated blood pressure ≥160/110mmHg	0.50	0.13-1.88	LOW
Fetal or neonatal death	0.14	0.01-2.69	VERY LOW
Maternal hypotension	**0.06**	**0.00-0.99**	**LOW**

Table 6.2.3: Comparison of outcomes between IV labetalol and IV diazoxide

IV labetalol versus oral immediate release (IR) nifedipine

A total of 7 RCTs with a combined sample size of 731 women compared the use of IV labetalol to oral IR nifedipine (351-356). The use of IR nifedipine was associated with a shorter time taken (from time of administration of agent) to achieve target blood pressure (mean time in minutes 29.8 vs 41, CI 1.37-7.04) and fewer doses to achieve target blood pressure (mean doses 2.1 vs 2.6, CI 0.12-0.35) (Table 6.2.4)

Outcome	Risk Ratio/Mean Difference	Confidence interval	Quality of evidence
Eclampsia	1.70	0.75-3.84	MODERATE
Persistently elevated blood pressure ≥160/110mmHg	0.90	0.39-2.07	LOW
Number of doses required to achieve target BP (MD)*	**0.23**	**0.12-0.35**	**HIGH**
Time required to achieve target BP (MD)*	**4.21**	**1.37-7.04**	**MODERATE**
Any maternal side effects	1.39	0.98-1.97	MODERATE
Admission into NICU	0.88	0.64-1.22	HIGH
Maternal admission into ICU	5.00	0.25-99.16	VERY LOW

Table 6.2.4 : Comparison of outcomes between IV labetalol and oral immediate release (IR) nifedipine

Oral immediate release (IR) nifedipine versus IV hydralazine

A total of 7 RCTs with a combined sample size of 434 women were examined in this sub-analysis. There was a lower rate of persistently elevated blood pressure (≥160/110mmHg) (RR 0.49, CI 0.35-0.68) and less number of doses (mean 1.2 vs 1.35, CI -0.52 to -0.02) required to achieve target BP with oral IR nifedipine compared to IV hydralazine (Table 6.3.5). There was no difference in the other outcomes examined (Table 6.2.5)

Outcome	Risk Ratio/Mean Difference	Confidence interval	Quality of evidence
Persistently elevated blood pressure ≥160/110mmHg	**0.49**	**0.35-0.68**	**MODERATE**
Number of doses required to achieve target BP (MD)*	**-0.27**	**-0.52 to -0.02**	**MODERATE**
Time required to achieve target BP (MD)*	5.36	-2.34 to13.06	MODERATE
Fetal or neonatal death	1.48	0.40-5.48	VERY LOW
Maternal hypotension	2.92	0.32-26.90	VERY LOW
Any maternal side effects	0.82	0.60-1.12	MODERATE
Fetal heart rate deceleration	0.33	0.04-2.99	LOW
Admission into NICU	1.64	0.57-4.68	VERY LOW

Table 6.2.5: Comparison of outcomes between oral immediate release nifedipine and IV hydralazine

IV hydralazine versus IV diazoxide

A single RCT with a sample size of 124 women examined the use of IV hydralazine to IV diazoxide (357). In comparison to IV diazoxide, the use of IV hydralazine was associated with a higher rate of persistently elevated blood pressure (RR 2.23, CI 1.22-4.44) and longer time taken to achieve target blood pressure (mean time in minutes 34 mins vs 19 mins, CI 9.37-20.63). The use of IV hydralazine was also associated with a lower rate of target blood pressure achieved (RR 0.64, CI 0.46-0.89)(Table 6.2.6). These findings, however, were based on a single study with a small sample size.

Outcome	Risk Ratio/Mean Difference	Confidence interval	Quality of evidence
Persistently elevated blood pressure ≥160/110mmHg	**2.32**	**1.22-4.44**	**LOW**
Target blood pressure achieved	**0.64**	**0.46-0.89**	**MODERATE**
Time in minutes to achieve target BP (MD)*	**15.00**	**9.37-20.63**	**LOW**
Maternal hypotension	2.91	0.12-69.99	VERY LOW
All maternal side effects	1.10	0.60-2.00	LOW
Non-reassuring CTG during therapy	0.98	0.50-1.93	LOW
Perinatal death	7.42	0.39-140.06	VERY LOW
Stillbirth	5.30	0.26-107.70	VERY LOW
Newborn hypoglycaemia	0.88	0.29-2.71	LOW

Table 6.2.6: Comparison of outcomes between IV hydralazine and IV diazoxide

Oral labetalol versus oral methyldopa

A total of 2 RCTs with a combined sample size of 668 women were examined in comparing the use of oral labetalol and methyldopa. The dosing regimen varied between both studies (Table 6.2.7). There was no difference in the outcomes examined, however this is based on two studies with heterogeneity in prescription of therapy.

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Persistently elevated blood pressure ≥160/100mmHg	1.01	0.78-1.29	MODERATE
All maternal side effects	1.36	0.31-6.03	LOW
Admission into NICU	1.05	0.74-1.50	MODERATE

Table 6.2.7: Comparison of outcomes between oral labetalol and oral methyldopa

Rationale for recommendation

There remains a significant paucity in the literature to suggest the optimal blood pressure target in managing acute (severe) hypertension in pregnancy. Based on the studies examined, 9 studies used a target of ≤150/100mmHg, 2 studies used a target of <160/100mmHg, 5 studies used a target diastolic blood pressure of ≤100mmHg, 1 study used a target of <140/90mmHg and 1 study used a 25% reduction in mean aterial pressure as the treatment target. Given the significant heterogeneity in target, we suggest a target of of <160/110mmHg or as clinically indicated until more data on an optimal target is available (Flow chart 6.2).

Based on the analyses above, short acting agents, oral immediate release nifedipine, IV/oral labetalol, IV hydralazine and IV diazoxide are effective in managing acute hypertension (Flow chart 6.3). Oral IR nifedipine and IV diazoxide are associated with short time taken to achieve target blood pressure. Oral IR nifedipine was also associated with less frequent dosing to achieve target blood pressure. Access to oral IR nifedipine and IV diazoxide however, may be restricted is some parts of Australia and New Zealand.

Given the overall efficacy of these agents in managing acute hypertension, the choice of short acting antihypertensive should be based on the clinician's and unit's access and familiarity with the agent of choice.

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	Severe hypertension should be treated with the first line agents oral nifedipine, oral labetalol, IV labetalol or IV hydralazine
Australian Pregnancy Care Guidelines 2019	No recommendations made
NICE 2019	Treat women with severe hypertension who are in critical care during pregnancy or after birth immediately with 1 of the following: • labetalol (oral or intravenous) • oral nifedipine • intravenous hydralazine In women with severe hypertension who are in critical care, monitor their response to treatment: • to ensure that their blood pressure falls • to identify adverse effects for both the woman and the baby • to modify treatment according to response Consider using up to 500 ml crystalloid fluid before or at the same time as the first dose of intravenous hydralazine in the antenatal period
SOMANZ 2015	A variety of medications have been used for the treatment of severe hypertension in pregnancy (IV labetalol, IV hydralazine, IV diazoxide and oral nifedipine). The most important consideration in choice of antihypertensive agent is that the unit has experience and familiarity with that agent.

Research priorities

There is a need for more data on the appropriate target blood pressure in managing acute (severe) hypertension.

Target BP <160/110 (PP)^

Continuous fetal monitoring (CTG) and repeated maternal blood pressure monitoring (at least every 10-15 minutes) should be considered throughout treatment of acute hypertension (PP)
^ Target BP should be individualised particularly in the presence of features of fetal compromise

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Flowchart 6.2: Management of acute hypertension (PDF)

	Antihypertensives	Class of agent	Onset of action	Dose (Start from low dose and titrate as required)
FIRST LINE*	**Oral Nifedipine (IR)	Calcium channel blocker	30-45 minutes	10-20mg every 30 minutes maximum of 45mg
	±IV Hydralazine	Vasodilator	15-20 minutes	5-10mg every 20 minutes maximum of 30 mg
	***±IV Labetalol	Beta blocker	5 minutes	20-40mg every 10-15 minutes maximum of 80mg
	±IV Diazoxide	Benzothiazide diuretic	3-5 minutes	15mg every 5-10 minutes
	#Oral Methyldopa	Alpha blocker	30-120 minutes	1,000mg as a single dose
	#Oral Labetalol	Beta blocker	30-120 minutes	200mg up to 4 doses every hour

The use of the agents above for management of acute hypertension should be done concurrently with regular antihypertensives (Flow chart 5.3) to avoid rebound acute hypertension

SECOND & THIRD LINE	Persistent or refractory severe hypertension may require repeated doses of these agents or even an intravenous infusion of labetalol 20-160 mg/hr† or hydralazine 10-20 mg/hr†, titrated to the blood pressure response (PP) Magnesium infusion should be initiated in refractory hypertension (≥160/110) or if features of cerebral irritation are present (irrespective of blood pressure) (Flowchart 6.7)

*The most important consideration in choice of antihypertensive agent is that the unit has access and familiarity with that agent
**Supply and access maybe limited in Australia and New Zealand
± Administration of IV agents should be followed by a 10-20mls normal saline intravenous flush to ensure systemic circulation of the administered agent
Slower onset of action (up to 2 hours). Use can be individualised based on clinical setting (i.e. : in the absence of short acting agents)
† 250mls IV fluid preloading (normal saline 0.9%) should be considered to minimize the risk of hypotension (PP)

6.3: Timing of birth in preeclampsia

Recommendation

6.3.1 Delivery should be initiated in women with preeclampsia at ≥37 weeks. (2D)

6.3.2 Decision for expectant management or immediate delivery in women with preeclampsia <37 weeks should be made based on maternal and fetal indications (Table 6.3.2). The decision should be made through an informed shared decision-making process with the woman. (2D)

6.3.3 Delivery should be considered at any gestation in the event of deterioration (Table 6.3.2). (PP)

6.3.4 Women with preeclampsia at risk of early preterm delivery should be considered for transfer to a unit with appropriate level of neonatal care. (PP)

6.3.5 There is limited data to support the use of angiogenic biomarkers in determining timing and indication of delivery (Recommendations 4.2 and 4.3). (2B)

6.3.6 Consider the use of corticosteroid and magnesium sulphate (for fetal neuro protection) in women at risk of early preterm delivery (<34 weeks) (Recommendations 6.5 and 6.6). (2A)

Description of intervention

Preeclampsia is a progressive disorder and at present, delivery remains the definitive management.

Immediate management refers to delivery planned within 48 hours, usually after blood pressure stabilisation and corticosteroid administration to accelerate fetal pulmonary maturity. Expectant management refers to prolongation of the pregnancy beyond these 48 hours with close maternal and fetal monitoring for features suggesting deterioration.

Summary of evidence, risk of harm and quality of evidence

A total of 7 RCTS with a combined sample size of 960 women in each arm. Of the 7 RCTs; 4 RCTS examined immediate management to expectant management in women with preeclampsia at <34 weeks gestation (sample size of ~225 women in each arm) (358-360), 2 RCTs examined immediate management to expectant management in women with preeclampsia between 34-36^{+6} weeks gestation (sample size ~ 610 women in each arm) (361, 362) and 1 RCT examined immediate management to expectant management in women with preeclampsia ≥37 weeks gestation (123 women in each arm)(333). Women with stable chronic and gestational hypertension were excluded from this analysis.

Immediate management in women with preeclampsia at 34-36^{+6} and ≥37 weeks of gestation was associated with a lower rate of composite adverse maternal outcome with a RR of 0.75(CI 0.56-0.99) and RR of 0.61 (CI 0.45-0.82) respectively (moderate certainty of evidence). Immediate management in women with preeclampsia at 34-36^{+6} weeks gestation was also associated with a higher rate neonatal respiratory distress syndrome (RR 4.82, CI 1.07-21.65)(VERY LOW CERTAINTY OF EVIDENCE) and a higher rate of neonatal ventilatory support requirements (RR 1.62, CI 1.27-2.07)(low certainty of evidence) in women with preeclampsia at <34 weeks when compared to expectant management.

Outcome	Gestation	Risk Ratio	Confidence interval	Quality of evidence
Maternal mortality	34-36^{+6}	0.34	0.01-8.22	VERY LOW
Composite adverse maternal outcome	<34	0.45	0.14-1.43	VERY LOW
Composite adverse maternal outcome	**34-36^{+6}**	**0.75**	**0.56-0.99**	**MODERATE**
Composite adverse maternal outcome	**≥37**	**0.61**	**0.45-0.82**	**MODERATE**
Eclampsia	<34	0.98	0.06-15.58	VERY LOW
Eclampsia	34-36^{+6}	0.61	0.16-2.30	VERY LOW
Pulmonary oedema	<34	0.45	0.07-3.00	VERY LOW
Pulmonary oedema	34-36^{+6}	0.50	0.05-5.53	VERY LOW
HELLP syndrome	<34	1.20	0.75-1.91	VERY LOW
HELLP syndrome	34-36^{+6}	0.64	0.26-1.59	VERY LOW
Renal impairment	<34	0.32	0.05-1.99	VERY LOW
Renal impairment	34-36^{+6}	0.76	0.17-3.35	VERY LOW
Placental abruption	**<34**	**0.42**	**0.18-0.96**	**VERY LOW**
Placental abruption	34-36^{+6}	1.01	0.25-4.00	VERY LOW
Caesarean section	<34	1.01	0.91-1.12	LOW
Caesarean section	≥37	0.76	0.46-1.24	LOW
Neonatal mortality	<34	0.92	0.56-1.50	VERY LOW
Neonatal respiratory distress syndrome	**34-36^{+6}**	**4.82**	**1.07-21.65**	**VERY LOW**
Necrotizing enterocolitis	34-36^{+6}	1.79	0.84-3.81	VERY LOW
Neonatal seizure	<34	1.47	0.25-8.76	VERY LOW
Neonatal seizure	34-36^{+6}	3.03	0.12-74.08	VERY LOW
Admission into NICU	<34	1.19	0.89-1.60	VERY LOW
Admission into NICU	34-36^{+6}	1.19	0.94-1.50	VERY LOW
Neonatal ventilatory support	<34	1.62	1.27-2.07	LOW
Neonatal ventilatory support	34-36^{+6}	0.95	0.64-1.39	LOW

Table 6.3.1: Comparison of outcomes between immediate and expectant management based on gestation

Rationale for recommendation

The current data suggest a lower rate of maternal composite outcomes with immediate management in women with preeclampsia at ≥37 weeks and 34-36^{+6} weeks. Immediate management in women with preeclampsia, however, is also associated with a higher rate of neonatal respiratory distress syndrome. Therefore, delivery should be initiated in women with preeclampsia ≥37 weeks. However, the decision for expectant management or immediate delivery in women with preeclampsia <37 weeks should be made based on the maternal and fetal clinical stability.

In the event of deterioration (Table 6.3.2), delivery should be considered at any gestation (PP)

- Neurological features (such as eclampsia, severe intractable headache or repeated visual scotomata)
- Repeated episodes of severe hypertension despite maintenance treatment with multiple antihypertensive agents
- Pulmonary oedema
- Progressive thrombocytopenia or platelet count < 50 × 10^9/L
- Abnormal (>90micromol/l) and rising serum creatinine
- Abnormal and rising liver enzymes
- Hepatic rupture
- Abruption with evidence of maternal or fetal compromise
- Non-reassuring fetal status (including death)

Table 6.3.2 : Features to suggest clinical and biochemical deterioration in women with preeclampsia

There remains inadequate data at present to support the use of angiogenic biomarkers (sFlt1/PlGF ratio and PlGF based testing) in determining timing and indication for delivery (Recommendations 4.2 and 4.3). Therefore, we do not recommend its use at present.

Where preterm delivery prior to 34 weeks is required, magnesium sulphate and corticosteroid can be used to minimize neonatal morbidity and mortality (Recommendations 6.5 and 6.6).

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	At <33^{+6}, Expectant management should be considered, but only in hospitals where very preterm infants and sick mothers can be cared for At 34^{+0}-36^{+6} weeks, initiation of delivery should be discussed At ≥37 weeks, initiation of delivery is recommended
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Before 34 weeks, continue surveillance unless there are indications for planned early birth. From 34^{+1}-36 weeks, continue surveillance unless there are indications for planned early birth. From 37 weeks onwards, Initiate birth within 24–48 hours
SOMANZ 2015	Timing of delivery is dependent upon the severity of the maternal disease and the gestation at which preeclampsia presents: • < 32 weeks : Consult and transfer to Tertiary institution: likely to need preterm delivery. Aim to prolong pregnancy where possible • 32-36^{+6}: Aim to prolong pregnancy where possible, delivery in institution with appropriate Paediatric care • ≥37 weeks : Plan delivery on best day in best way

Research priorities

The use of angiogenic biomarkers in determining indication for delivery remains unclear. More robust data on its positive and negative predictive value and clinical utility in assisting with determining timing of delivery in preeclampsia will be beneficial (Recommendations 4.2 and 4.3)

6.4 : Use of corticosteroid for fetal lung maturation in women with preeclampsia at risk of preterm delivery

Recommendations

6.4.1 Use of corticosteroid (either betamethasone or dexamethasone) is recommended in women with preeclampsia who are at risk of delivery <34^{+6} weeks of gestation. (2A)

6.4.2 There is insufficient data to recommend routine use of corticosteroid in women with preeclampsia who are at risk of delivery between 34^{+6}-36 weeks of gestation. The use of corticosteroid in this setting should be individualised based on clinical assessment and through an informed shared decision-making process with the woman. (2B)

6.4.3 Redosing of corticosteroid can be considered in women with preeclampsia who remain at risk of delivery <34^{+6} weeks of gestation 7-14 days following initial single dose of corticosteroid. (2A)

Description of intervention

Respiratory distress syndrome (RDS) is a serious complication of preterm birth and the primary cause of early neonatal death and disability. It affects up to half of babies born before 28 weeks and a third of babies born before 32 weeks. Respiratory failure in these infants occurs as a result of surfactant deficiency and poor lung anatomical development. Neonatal survival after preterm birth improves with increasing gestation at birth, however, those who survive early neonatal care are at increased risk of long-term neurological disability.

The use of corticosteroid in women at risk of preterm birth has been shown to improve neonatal morbidity and mortality, however, there remains a significant paucity in data on the use of corticosteroid specifically in women with preeclampsia who are at risk of preterm delivery. This is in addition to the general uncertainty with the difference in corticosteroid regimen, gestation of therapy and redosing of corticosteroids.

Summary of evidence and rationale for recommendation

A total of 28 RCTs with a combined sample size of 12,054 women and 12,774 infants were examined (363-386). The studies examined women at risk of preterm delivery from all causes (not specific to preeclampsia). There was significant heterogeneity in the gestation of inclusion and corticosteroid regimen used (Table 6.4.1). Given this, 4 sub-analysis were conducted: (1) Corticosteroid (all) compared to placebo (2) Corticosteroid (all) at <34 weeks gestation compared to 34-36 weeks gestation, (3) Types of corticosteroid and (4) Single dose compared to repeated dosing (redosing)

Study	Sample size	Inclusion gestation	Corticosteroid regimen
Amorim *e al* 1999	220 women 220 infants	<34 weeks	12 mg betamethasone IM, repeated after 24 hours and weekly thereafter
Attawattanakul *et al* 2015	194 women 194 infants	34 to 36 weeks	6 mg dexamethasone IM, up to 4 doses 12 hours apart.
Balci*et al* 2010	100 women 100 infants	34 to 36 weeks.	A single dose of 12 mg betamethasone IM
Block *et al* 1977	167 women 169 infants	Not specified	Group A: 12 mg betamethasone IM repeated after 24 hours if delivery had not occurred Group B: 125 mg methylprednisolone IM repeated after 24 hours if delivery had not occurred Group C: Placebo
Collaborative *et al* 1981	696 women 757 infants	26 to 37 weeks	4 doses of 5 mg dexamethasone phosphate IM 12 hours apart
Dexiprom *et al* 1999	204 women 208 infants	<34 weeks	2 doses of 12 mg dexamethasone IM 24 hours apart
Fekih *et al* 2002	118 women 131 infants	<34 weeks	2 doses of 12 mg dexamethasone IM 24 hours apart and repeated weekly
Gamsu *et al* 1989	251 women 268 infants	<34 weeks	4 mg betamethasone IM, up to 6 doses 8 hours apart
Garite *et al* 1992	76 women 82 infants	<28 weeks	2 doses of 12 mg betamethasone IM administered 24 hours apart, repeated weekly if still < 28 weeks
Gyamfi-Bannerman *et al* 2016	2,831 women 2,831 infants	34 to 36 weeks	2 doses of 12 mg betamethasone IM administered 24 hours apart
Kari *et al* 1994	157 women 189 infants	<32 weeks	4 doses of 6 mg dexamethasone sodium phosphate IM 12 hours apart
Lewis *et al* 1996	79 women 79 infants	<34 weeks	2 doses of 12 mg betamethasone IM administered 24 hours apart, repeated weekly
Liggins *et al* 1972	1,142 women 1,218 infants	24-36 weeks	2 doses of 12 mg betamethasone IM administered 24 hours apart
Lopez *et al* 1989	40 women 40 infants	27-35 weeks	2 doses of 12 mg betamethasone IM administered 24 hours apart

Continued over >

Study	Sample size	Inclusion gestation	Corticosteroid regimen
Mansouri *et al* 2010	200 women 200 infants	34-36 weeks	2 doses of 12 mg betamethasone IM administered 24 hours apart
Morales *et al* 1989	165 women 165 infants	<34 weeks	2 doses of 12 mg betamethasone IM administered 24 hours apart, repeated weekly
Morrison *et al* 1978	196 women 196 infants	<34 weeks	Hydrocortisone 100 mg per mL. Five ml administered every 12 hours over a 48-hour period.
Nelson *et al* 1985	44 women 44 infants	<34 weeks	2 doses of 6 mg or 12 mg betamethasone IM 12 hours apart
Ontela *et al* 2018	309 women, 309 infants	34 to 36 weeks	4 doses of 6 mg dexamethasone IM 12 hours apart
Porto *et al* 2011	320 women 320 infants	34 to 36 weeks	2 doses of 12 mg betamethasone IM administered 24 hours apart
Qublan *et al* 2001	139 women 139 infants	<34 weeks	4 doses of 6 mg dexamethasone IM 12 hours apart, repeated if women had not delivered after 1 week.
Schmidt *et al* 1984	144 women 149 infants	<32 weeks	Group A: 2 doses hydrocortisone 250 mg IM given 24 hours apart. Group B: 2 doses methylprednisolone 125 mg IM doses given 24 hours apart. Group C: 2 doses betamethasone 12 mg IM given 24 hours apart. Control: placebo
Schutte *et al* 1980	104 women 122 infants	<32 weeks.	8 mg betamethasone phosphate and 6 mg betamethasone acetate IM repeated after 24 hours
Shanks *et al* 2010	32 women 32 infants	34 to 36 weeks	2 doses of 12 mg betamethasone IM administered 24 hours apart
Silver *et al* 1996	75 women 96 infants	<29 weeks	4 doses of 5 mg dexamethasone IM 12 hours apart, repeated weekly
Teramo *et al* 1980	74 women 80 infants	<35 weeks	2 doses of 12 mg betamethasone IM administered 24 hours apart
WHO 2020	2,852 women 3,070 infants	<34 weeks	6 mg dexamethasone administered every 12 hours, to a maximum of four doses
WHO 2022	782 women 837 infants	34 to 36 weeks	6 mg dexamethasone administered every 12 hours, to a maximum of four doses

Table 6.4.1 :Characteristics of studies in used in sub-analysis (1),(2),(3)

(1) Corticosteroid (all) compared to placebo

All above listed 27 RCTs with a combined sample size of 11,272 women and 11,925 were examined in this sub-analysis. The use of corticosteroid in women at risk of preterm delivery was associated with a lower rate of the following outcomes compared to placebo are as listed in Table 6.4.2.

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Perinatal death	**0.85**	**0.77-0.93**	**HIGH**
Neonatal death	**0.78**	**0.70-0.87**	**HIGH**
Neonatal respiratory distress syndrome (all)	**0.71**	**0.65-0.78**	**HIGH**
Moderate to severe neonatal respiratory distress syndrome	**0.70**	**0.58-0.83**	**HIGH**
Intraventricular haemorrhage (all)	**0.58**	**0.45-0.75**	**HIGH**
Developmental delay in childhood	**0.51**	**0.27-0.97**	**HIGH**
APGAR score of <7 at 5 minutes	**0.88**	**0.78-0.98**	**HIGH**
Surfactant use	**0.65**	**0.50-0.85**	**HIGH**
Systemic infection in the first 48 hours of life	**0.60**	**0.41-0.88**	**HIGH**
Infection while in neonatal ICU	**0.79**	**0.64-0.98**	**HIGH**
Necrotizing enterocolitis	**0.50**	**0.32-0.78**	**HIGH**

Table 6.4.2 : Comparison of outcomes between the use of corticosteroid (irrespective of gestation) to placebo

(2) Corticosteroid (all) at <34 weeks gestation compared to 34-36 weeks gestation

A total of 22 studies with a combined sample size of 7,689 women and 7,703 infants were examined in this sub-analysis where data was analysed based on the gestation of first dose of corticosteroid (<34 weeks or between 34-36 weeks).

Use of corticosteroid in women <34 weeks gestation demonstrated a lower rate of perinatal death (RR 0.82, CI 0.74-0.91) (high certainty of evidence), neonatal death (RR 0.75, CI 0.66-0.84) (high certainty of evidence), intraventricular haemorrhage (RR 0.56, CI 0.42-0.74)(high certainty of evidence), systemic infection in the first 48 hours of life (RR 0.60, CI 0.39-0.93)(high certainty of evidence) and necrotising enterocolitis (RR 0.42, CI 0.20-0.90) (high certainty of evidence) compared the use of corticosteroid between 34-36 weeks (Table 6.4.3)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
perinatal death (<34 weeks)	**0.82**	**0.74-0.91**	**HIGH**
perinatal death (34-36 weeks)	0.93	0.52-1.66	HIGH
neonatal death (34 weeks)	**0.75**	**0.66-0.84**	**HIGH**
neonatal death (34-36 weeks)	0.95	0.47-1.90	HIGH
intraventricular haemorrhage (<34 weeks)	**0.56**	**0.42-0.74**	**HIGH**
intraventricular haemorrhage (34-36 weeks)	4.91	0.24-102.90	VERY LOW
systemic infection in the first 48 hours of life (<34 weeks)	**0.60**	**0.39-0.93**	**HIGH**
systemic infection in the first 48 hours of life (34-36 weeks)	0.67	0.19-2.29	MODERATE
necrotising enterocolitis (<34 weeks)	**0.42**	**0.20-0.90**	**HIGH**
necrotising enterocolitis (34-36 weeks)	1.49	0.25-8.81	LOW

Table 6.4.3 : Comparison of outcomes between the use of corticosteroid <34 weeks of gestation and 34-36 weeks of gestation

(3) Types of corticosteroids

A total of 21 studies with 10,875 women and 10,944 infants were examined for this sub-analysis. Only studies that used the commonly prescribed dexamethasone or betamethasone were included in this analysis. Studies that used methylprednisone, hydrocortisone or prednisone were excluded from this analysis.

The use of betamethasone demonstrated a lower rate of moderate to severe respiratory distress syndrome (RR 0.50, CI 0.37-0.67)(moderate certainty of evidence) and intraventricular haemorrhage (RR 0.48, CI 0.34-0.68)(high certainty of evidence) compared to dexamethasone. The use of betamethasone and dexamethasone were equally beneficial in reducing the risk of perinatal death, neonatal death and respiratory distress syndrome (Table 6.4.4) however there was significant variation in the prescription of dexamethasone and betamethasone respectively (Table 6.4.1

Outcome	Risk Ratio	Confidence interval	Quality of evidence
perinatal death (betamethasone)	**0.85**	**0.77-0.95**	**HIGH**
perinatal death (dexamethasone)	**0.82**	**0.69-0.99**	**HIGH**
neonatal death (betamethasone)	**0.72**	**0.59-0.89**	**HIGH**
neonatal death (dexamethasone)	**0.81**	**0.71-0.91**	**MODERATE**
intraventricular haemorrhage (betamethasone)	**0.48**	**0.34-0.68**	**HIGH**
intraventricular haemorrhage (dexamethasone)	0.78	0.45-1.13	HIGH
Neonatal respiratory distress syndrome (betamethasone)	**0.63**	**0.55-0.71**	**MODERATE**
Neonatal respiratory distress syndrome (dexamethasone)	**0.80**	**0.70-0.92**	**MODERATE**
Moderate to severe respiratory distress syndrome (betamethasone)	**0.50**	**0.37-0.67**	**MODERATE**
Moderate to severe respiratory distress syndrome (dexamethasone)	0.84	0.68-1.04	MODERATE

6.4.4 : Comparison of outcomes between the use of dexamethasone and betamethasone

(4) Single treatment compared to repeated treatment

A total of 10 studies with 4,608 women and 5,589 infants from the PRECISE individual patient data (IPD) meta-analysis were examined in this analysis. For the purpose of this analysis, only studies that compared a single course of corticosteroid to redosing ≥14 days following the first course were examined (Table 6.4.5). All studies included women at <34 weeks of gestation. Redosing at > 34 weeks of gestation was not examined in this analysis. The studies in this analysis included women who were at risk of preterm delivery from all causes (not specific to preeclampsia).

Study	Sample size	Inclusion gestation	Corticosteroid regimen
Aghajafari *et al* 2002	12 women 16 infants	<30 weeks, ≥ 7 days following a single course of corticosteroid	2× 12 mg betamethasone 24 hours apart repeated weekly until 33 weeks or birth
Crowther *et al* 2006	982 women 1,147 infants	<32 weeks, ≥ 7 days following a single course of corticosteroid	1× 11.4 mg betamethasone Repeated weekly until <32 weeks
Garite *et al* 2009	437 women 577 infants	<33 weeks, ≥ 14 days following a single course of corticosteroid	2× 12 mg betamethasone 24 hours apart or 4× 6 mg dexamethasone, 12 hours apart repeated once if birth expected in ≤7 days
Guinn *et al* 2001	502 women 496 infants	<33 weeks, ≥ 7 days following a single course of corticosteroid	2× 12 mg betamethasone, 24 hours apart repeated weekly until 34 weeks
Mazumder *et al* 2008	76 women 76 infants	<33 weeks, ≥ 7 days following a single course of corticosteroid	2× 12 mg betamethasone, 24 hours apart, repeated weekly until 34 weeks gestation
McEvoy *et al* 2002	37 women 37 infants	<33 weeks, ≥ 7 days following a single course of corticosteroid	2× 12mg betamethasone, 24 hours apart repeated weekly until 34 weeks gestation or until birth
McEvoy *et al* 2010	85 women 113 infants	<34 weeks, ≥ 7 days following a single course of corticosteroid	2× 12 mg betamethasone, 24 hours apart with a single repeat course of corticosteroid
Murphy *et al* 2008	1,858 women 2,318 infants	<32 weeks, ≥ 14 days following a single course of corticosteroid	2× 12 mg betamethasone, 24 hours apart, repeated fortnightly until 33 weeks gestation
TEAMS, UK	156 women 182 infants	<32 weeks, ≥ 14 days following a single course of corticosteroid	2× 12 mg betamethasone, 12 or 24 hours apart, repeated every 7 days
Wapner *et al* 2006	495 women 594 infants	<32 weeks, ≥ 7 days following a single course of corticosteroid	2× 12 mg betamethasone , 24 hours apart or 4× 6 mg dexamethasone 12 hours apart, repeated weekly until 34 weeks gestation
Kari *et al* 1994	157 women 189 infants	<32 weeks	4 doses of 6 mg dexamethasone sodium phosphate IM 12 hours apart

Table 6.4.5 : Characteristic of studies examined in the sub-analysis examining the effect of corticosteroid re-dosing

Redosing of corticosteroid ≥14 days following a single course of corticosteroid in women <34 weeks of gestation was associated with a lower rate of neonatal respiratory support use (RR 0.86, CI 0.80-0.93) (high certainty of evidence). There was no difference in the rate of combined infant outcomes, death or neurosensory disability or maternal sepsis (Table 6.4.6)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Combined infant outcomes*	0.90	0.79.1.02	HIGH
Use of neonatal respiratory support	**0.86**	**0.80-0.93**	**HIGH**
Death or neurosensory disability	1.03	0.95-1.1.2	HIGH
Maternal sepsis	0.97	0.86-1.10	HIGH

6.4.6 : Comparison of outcomes between redosing and placebo

Rationale for recommendations

There is strong evidence to support the use of corticosteroid to reduce the rate of neonatal morbidity and mortality in women at risk of preterm delivery (<34 weeks). The data, however, is not specific to women who are risk of preterm delivery from preeclampsia. Given this, a 2A recommendation is made in place of a 1A recommendation. Based on the evidence reviewed and in maintaining consistency with the recommendation made in the New Zealand and Australia Clinical Practice Guidelines 2015, we recommend the use of corticosteroid in women at risk of preterm delivery at <34^{+6} weeks of gestation.

The current data does not suggest a significant difference between the use of dexamethasone over betamethasone. Therefore, either corticosteroid can be utilised based on local policy.

The current data also does not suggest a significant benefit with the use of corticosteroid between 34^{+6}-36 weeks of gestation. This data, once again, is not specific to women a risk of preterm delivery from preeclampsia. Therefore, the decision on the use of corticosteroid between 34^{+6}-36 weeks of gestation should be individualised based on the clinical assessment and through a shared, informed decision-making process with the woman.

The data on redosing of corticosteroid appears strongest in women who remains at risk of preterm delivery at <34^{+6} weeks of gestation 7-14 days from initial single course of corticosteroid. Therefore, redosing with corticosteroids can be considered in these women. The data, however, is not specific to women who are risk of preterm delivery from preeclampsia. Given this, a 2A recommendation is made in place of a 1A recommendation.

* All (fetal,neonatal,infant,child) death, severe respiratory distress syndrome, grade 3 or 4 intraventricular haemorrhage, necrotising enterocolitis, retinopathy or prematurity

Recommendations by other guidelines

Guideline	Recommendation
ISSHP 2022	Antenatal corticosteroids, in a single course, should be administered to women with HDPs in line with recommendations for any woman at < 34^{+0} weeks who is at risk of birth within the next 7 days. A single repeat course of steroids can be administered prior to 34 weeks if the woman remains pregnant at least 7 days (WHO) to 14 days (ACOG) after the initial course, and she remains at high risk of preterm birth within the next 7 days. Corticosteroids can be administered between 34^{+0} and 36^{+6} weeks in women with pre-eclampsia or gestational hypertension at risk for delivery, among women with singleton pregnancies who have not received steroids before and are non-diabetic
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Offer maternal corticosteroids to women between 24^{+0} and 33^{+6} weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM Consider maternal corticosteroids for women between 34^{+0} and 35^{+6} weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM Consider a single repeat course of maternal corticosteroids for women less than 34^{+0} weeks of pregnancy who: • have already had a course of corticosteroids when this was more than 7 days ago, and • are at very high risk of giving birth in the next 48 hours. Do not give more than 2 courses of maternal corticosteroids for preterm birth
SOMANZ 2015	Infants born to pregnancies complicated by hypertensive disease of pregnancy, treated with corticosteroids, had significantly reduced risk of neonatal death, RDS, and cerebrovascular haemorrhage. The optimal choice of steroid (Betamethasone or Dexamethasone), mode of administration or timing of dosage regime (12 hourly versus 24 hourly dosage) remains uncertain. The administration of further courses of corticosteroid in women who remain undelivered and still at risk of preterm birth after an initial course of corticosteroids remains controversial

Research opportunities

The remains an important need for more data (ideally through RCTs) on the following:

- Use of corticosteroid specifically in women at risk of preterm delivery from preeclampsia
- Optimal corticosteroid regimen (type of corticosteroid, dose, duration, benefit of redosing) in women at risk of preterm delivery from preeclampsia
- Long term infant and childhood follow up data on the use of antenatal corticosteroid in women with preeclampsia with/without fetal growth restriction

6.5 Use of magnesium for fetal neuroprotection in women preeclampsia at risk of preterm delivery

Recommendation

6.5.1 The use of magnesium sulphate for fetal neuroprotection in women with preeclampsia at risk of preterm delivery <30 weeks of gestation is strongly recommended. (2A)

6.5.2 Decision on the use of magnesium sulphate for fetal neuroprotection in women with preeclampsia at risk of delivery between 30-34 weeks of gestation should be individualised based on clinical assessment and through a shared informed decision making process with the woman. (PP)

Description of intervention

Infants born preterm (less than 37 weeks) have an increased risk of mortality during their first few weeks of life and infants who survive the risk of prematurity remain at a higher risk of neurodevelopmental impairments including cerebral palsy, cognitive dysfunction, and sensory impairments (blindness and deafness) and in turn a significant risk of substantial disability.

A Cochrane systematic review in 2009 by Doyle *et al* which examined 5 RCTs, 4 of which administered magnesium sulphate specifically with fetal neuroprotective intent demonstrated a 15% relative reduction in the risk of newborn death or cerebral palsy (risk ratio (RR) 0.85, 95% CI 0.74 to 0.98; four trials; 4,446 infants). This review established the neuroprotective role of antenatal magnesium sulphate given to women at risk of preterm birth, showing that 63 babies (95% CI 44 to 155) would need to be treated to benefit one baby by avoiding cerebral palsy, and 42 babies (95% CI 24 to 346) would need to be treated to benefit one baby by avoiding death or cerebral palsy (387).

Summary of evidence and rationale for recommendation

This analysis was conducted based on the individual patient data (IPD) meta-analysis of the RCTs in the 2009 Cochrane review (AMICABLE) and a RCT which was published following the IPD (Wolf *et al* 2020)(388, 389). For the purpose of this review, IPD from 4 RCTs which administered magnesium sulphate specifically with fetal neuroprotective intent were examined (Table 6.5.1). Studies which administered magnesium for the purpose of prevention of eclampsia or as tocolytics were excluded.

Data from the IPD meta-analysis had a combined samples size of 2,230 women in each arm and the newer RCT consisted of ~340 women in each arm. All studies included women at risk of preterm delivery from all causes and not specific to preeclampsia.

A majority of the studies (RCTs in IPD and newer RCT) examined the use of magnesium sulphate in women of <30 weeks gestation (Table 6.5.1) therefore a meaningful comparison between the use of magnesium sulphate before <30 and <34 weeks of gestational was not feasible. There was also heterogeneity in the prescription of magnesium sulphate (Table 6.5.1).

Study	Sample size	Magnesium regimen	Mean gestation at which magnesium sulphate was administered (in weeks)
Crowther *et al* 2003 (ActoMgSo4)	1,062 women 1,255 fetuses	4g over 20 minutes followed by 1g/h until birth or 24 hours (which ever came first)	27.03
Marrett *et al* 2006 (PREMAG)	564 women 691 fetuses	4g over 30 minutes	29.42
Mittendorf *et al* 2002 (MAGNET)	51 women 68 fetuses	4g over 15 minutes	32.30
Rouse *et al* 2008 (BEAM)	2,241 women 2,444 fetuses	6g over 30 minutes and 2g/hr for 12 hours or delivery (which ever comes first)	29.30
Wolf *et al* 2020	680 women 697 featuses	5g over 20-30 minutes followed by 1g/h until birth or 24 hours (which ever came first)	30.5

Table 6.5.1 : Characteristics of studies examined

Based on the analysis, the use of magnesium sulphate in women at risk of preterm delivery demonstrated a lower rate of death or cerebral palsy (RR 0.86, CI 0.75-0.98), cerebral palsy (any) (RR 0.68, CI 0.52-0.94), cerebral palsy (moderate) (RR 0.64, CI 0.44-0.90) and gross motor dysfunction (RR 0.84, CI 0.722-0.99) and Grade 3 or 4 neonatal intraventicular haemorrhage (RR 0.78,CI 0.62-0.98)(Table 6.2.2). The use of magnesium sulphate was also found to be associated with a higher rate of cessation due to maternal side effects (RR 3.50, CI 1.60-7.67)(Table 6.6.2).

Outcome	Risk reduction	Confidence interval	Quality of evidence
Paediatric mortality (early and later)	0.97	0.73-1.29	HIGH
Death or cerebral palsy	**0.86**	**0.75-0.98**	**HIGH**
Death or any neurosensory disability	0.97	0.97-1.03	HIGH
Cerebral palsy (any)	**0.68**	**0.54-0.86**	**HIGH**
Cerebral palsy (moderate)	**0.64**	**0.44-0.90**	**HIGH**
Cerebral palsy (severe)	0.57	0.27-1.19	HIGH
Gross motor dysfunction	**0.84**	**0.72-0.99**	**HIGH**

Continued over >

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Blindness	0.84	0.66-1.06	HIGH
Deafness	1.10	0.83-1.45	HIGH
Developmental delay or intellectual impairment	0.99	0.91-1.07	HIGH
Major neurological disability	0.99	0.84-1.16	HIGH
Neonatal respiratory distress syndrome	1.00	0.94-1.06	HIGH
Neonatal sepsis	1.07	0.94-1.22	HIGH
Necrotizing enterocolitis	1.22	0.98-1.53	HIGH
Any retinopathy of prematurity	1.02	0.92-1.14	HIGH
Intraventricular haemorrhage (any)	0.96	0.86-1.07	HIGH
Intraventricular haemorrhage (Grade 3 or 4)	**0.78**	**0.62-0.98**	**HIGH**
Cystic periventricular leukomalacia	0.93	0.68-1.27	HIGH
Apgar score <7 at 5minutes	1.00	0.88-1.14	HIGH
Neonatal convulsions	0.78	0.56-1.09	HIGH
Ongoing neonatal respiratory support beyond 28 days	1.0	0.9-1.1	HIGH
Cessation of therapy due to maternal adverse effects	**3.50**	**1.60-7.67**	**LOW**

Table 6.5.2 : Comparison of outcomes between magnesium sulphate and placebo for neuroprotection

Rationale for recommendations

There is strong evidence to suggest a lower rate of neonatal morbidity and mortality with the use of magnesium sulphate in women at risk of preterm delivery. This data however is not specific to women at risk of preterm delivery from preeclampsia. The studies in the data were largely inclusive of women <30 weeks of gestation. For these reasons, a 2A recommendation is made in place of a 1A recommendation with a cut off gestation of <30 weeks.

Recommendations made by other guidelines

Guideline	Recommendation
ISSHP 2022	Magnesium sulphate may be administered while women at preterm gestational ages are being considered for expectant care; if investigations reveal that they do not require immediate birth, it is reasonable to stop magnesium sulphate and re-evaluate its need when timed birth is considered or there is spontaneous onset of labour.
Australian Pregnancy Care Guidelines 2019	No recommendations made
NICE 2019	For women between 23^{+0} and 23^{+6} weeks of pregnancy who are in established preterm labour or having a planned preterm birth within 24 hours, discuss with the woman (and her family members or carers, as appropriate) the use of intravenous magnesium sulfate for neuroprotection of the baby, in the context of her individual circumstances. Offer intravenous magnesium sulfate for neuroprotection of the baby to women between 24^{+0} and 29^{+6} weeks of pregnancy who are: • in established preterm labour, or • having a planned preterm birth within 24 hours Consider intravenous magnesium sulfate for neuroprotection of the baby for women between 30^{+0} and 33^{+6} weeks of pregnancy who are: • in established preterm labour, or • having a planned preterm birth within 24 hours • Give a 4 g intravenous bolus of magnesium sulfate over 15 minutes, followed by an intravenous infusion of 1 g per hour until the birth or for 24 hours (whichever is sooner)
SOMANZ 2015	There is now established Level I evidence that magnesium sulphate should be administered to women requiring preterm delivery for the purposes of fetal neuroprotection. The National Health and Medical Research Council endorsed Australian national guidelines recommend administration of magnesium sulphate for all women at risk of preterm delivery prior to 30 weeks

Research opportunities

More data on the efficacy of magnesium for fetal neuroprotection between 30-34 weeks is required, particularly in women with preeclampsia

6.6 Use of magnesium and anticonvulsants for the management and prevention of eclampsia

Recommendation

6.6.1 Prophylactic magnesium sulphate with an intravenous loading dose of 4g followed by maintenance at 1g/hr for 24 in total or from time of last seizure is strongly recommended in women at risk of eclampsia or recurrent eclampsia. (1A)

6.6.2 There is inadequate evidence to support an alternative magnesium regimen or the use of anticonvulsants for the prevention of eclampsia. (2D)

Proposed treatment pathway in managing eclampsia (Flow chart 6.6) (PP)

Description of intervention

Eclampsia is defined as the occurrence of one or more seizures in association with the syndrome of preeclampsia. While it is rare in most developed countries, eclampsia complicates between one in 100 and one in 1,700 deliveries in low- and middle-income countries respectively (WHO 1988). Eclampsia accounts for 50,000 deaths a year worldwide, which is about 10% of direct maternal deaths (Duley 1992).

Magnesium sulphate is the agent of choice in preventing and treating eclampsia. In preeclampsia, stimulation of N-methyl-D-aspartate (NMDA) receptors by neurotransmitters such as glutamate are thought to contribute towards seizure activities when neuronal networks are over-activated. Magnesium is thought to prevent and control eclamptic seizures by inhibiting NMDA receptors while also contributing towards cerebral vasodilatation. Magnesium is also a calcium antagonist and is thought to play a role in the regulating the cerebral endothelium in reducing cerebral oedema and seizure activity.

Most guidelines recommend the use of a 4g intravenous loading dose followed by an intravenous maintenance regimen of 1g/hr for 24 hours in total or from time of last seizure (Zuspan regimen), however, current data consist of a significant variation in the proposed magnesium regimen. Some studies have examined the use of intramuscular regimen which starts with 14 g loading (4g IV and 10g IM) followed by a maintenance regimen of 5 g IM every 4 hours for 24 hours (Pritchard regimen). Other studies have proposed a modified Zuspan or Pritchard regimen which involves a shorter maintenance regimen of ≤12 hours or an alternative Zuspan or Pritchard regimen which involves loading dose only without maintenance. The variation in regimen used has resulted in significant heterogeneity in the current literature.

Another issue lies in identifying women at risk of eclampsia as ~ 1% to 2% of those with preeclampsia develop eclampsia. Based on the current literature (SOMANZ 2015, ISSHP 2022), we propose considering the use of prophylactic magnesium in women with:

- Persisting or resistant severe hypertension (≥160/110)
- Features of neurological irritability (ongoing or recurring severe headaches, visual scotomata, clonus, hyperreflexia)

This analysis is aimed at examining the efficacy and optimal regimen of magnesium sulphate in preventing and treating eclampsia.

Summary of evidence, risk of harm and quality of evidence

Five sub-analyses were conducted for this review: (1) Efficacy of magnesium vs placebo in reducing the risk of eclampsia or recurrent eclampsia, (2) Comparison between ≤12 hours (short) and 24 hours (regular) maintenance therapy, (3) Comparison between loading only and loading with maintenance regimen, (4) Comparison between intravenous and intramuscular magnesium regimen and (5) Comparison of anticonvulsants to magnesium infusion in preventing eclampsia.

(1) Efficacy of magnesium versus placebo in reducing the risk of eclampsia or recurrent eclampsia

A total of 3 RCTs with a combined sample size of ~5,430 women in each arm were examined in this sub-analysis (390-392). All three studies utilized the currently recommended Zuspan regimen of 4g intravenous loading of magnesium sulphate followed by maintenance of 1g/hr until 24 hours after delivery or last seizure. The use of magnesium infusion (as per the Zuspan regimen) compared to placebo demonstrated a lower rate of eclampsia RR 0.38 (CI 0.27-0.55) (high certainty of evidence) and placental abruption RR 0.65 (CI 0.50-0.85) (moderate certainty of evidence). There was no difference in the other outcomes examined (Table 6.6.1).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Eclampsia	**0.38**	**0.27-0.55**	**HIGH**
Maternal mortality	0.54	0.26-1.10	MODERATE
Maternal stroke	0.50	0.13-2.00	MODERATE
Maternal pulmonary oedema	0.97	0.60-1.57	HIGH
Maternal acute kidney injury	0.80	0.55-1.17	HIGH
Raised maternal liver enzymes	0.78	0.54-1.11	HIGH
Placental abruption	**0.65**	**0.50-0.85**	**MODERATE**
Maternal low platelet	0.85	0.61-1.16	HIGH
Maternal cortical blindness	1.50	0.42-5.31	LOW
Maternal ICU admission	0.97	0.72-1.30	HIGH
Maternal ventilation	1.67	0.93-2.99	MODERATE
Stillbirth	0.99	0.87-1.12	HIGH
Neonatal mortality	1.16	0.94-1.43	HIGH
Neonatal admission into NICU	1.01	0.96-1.06	HIGH
Neonatal ventilation	1.07	0.93-1.22	HIGH
Neonatal seizure	0.76	0.50-1.14	HIGH

Table 6.6.1 : Comparison of outcomes between standard Zupan magnesium regimen to placebo

(2) Comparison between ≤12 hours and 24 hours maintenance therapy

A total of 5 RCTs with a combined sample size of ~810 in each arm were examined in this sub-analysis. Three studies compared a modified Zuspan regimen (4g IV loading followed by an intravenous magnesium infusion at 1g/hr for ≤12 hours) to the standard Zuspan regimen (4g IV loading followed by an intravenous magnesium infusion at 1g/hr for a total of 24 hours) (393-395). Two studies compared a modified Pritchard regimen of 14g loading (4g IV and 10g IM) followed by maintenance of 5g IM every 4 hours for ≤ 12hours to the standard Pritchard regimen (14g loading; 4g IV and 10g IM followed by maintenance at 5g IM every 4 hours for 24 hours) (396, 397).

A comparison between the modified (shorter maintenance regimen) and the standard regimen did not demonstrate a difference in the outcomes examined (Table 6.6.2). This data, however, was heterogenous and was based on evidence with very low level of certainty.

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Eclampsia	2.08	0.64-6.79	VERY LOW
Maternal mortality	1.02	0.07-15.48	VERY LOW
Maternal stroke	2.02	0.19-21.75	VERY LOW
Maternal pulmonary oedema	1.50	0.26-8.50	VERY LOW
Maternal acute kidney injury	0.51	0.05-5.43	VERY LOW
Maternal cortical blindness	1.02	0.07-15.48	VERY LOW
Maternal ICU admission	0.82	0.36-1.87	MODERATE
Stillbirth	0.51	0.21-1.21	LOW
Neonatal mortality	1.00	0.26-3.86	LOW
Neonatal admission into NICU	1.33	0.60-2.99	MODERATE

Table 6.6.2 Comparison of outcomes between ≤12 hours and 24 hours magnesium maintenance therapy

(3) Comparison between loading only and loading with maintenance regimen

A total of 4 RCTs with a combined sample size of 374 women in the loading only arm and 448 women in the loading with maintenance regimen were examined. Three studies compared a modified loading only Pritchard regimen (14g IM) to the standard Pritchard regimen of 14g IV loading followed by maintenance with 5g IV every 4 hours for 24 hours (398-400). One study compared a modified loading only Zuspan regimen (4g IV only) to the standard Zuspan regimen of 4g IV loading followed by an IV maintenance at 1g/hr for 24 hours (395).

There was no difference in the outcomes examined between the use of a loading only regimen to a loading and maintenance regimen (Table 6.6.3). This is however based on a small sample size with overall low certainty of evidence.

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Eclampsia	1.57	0.57-4.35	VERY LOW
Maternal mortality	2.59	0.11-61.75	VERY LOW
Maternal pulmonary oedema	0.11	0.01-2.05	VERY LOW
Maternal acute kidney injury	4.00	0.45-35.48	VERY LOW
Placental abruption	1.14	0.42-3.09	VERY LOW
Maternal low platelet	2.00	0.51-7.89	VERY LOW
Maternal ICU admission	0.65	0.35-1.29	MODERATE
Stillbirth	0.96	0.64-1.43	MODERATE
Neonatal mortality	0.84	0.49-1.43	MODERATE
Neonatal admission into NICU	0.96	0.76-1.20	MODERATE
Neonatal ventilation	1.04	0.62-1.74	MODERATE

Table 6.6.3 :Comparison of outcomes between loading only and loading with maintenance magnesium regimen

(4) Comparison between intravenous and intramuscular magnesium regimen

A total of 4 RCTs with a combined sample size of 506 women in the standard Pritchard IM regimen and 218 women in the standard Zuspan IV regimen were analysed in this sub-analysis (401-404).

There was no difference in the outcomes examined between both magnesium regimens, however, this is based on a small sample size with evidence of very low-level certainty (Table 6.6.4).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Eclampsia	1.23	0.57-2.67	VERY LOW
Maternal mortality	1.74	0.73-4.15	VERY LOW
Maternal pulmonary oedema	0.79	0.51-1.22	LOW
Maternal acute kidney injury	0.94	0.38-2.32	VERY LOW
Raised maternal liver enzyme	2.50	0.76-8.19	VERY LOW
Maternal stroke	1.25	0.42-3.68	VERY LOW
Maternal magnesium toxicity	0.82	0.40-1.68	VERY LOW
Stillbirth	1.16	0.69-1.95	LOW
Neonatal mortality	1.42	0.87-2.33	VERY LOW
Neonatal admission into NICU	0.76	0.24-2.44	VERY LOW
Neonatal ventilation	0.76	0.24-2.44	VERY LOW

Table 6.6.4: Comparison of outcomes between intravenous and intramuscular magnesium regimen

(5) Comparison of anticonvulsants to magnesium infusion in preventing eclampsia.

A total of 5 RCTs were examined to compare the efficacy of anticonvulsants to magnesium infusion in preventing eclampsia. The studies had significant heterogeneity with the magnesium and anticonvulsant regimen.

Four studies examined the use of phenytoin to magnesium sulphate; 2 of the studies used the intramuscular Pritchard magnesium sulphate regimen while 2 studies used the intravenous Zuspan magnesium sulphate regimen. Of the 4 studies, 2 studies used a 1g loading dose of IV phenytoin followed by 500mg of oral phenytoin 10 hours later (405, 406). One study used an intravenous phenytoin loading dose based on weight (1g, 1.25g or 1.5g) followed 500mg of oral phenytoin 8-10 hours following loading dose (407). One study used an intravenous phenytoin loading dose based on weight (15mg/kg) followed by oral phenytoin at 200mg every 8 hours for 24 hours (408). One study examined the use of the intravenous Zuspan magnesium sulphate regimen to 30mg of intravenous diazepam at 60mcg/hr.

The use of magnesium sulphate demonstrated a lower rate of eclampsia compared to phenytoin (RR 0.08, CI 0.01-0.60) (VERY LOW CERTAINTY OF EVIDENCE) (Table 6.6.5). This was, however, based on data with significant heterogeneity. There was no difference with the other outcomes examined (Tables 6.6.5 and 6.6.6)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Eclampsia	**0.08**	**0.01-0.60**	**VERY LOW**
Stillbirth	0.62	0.27-1.41	VERY LOW
Neonatal admission into NICU	1.00	0.63-1.59	LOW

Table 6.6.5: Comparison of outcomes between magnesium sulphate and phenytoin in preventing preeclampsia

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Eclampsia	3.00	0.13-69.31	VERY LOW

Table 6.6.6: Comparison of outcomes between magnesium sulphate and diazepam in preventing preeclampsia

Rationale for recommendation

The review of the evidence suggests that the use of intravenous magnesium sulphate (Zuspan regimen) is beneficial in reducing the risk of eclampsia. There remains inadequate data to support the use of alternative regimens or the use of anticonvulsants in preventing eclampsia.

The recommendation in relation to the use of anticonvulsants is not applicable in pregnant women with known seizure disorders.

Recommendations made by other guidelines

Guideline	Recommendation
ISSHP 2022	Women with preeclampsia who have proteinuria and severe hypertension, or hypertension with neurological signs or symptoms, should receive magnesium sulphate for eclampsia prevention. The dosing regimens used in the Eclampsia and Magpie trials are recommended, along with a protocol for monitoring and treatment of toxicity.
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	A loading dose of 4 g magnesium sulphate should be given intravenously over 5 to 15 minutes, followed by an infusion of 1 g/hour maintained for 24 hours. Do not use diazepam, phenytoin or other anticonvulsants as an alternative to magnesium sulphate in women with eclampsia
SOMANZ 2015	The drug of choice for the prevention of eclampsia is magnesium sulphate, given as a 4g loading dose (diluted in normal saline) followed by an infusion of 1g/hour

Research priorities

More data on the efficacy and risk of toxicity with the various magnesium sulphate regimen is required, particularly in assessing its applicability in women with underlying renal impairment.

Resuscitation

A – Airway
B- Breathing
C- Circulation

Place patient in left lateral position

Insert two large bore intravenous cannulas

Initiate $MgSO_4$ infusion *(1A)*

Loading dose : 4g over 20 minutes
Maintenance : 1g/hr until 24 hours after delivery or last seizure

Reduce dose by 50% in patients with renal impairment or suspected renal impairment (PP)

Is the SBP ≥ 160 mmHg or DBP ≥ 110 mmHg or both?

YES → **Aim to reduce to SBP < 160 mmHg and DBP < 110 mmHg**

(Flow chart 6.2)

NO ↓

Is seizure prolonged?

YES ← ***If seizure prolonged (PP) :***

- diazepam 5-10mg (IV)
- midazolam 5-10mg (IV or IM)

NO ↓

Evaluation for delivery

- Airway support
- Expedite urgent transfer
- where required

Monitoring while on magnesium sulphate infusion (PP)

**Routine serum magnesium level is not recommended unless renal function is compromised*

Every 30 minutes	**Every hour**	**Fetal**
Blood pressure Pulse oximetry Heart rate Respiratory rate	Reflexes Urine output	Continuous cardiotocography where appropriate

Features of magnesium toxicity

Decreased or absent reflexes
Reduction in respiratory rate (≤12/min for 15 minutes)
Drowsiness
Slurred speech

If toxicity is suspected, cease the MgSO4 infusion and assess serum magnesium level. If toxicity present (based on clinical features +/- serum magnesium of >3.5mmol/l), administer calcium gluconate 10% (10 mL in 100 mL normal saline IV over 10 min) (PP)

MgSO4 – Magnesium Sulphate | (1A) – Based on 1A quality evidence | (PP) – Practice point | (IV) – intravenous (IM) - intramuscular

DISCLAIMER : This flowchart provides a guidance based on the evidence at the time of which this guidelines was developed. Management of eclampsia must be done in accordance with local protocol where applicable

CLICK HERE FOR A PDF COPY

Flow sheet 6.6: Management of eclampsia (PDF)

6.7 Use of corticosteroid in the management of HELLP syndrome

Recommendations

6.7.1 The use of corticosteroid in managing HELLP syndrome is recommended against until more data is available. (2C)

The use of corticosteroid for fetal lung maturation in women at risk of preterm birth is discussed separately (Recommendation 6.4)

Description of intervention

The syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP) is a manifestation of placental dysfunction and complicates approximately 0.5% to 0.9% of all pregnancies. For HELLP syndrome to be diagnosed, there must be microangiopathic haemolysis, thrombocytopenia, and abnormalities of liver function. There is no consensus, however, on the specific thresholds of hematologic and biochemical values to use in establishing the diagnosis of HELLP syndrome.

The presence of HELLP syndrome is associated with significant maternal mortality and morbidity including acute renal and liver failure, disseminated intravascular coagulopathy and pulmonary oedema. Approximately 70% of pregnancies complicated by HELLP syndrome require preterm delivery with 15% occurring at extremely preterm gestational age (before 27 completed weeks' gestation).

Some studies have proposed a benefit with the use of corticosteroids in managing HELLP syndrome. This review is aimed at summarizing the evidence from randomized controlled trials (RCTs) examining the maternal and perinatal effects of corticosteroid administration in women with HELLP syndrome.

Summary of evidence and rationale for recommendation

A total of 7 RCTs with a combined sample size of ~230 women in each arm were examined in this analysis. 3 RCTS (409-411) commenced steroid in the antenatal period and ceased at delivery, 2 RCTs commenced steroid in the immediate post-partum period (412, 413) and 2 studies utilized steroid antenatally which was continued for up to 3 days post-natally (414, 415). Of the 7 studies, 5 studies examined the use of IV dexamethasone (409, 412-415), 1 study examined oral prednisone (389) and 1 study examined IV betamethasone (410) against placebo. There was no difference in outcomes examined (Table 6.7)

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Maternal death	0.77	0.25-2.38	MODERATE
Antenatal steroid	0.35	0.02-8.08	LOW
Postpartum steroid	0.67	0.13-3.46	LOW
Mixed (Antenatal and post-partum)	1.17	0.19-7.05	LOW
Eclampsia			
Mixed (Antenatal and post-partum)	0.89	0.40-2.01	MODERATE
Placental abruption			
Antenatal steroid	1.07	0.07-15.57	LOW
Maternal liver haematoma or rupture			
Antenatal steroid	0.22	0.03-1.83	VERY LOW
Maternal pulmonary oedema	0.72	0.23-2.09	MODERATE
Antenatal steroid	1.00	0.07-15.26	VERY LOW
Postpartum steroid	0.35	0.07-1.72	MODERATE
Mixed (Antenatal and post-partum)	1.47	0.24-9.14	LOW
Maternal renal failure	0.88	0.53-1.46	MODERATE
Antenatal steroid	1.50	0.61-3.69	VERY LOW
Postpartum steroid	0.66	0.30-1.42	MODERATE
Mixed (Antenatal and post-partum)	0.75	0.28-2.04	MODERATE
Length of stay in hospital	-0.72	-2.03 to 0.58	VERY LOW
Antenatal steroid	0.04	-0.87 to 0.96	MODERATE
Postpartum steroid	-2.27	-6.37 to 1.83	VERY LOW
Mixed (Antenatal and post-partum)	0.15	-1.77 to 2.07	MODERATE
Perinatal death			
Antenatal steroid	0.64	0.21-1.97	VERY LOW
Gestational age of delivery			
Antenatal steroid	-0.30	-1.30 to 0.70	LOW
Change in platelet count (rate of decline or difference in actual count)	0.67	0.24-1.10	
Antenatal steroid	0.52	-0.19 to 1.24	VERY LOW
Postpartum steroid	1.21	0.34-2.07	VERY LOW
Change in ALT (rate of increase or difference in actual count)			
Antenatal steroid	**-0.58**	**-1.12 to -0.04**	**VERY LOW**
Change in AST (rate of increase or difference in acute count)			
Antenatal steroid	**-0.39**	**-1.09 to -0.02**	**VERY LOW**

Table 6.7.1 : Comparison of outcomes with and without the use of corticosteroid in women with HELLP syndrome

Rationale for recommendations

There remains heterogeneity in the current data with limited evidence to suggest significant benefit with the use of corticosteroids in managing HELLP syndrome. Therefore, we recommend against the use of corticosteroid in managing HELLP syndrome until more data is available. This recommendation is not applicable to the use of corticosteroid in women at risk of preterm birth.

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	Do not administer corticosteroids to hasten resolution of HELLP syndrome
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Do not use dexamethasone or betamethasone for the treatment of HELLP syndrome.
SOMANZ 2015	Steroid therapy is not indicated for the management of thrombocytopenia or hepatic dysfunction in women with preeclampsia, even with HELLP syndrome

Research opportunities

There remains inadequate data on the use of corticosteroid in managing HELLP syndrome. More data on the timing of initiation, type of corticosteroid and duration of therapy will be beneficial.

6.8 Venous thromboprophylaxis in preeclampsia

Recommendations

6.8.1 Women's risk of venous thromboembolism (VTE) and need for VTE prophylaxis should be made based on the current local hospital or state-based protocol or policy. In the absence of which, the included VTE risk in pregnancy assessment tool (Flow chart 6.8) can be utilised. (PP)

6.8.2 Risk assessment should be conducted in early pregnancy (first trimester) or pre-conception, at every admission into hospital, at the time of diagnosis of preeclampsia or new intercurrent medical issue and in the immediate post-partum period. (PP)

These recommendations are not applicable to women who require therapeutic anticoagulation for established VTE or for other medical indications (Please refer to SOMANZ's Position Statement on Pulmonary Embolism in Pregnancy and Post-partum 2021)

Description of intervention

Women with preeclampsia are reported to have a variable risk of venous thromboembolism (VTE) based on the stage of their pregnancy (the highest-risk being the postpartum period) and severity of preeclampsia (416, 417). A Norwegian register-based case-control study of 600,000 pregnancies reported a four-fold increased risk of VTE in patients with preeclampsia in the postpartum period (418). Additionally, where preeclampsia is associated with significant hypoalbuminaemia, women may have up to a five-fold increased risk of VTE compared to the risk of normal pregnancy-associated VTE (417).

The elevated baseline pregnancy-associated VTE risk is further increased by additional maternal and obstetric complications, therefore, highlighting the importance of VTE risk assessment to detect risk factors in early pregnancy, through the antenatal period (in the event of new intercurrent medical issue), admission into hospital and in the post-partum period (416, 417).Current VTE risk assessment protocols are based on the cumulative presence of multiple risk factors, of which preeclampsia is one component (Flowchart generated based on : https://www.rcog.org.uk/media/qejfhcaj/gtg-37a.pdf)

Rationale for recommendation

Despite the known risk of VTE in preeclampsia, at the time of this review, there remains no RCTs that have examined the effect of routine thromboprophylaxis, such as low-molecular weight heparin, in minimizing VTE in women with preeclampsia.

Given this, the recommendation for VTE in women with preeclampsia has been adapted based on the current national and international guidelines on VTE in pregnancy (https://www.rcog.org.uk/media/qejfhcaj/gtg-37a.pdf).

Based on the current knowledge on the risk of VTE in pregnancy, we recommend the following practice points:

1) Women's risk of venous thromboembolism and need for VTE prophylaxis should be made based on the currently recommended VTE risk in pregnancy assessment tool (Flow chart 6.8)
2) Risk assessment should be conducted in early pregnancy (first trimester) or pre-conception, at every admission into hospital, at the time of diagnosis of preeclampsia or new intercurrent medical issue and in the immediate post-partum period
3) These recommendations are not applicable to women who require therapeutic anticoagulation for established VTE or for other medical indications (Please refer to SOMANZ's Position Statement on Pulmonary Embolism in Pregnancy and Post-partum 2021)(https://www.somanz.org/content/uploads/2021/06/SOMANZ_PE_Guide_2021-Final-20210622.pdf

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	No recommendation made
SOMANZ 2015	All women should undergo risk factor assessment for VTE in early pregnancy. This assessment should be repeated if a pregnant woman is admitted to hospital or develops a complication. Hospitalised women are generally less mobile and mechanical thromboprophylaxis such as graduated compression stocking should be considered. Preeclampsia is considered major risk factor for VTE and pharmacological prophylaxis is indicated in a woman who has 2 major or 1 major and 2 minor risk factors as recommended in the Australian guidelines, unless there are surgical contraindications

Research priorities

Data on the use of thromboprophylaxis specifically in women with preeclampsia is required in understanding the risk and benefit of thromboprophylaxis in both the antenatal and post-partum period

VTE risk assessment should be conducted in the following instances:

- Preconception period or in the first trimester
- At every in-patient admission into hospital
- When there is a new intercurrent medical issue
- In the immediate post-partum period

Risk factors	Score	Tick
Pre-existing risk factors		
Previous VTE (except for single event VTE provoked by major surgery)	4	
Previous VTE provoked by major surgery	3	
Known high-risk thrombophilia (Asymptomatic high-risk thrombophilia: homozygous factor V Leiden/compound heterozygote Protein C or S deficiency)	3	
Concurrent medical comorbidities (i.e. : malignancy, cardiac failure, active systemic lupus erythematosus, active inflammatory poly arthropathy, active inflammatory bowel disease, nephrotic syndrome, type 1 diabetes mellitus with nephropathy, sickle cell disease, current intravenous drug user)	3	
Family history of unproved or oestrogen related VTE in first degree relative	1	
Known low-risk thrombophilia (Asymptomatic low-risk thrombophilia: prothrombin gene mutation or heterozygous factor V Leiden)	1	
Age (>35 years)	1	
Obesity with BMI ≥30-39	1	
Obesity with BMI ≥40	2	
Parity ≥3	1	
Current smoker	1	
Gross varicose veins	1	
Obstetric risk factors		
Preeclampsia in current pregnancy	1	
Use of assisted reproductive technology (ART) or in vitro fertilisation (IVF) in current pregnancy	1	
Multi-gestational pregnancy	1	
Emergency caesarean section	2	
Elective caesarean section	1	
Mid-cavity or rotational operative delivery	1	
Prolonged labour (>24 hours)	1	
Post-partum haemorrhage (>1 litre)	1	
Preterm birth in current pregnancy (<37 weeks)	1	
Stillbirth in current pregnancy	1	
Transient risk factors		
Any surgical procedure in the pregnancy or puerperium (i.e. appendicectomy, post-partum sterilisation)	3	
Hyperemesis	3	
Ovarian hyperstimulation syndrome in the first trimester	4	
Current systemic infection	1	
Immobility or dehydration	1	
Total score		

- If total score is ≥4 antenatally, consider thromboprophylaxis from the first trimester
- If total score is 3 antenatally, consider thromboprophylaxis from 28 weeks of gestation or at the time when risk factors changes (i.e. intercurrent illness)
- If total score is ≥ 2 postnatally, consider thromboprophylaxis for at least 10 days
- All women who require thromboprophylaxis antenatally, has a history of previous VTE, has a high-risk thrombophilia or has a low-risk thrombophilia + family history of VTE will require post-partum thromboprophylaxis for 6 weeks
- All women who are admitted into hospital antenatally, especially with prolonged admission (≥ 3 days) should be considered for thromboprophylaxis

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Flow sheet 6.8: VTE Risk assessment table

The VTE risk assessment score sheet has been adapted based on the Royal College of Obstetricians and Gynaecologist's 'Reducing the Risk of Thrombosis and Embolism during Pregnancy and the Puerperium' guideline (Version 2015)(Green-top Guideline No. 37a)

6.9 Plasma expansion in women with preeclampsia

Recommendation

6.9 Routine plasma expansion for management of preeclampsia is recommended against until more data are available. (2C)

Description of intervention

Maternal plasma volume increases progressively during the second half of pregnancy with the greatest increase in women with multiple pregnancies and least for those with small for gestational age newborns (419). Intravascular plasma volume is thought to be reduced amongst women with preeclampsia due to loss of fluid into the extravascular space with preeclampsia associated hypoalbuminaemia, although there is clinical variation around this finding. This association has led to the suggestion that plasma volume expansion, as part of the management of preeclampsia, could potentially improve maternal and uteroplacental circulation (419). The use of volume expansion in women with preeclampsia, however, raises concerns in relation to the risk of pulmonary oedema (420).

Acute pulmonary oedema is one of the leading causes of intensive care admissions in women with preeclampsia (421). Pulmonary oedema is thought to occur in preeclampsia due to two critical factors: reduced plasma oncotic pressure and raised pulmonary hydrostatic pressure (due to systolic/diastolic ventricular dysfunction), therefore, fluid balance mismanagement can increase the risk of pulmonary oedema in women with preeclampsia (422-425).

While some studies argue that plasma volume expansion allows more aggressive antihypertensive therapy, to improve maternal and fetal outcomes, the evidence for this remains largely unclear with conflicting data, particularly in relation to the risk of iatrogenic pulmonary oedema (426, 427).

Summary of evidence and quality of evidence

A total of 9 RCTs examined the use of colloid for plasma expansion against the use of either placebo (normal saline or Ringer's solution) or no intravenous fluid in examining the influence of plasma expansion in the management of preeclampsia. Of the 9 RCTs, data in 3 RCTs were derived from the same study (420, 428, 429), based on which, this analysis has a combined sample size of 1,360 women. A summary of the fluid regimen used is provided in Table 6.9.1.

Only 1 pilot RCT, with a sample size of 46 women examined the difference between restricted and liberal intravenous fluid administration with the use of Ringer's solution (430). The study examined for a difference between the use of 1,500 ml (liberal) and 250ml (restricted) of Ringer's solution administered intraoperatively in women with preeclampsia undergoing caesarean section under spinal anaesthesia (430).

Study	Sample size	Type of plasma expansion examined	Fluid regimen in intervention group
Wang *et al* 2015	40	7.2% HES in hypertonic saline vs placebo	500 mls of 7.2% HES in hypertonic saline (single dose)
Rep *et al* 2008 (PETRA)	172	6% HES vs NIL	250mls 6% HES twice a day over 4 hours
Metsaars *et al* 2006	37	6% HES vs NIL	250 mls 6% HES twice a day over 4 hours
Ganzevoort *et al* 2005a (PETRA)	215	6% HES vs NIL	250 mls 6% HES twice a day over 4 hours
Ganzevoort *et al* 2005b (PETRA)	216	6% HES vs NIL	250 mls 6% HES twice a day over 4 hours
Heilmann *et al* 2001	20	10% HES vs placebo	500ml of 10% HES over 4 hours (single dose)
Lowe *et al* 1993	15	3.5% Haemaccel vs placebo	500 mls of Haemaccel (single dose)
Belfort *et al* 1989	10	3.5% Haemaccel vs NIL	200 mls of 3.5% Haemaccel followed by successive 200 mls of 3.5% Haemaccel until pulmonary capillary wedge pressure increases to a minimum of ≥16mmHg. Both groups received hydralazine infusion for blood pressure management
Sehgal *et al* 1980	32	40% Dextran vs plasma-Lyte vs placebo	Expansion: (a) plasma-Lyte 500 ml over eight hours day one, 250 ml over four hours day two (b) dextran 40 1,000 ml over eight hours day one, 500 ml over four hours day two (c) Placebo

Table 6.9.1: Summary of studies comparing plasma expansion with colloid vs placebo or no fluids HES= Hydroxyethyl starch, NIL=no placebo

Comparison of plasma expansion with colloid to placebo or no fluids demonstrated a rise in urine output following plasma expansion (0.45 litres vs 0.25 litres, RR 0.21(CI 0.03 -0.40) (moderate quality of evidence). There was, however, no difference in all other outcomes examined (Table 6.9.2).

Outcome	Risk Ratio	Confidence interval	Quality of evidence
Eclampsia	0.95	0.14-6.59	LOW
Combined adverse maternal outcome	1.12	0.52-2.38	LOW
Pulmonary oedema	1.58	0.39-6.43	LOW
Mean arterial pressure	-5.0	-23.82 to 13.82	MODERATE
Systemic vascular resistance	-0.61	-15.49 to 14.27	MODERATE
Antihypertensive requirements	1.09	0.95-1.25	MODERATE
Prolongation of pregnancy in days	-3.10	-8.44 to 2.24	MODERATE
Placental abruption	1.37	0.14-13.57	LOW
Perinatal death	1.89	0.81-4.38	LOW
Preterm delivery	1.37	0.42-4.51	VERY LOW
Adverse neurodevelopmental outcome of offspring at 1 year of age	0.60	0.31-1.18	LOW

Table 6.9.2 : Comparison of outcomes with and without plasma expansion

Comparison between liberal and restricted crystalloid did not demonstrate a difference in the of acute kidney injury RR 1.0 (CI 0.52-1.93) (low quality of evidence).

Rationale for recommendations

There remains inadequate data to suggest that volume expansion is beneficial in improving maternal and fetal outcomes in women with preeclampsia. The analysis above has a relatively modest sample size of 1,360 women with significant risk of bias in most studies. Importantly, there remains inadequate data on the safety of volume expansion in women with preeclampsia.

Recommendations in other guidelines

Guideline	Recommendation
ISSHP 2022	Routine plasma volume expansion not recommended
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Do not use volume expansion in women with severe pre-eclampsia unless hydralazine (intravenous) is the antenatal antihypertensive of choice
SOMANZ 2015	Administration of fluid at a rate greater than normal requirements should only be considered for: 1. Women with severe preeclampsia immediately prior to parenteral hydralazine, regional anaesthesia or immediate delivery: 250 mL bolus 2. Initial management in women with oliguria where there is a suspected or confirmed deficit intravascular volume: 300 mL challenge, repeat with careful assessment As vascular permeability is increased in women with preeclampsia, administration of large volumes of intravenous fluid before or after delivery may cause pulmonary oedema and worsen peripheral oedema

Research priorities

More data on the safety and benefit of plasma volume expansion is required. The role of plasma expansion in the management of preeclampsia remains unclear

Part 7: Immediate Post-partum Care

7.1 Routine use of non-steroidal anti-inflammatory drugs (NSAIDs) for post-partum pain management in women with preeclampsia

Recommendation

7.1.1 The routine use of non-steroidal anti-inflammatory drugs (NSAIDs) in post-partum pain management in women with preeclampsia is conditionally recommended against until more data on safety is available. (2C)

7.1.2 Short term, in-patient use can be considered in the absence of an alternative analgesics. (PP)

Description of intervention

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for post-partum analgesia after delivery. The addition of NSAIDs to post-caesarean analgesic regimens has been shown to improve post-caesarean pain and reduce opioid requirements.

Despite these advantages, there are concerns over the use of NSAIDs in women with preeclampsia as these medications have been demonstrated to raise blood pressure in adults with chronic hypertension. The American College of Obstetricians and Gynaecologists' (ACOG) Hypertension in Pregnancy Task Force in 2013 suggested that NSAIDs be replaced by other analgesics in women with hypertension that persists for more than 1 day postpartum. However, data on the use of post-partum NSAIDs in women with preeclampsia remains conflicted at present.

Summary of evidence and rationale for recommendation

A total of 4 RCTs with a combined sample size of ~170 women in each arm were examined in this analysis. Three studies compared the use of ibuprofen 600mg every 6 hours to paracetamol 650mg every 6 hours from delivery to discharge (431-433). One study compared the use of ibuprofen 400mg every 8 hours compared to paracetamol 1g every 6 hours for 2-3 days (412).

Women with acute or chronic renal or liver impairment and NSAIDs intolerance were excluded in all studies.

There was no difference in the outcomes of interest between the use of NSAIDs and paracetamol, however, this data is based in a small sample size of 170 women in each arm with overall low quality of evidence (Table 7.1.1)

Outcome	Risk Ratio/Mean Difference	Confidence interval	Quality of evidence
Severe hypertension post-partum (>160/100mmHg)	1.32	0.73-2.38	VERY LOW
Mean post-partum MAP	1.12	0.52-2.38	LOW
(difference in mmHg)	0.18	-2.19 to 2.55	LOW
Post-partum antihypertensive use	1.15	0.18-1.61	MODERATE
Morphine use in MEQ (morphine equivalent)(mg)	-11.0	-45.93 to 23.93	LOW
Antihypertensive use at time of discharge (difference in number of agents)	1.06	0.79-1.43	HIGH
Duration of hospitalisation (difference in days)	-0.20	-0.73 to 0.33	MODERATE
Hypertension related readmission	2.68	0.29-25.01	LOW
Antihypertensive use at 6 weeks post-partum	1.69	0.78-3.68	LOW
Preterm delivery	1.37	0.42-4.51	VERY LOW
Adverse neurodevelopmental outcome of offspring at 1 year of age	0.60	0.31-1.18	LOW

7.1.1. Comparison of outcomes between the use of NSAIDs and paracetamol in the post-partum period

Rationale for recommendations

Current data is based on a small sample size with low certainty of evidence. Therefore, there remains inadequate data to verify the effect of NSAIDs in the post-partum period in women with preeclampsia.

This recommendation is not applicable to women without hypertensive disorders of pregnancy. The cautious use of NSAIDs in women with preeclampsia may be considered where adequate pain relief is not achieved with alternative analgesics. The studies cited above have all been undertaken in women in inpatient settings. Given the quality of the data, decisions to use NSAIDs and should be limited to use in the inpatient setting only and should made through an informed shared decision-making process with regular reassessment of analgesia requirements and blood pressure readings.

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	Non-steroidal anti-inflammatory drugs (NSAIDs) for postpartum analgesia may be used in women with pre-eclampsia if other analgesics are ineffective, and there is no acute kidney injury (AKI) or other risk factors for it
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	No recommendation made
SOMANZ 2015	Non-steroidal anti-inflammatory drugs are contraindicated as they may adversely affect hypertension, renal function and platelet function.

Research opportunities

More data on the safety of NSAIDs in pain management in women with a history of preeclampsia with a larger sample size is required.

7.2 Routine use of diuretics in the post-partum period

Recommendation

7.2 The short-term use of loop diuretics, in the in-patient setting, can be considered where clinically indicated (i.e. pulmonary oedema, clinical features of fluid overload) in managing post-partum hypertension in women with preeclampsia. (2C)

Description of intervention

Women with preeclampsia are often observed to have decreased blood pressure in the first 48 hours following delivery, however, this is closely followed by an increase in blood pressure between 3 to 6 days postpartum (435). This is largely attributed to the physiological changes in preeclampsia where following delivery, fluid that has been sequestered into the extravascular space mobilizes into the intravascular space producing a large an auto-transfusion (either from fluid resorption or from a change in circulating volume capacity) which results in increased circulating volume and can be associated with hypertension (435). Consequently, this is often associated with accelerated hypertension in the post-partum period. Give this, the use of loop diuretics, such as frusemide, have been proposed to minimise accelerated post-partum hypertension in women with preeclampsia, however, data on the efficacy of this intervention, particularly in relation to its effect on breastfeeding remains largely unclear.

Summary of evidence and rationale for recommendation

A total of 6 RCTs with a combined samples size of ~483 women in each arm were examined. All 6 studies examined the used of loop diuretics (frusemide in 5 studies and torsemide in 1 study). The dose and duration of loop diuretics differed in the studies. Four studies utilised 20mg of oral frusemide daily for 3-5 days, starting from the day of delivery (13, 436, 437). One study utilised 40 mg of frusemide daily for 7 days, starting from the day of delivery (438). One study examined the used of torsemide 20mg daily for 5 days (439). All studies excluded women with acute kidney injury and established pulmonary oedema.

The routine use of a loop diuretics in women with preeclampsia in the post-partum period was associated with a lower rate of persistent hypertension (≥140/90mmHg) with a RR of 0.50 (CI 0.26-0.95) (moderate level of certainty) with no difference in the other outcomes examined (Table 7.2.1). There was no difference in the rate of patient reported issues with breastfeeding RR 2.33 (CI 0.76-6.94) (low level of certainty).

Outcome	Risk Ratio/Mean Difference	Confidence interval	Quality of evidence
Persistent hypertension (≥140/90mmHg) post-partum	**0.5**	**0.26-0.95**	**MODERATE**
Severe hypertension post-partum (≥160/100mmHg)	0.81	0.39-1.66	LOW
Post-partum antihypertensive use in hospital	0.78	0.61-1.02	MODERATE
Post-partum antihypertensive use at time of discharge	0.93	0.75-1.15	MODERATE
Increase in antihypertensives during hospitalisation	0.65	0.36-1.16	LOW
Duration of hospitalisation	-0.03	-0.51 to 0.45	MODERATE
Rate of change in blood pressure (average SBP, DBP or MAP) over duration of hospitalisation	**-2.75**	**-5.02 to -0.48**	**MODERATE**
Post-partum eclampsia	0.20	0.01-4.05	VERY LOW
Hypertension related readmission	0.71	0.34-1.45	LOW
Patient report issues with breastfeeding	2.33	0.78-6.94	VERY LOW

7.2.1 Comparison of outcomes based on the use of diuretics vs placebo

Rationale for recommendations

The use of diuretics in the post-partum period was shown to reduce the rate of persistent post-partum hypertension with no obvious evidence of harm. However, given the limitation in the data (small sample size, heterogeneity in studies, inadequate data on adverse effect of concern (breastfeeding)), there isn't enough evidence to support the routine use of diuretics in women with preeclampsia in the post-partum period. Based on this, we recommend the use of loop-diuretics can be considered when there are clinical indications for its use. However, it's use should be limited to the in-patient setting only.

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	No recommendation made
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Where possible, avoid using diuretics to treat hypertension in women in the postnatal period who are breastfeeding or expressing milk
SOMANZ 2015	Diuretics should not be used in the absence of pulmonary oedema.

Research opportunities

More objective measures of the impact of loop diuretics on breastfeeding will be beneficial in understanding the influence of postpartum loop diuretics on breastfeeding.

7.3 : Antihypertensives in the post-partum period

Recommendation

7.3 There remains inadequate data to suggest the superiority of a single agent or group of agents in selecting antihypertensives for the management of hypertension in the post-partum period. The choice of antihypertensive (beta-blockers, methyldopa, hydralazine, nifedipine, enalapril, clonidine) should be made through a shared decision-making process, particularly in lactating women. (2D)

Description of intervention

A wide variety of medications are often used for lowering blood pressure in women who require antihypertensives in the post-partum period. The concern women have with the use of these agents in the post-partum period often relates to the safety of these medications in breastfeeding. However, data on the breast milk transmission of most of the commonly used agents remain sparse.

Calcium channel blockers

Commonly used calcium channel blocker in the post-partum period includes nifedipine, amlodipine and occasionally, diltiazem. Of all calcium channel blockers, nifedipine has been most extensively investigated in this setting with published safety information suggesting the absence of infant adverse effect with the use of nifedipine in the lactating mother (440-443).

Published evidence from several studies shows that nifedipine passes into breast milk in very small amounts (1.6% to 3.4% of the maternal weight-adjusted dose) after daily doses of 20 to 90mg (440, 444-446). These amounts are significantly lower than doses used therapeutically in infants from birth.

Beta-blockers

The excretion of beta-adrenergic blocking drugs into breastmilk is largely determined by their protein binding (447). Those with low binding are more extensively excreted into breastmilk. The pharmacokinetics of the three commonly used beta blockers are discussed below:

a) Labetalol - With 50% protein binding, 5% renal excretion and a moderate half-life, labetalol presents moderately low risk for accumulation in infants (447). At a dose of 600-1,200mg daily, the average dose received by breastfed infants is estimated to be between 0.004% and 0.07% of the maternal dose (448, 449). Effect on breastfed infants remains largely sparse with no reported infant adverse events with its use in lactating mothers.

b) Metoprolol - With 10% protein binding, 40% renal excretion and a moderate half-life, metoprolol presents moderately low risk for accumulation in infants (447). At a dose of 50-100mg daily, the average dose received by the breastfed infants is estimated to range from 0.005% and 0.01% of maternal dose (450-452). Infant side effects with exposure to metoprolol through breastmilk remains very sparse. Whilst there have been a few case reports of infant bradycardia, there has not be a statistically significant difference in the rate of infant adverse events with exposure to metoprolol through breastmilk (453).

c) Propranolol - With 87% protein binding, less than 1% renal excretion and a moderate half-life, propranolol presents a low risk for accumulation in infants (447). A fully breastfed infant is estimated to receive between <0.1 and 0.9% of the weight-adjusted maternal dosage of propranolol (449, 454). There remains a significant paucity in the literature on any infant adverse events with the use of propranolol in the lactating mother.

ACE-Inhibitors (Enalapril)

Enalapril is an inactive drug that is metabolised to the active metabolite enalaprilat. A study examining the use of Enalapril in the post-partum period demonstrated that enalaprilat milk levels were undetectable (<0.2 mcg/L) 4 hours a single dose of 5-10mg (455). Data on infant adverse events with Enalapril exposure through breastmilk remain sparse. There is a theoretical concern that ACE inhibitors could affect infant kidney development, particularly in infants with extreme prematurity, however this remains inadequately investigated.

Methyldopa

The limited studies to date have demonstrated an infant serum level of 0-90mcg/L of methyldopa following maternal ingestion of 250-1,000mg/day of methyldopa (456, 457). There remains paucity of data on infant adverse effect from methyldopa exposure through breastmilk.

Hydralazine

Based on two case series, the maximum infant serum level of hydralazine was estimated to be 13-25mcg/L with a dose of up to 150mg/day (458, 459). However, the remains a lack of infant adverse effects reported in the literature.

Summary of evidence, risk of harm and quality of evidence

A total of 4 studies were selected for this analysis (460-463). Studies that examined the management of acute (severe) hypertension with intravenous agents were excluded for this analysis. Similarly, studies that examined the used of diuretics in the immediate post-partum management of hypertension were excluded as this was analysis separately (Part 7.2).

Study	Intervention	Comparator	Sample size	Note
Beta blockers vs calcium channel blocker				
Sharma 2017	Labetalol 200-800mg BD	Controlled release Nifedipine 30-90mg Daily	50	Treated to a target BP of <150/100
Ainuddin 2019	Labetalol 100-1,200mg QID	Controlled release Nifedipine 30-90mg Daily	124	Treated to a target BP of <150/100
ACE-I (Enalapril) vs placebo				
Ormesher 2020	Enalapril 5mg daily for 1 week, 10mg daily for 2 weeks and 20mg daily maintenance dose	Placebo	70	
ACE-I (Captopril) vs Clonidine				
Noronha Neto 2017	Captopril maximum of 150mg daily	Clonidine maximum of 0.6mg daily	48	Oral hydralazine or nifedipine added if additional agents required

Table 7.3.1: Summary of studies examined

Given the small number of studies within each sub-groups and given the significant heterogeneity present, meta-analysis was not feasible. Given this, a summary of the findings from the studies above is presented below:

Beta-blockers versus calcium channel blockers

A total of 2 studies with a combined sample size of 174 women were examined. There was heterogeneity in the labetalol dose and dose titration. A limited meta-analysis demonstrated that calcium channel blocker took a shorter time in comparison to beta blocker to achieve the targeted blood pressure (RR 5.19 (CI 4.34-6.03)) with an average mean difference of 2 hours (LOW CERTAINTY of evidence). This finding however was largely skewed by a single study which had the largest contribution towards the pooled data (weight 99.6%).

There was no difference in the use of additional antihypertensives, additional intravenous antihypertensives, duration of hospitalisation and side effect profile. Neither study examined infant side effects in lactating mothers.

ACE-I (Enalapril) versus placebo

A single study with a sample size of 60 women (30 in each arm) was examined. The use of Enalapril was noted to be associated with more reported dry cough when compared to placebo (3 vs 0) (RR 7 (CI 0.38-129.93) (VERY LOW CERTAINTY of evidence). There was no difference in the rate of maternal mortality and rate of cardiac failure. This study aimed at examining cardiac remodelling outcomes and therefore did not include data on immediate post-partum blood pressure control, duration of hospitalisation or infant side effects in lactating mothers.

ACE-I (Captopril) versus Clonidine

A single study with a sample size of 88 women was examined. There was no difference in the rate of reported side effects, duration of hospitalisation, use of additional antihypertensives. The authors did not examine for infant side effects in lactating mothers.

Rationale for recommendation

There remains a significant paucity in the data to suggest the superiority of a single agent or a group of agents in managing hypertension in the post-partum period. Based on the current data and guidelines from other societies the choice of antihypertensives should be made through a shared decision-making process with the patient, particularly in lactating mothers.

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	Antihypertensive therapy administered antepartum should be continued after birth. The target dBP for postpartum antihypertensive treatment should be 85 mmHg, as antenatally
Australian Pregnancy Care Guidelines 2019	No recommendations made
NICE 2019	Advise women with hypertension who wish to breastfeed that their treatment can be adapted to accommodate breastfeeding, and that the need to take antihypertensive medication does not prevent them from breastfeeding. Make decisions on treatment together with the woman, based on her preferences. As antihypertensive agents have the potential to transfer into breast milk: • consider monitoring the blood pressure of babies, especially those born preterm, who have symptoms of low blood pressure for the first few weeks • when discharged home, advise women to monitor their babies for drowsiness, lethargy, pallor, cold peripheries or poor feeding. Offer enalapril to treat hypertension in women during the postnatal period, with appropriate monitoring of maternal renal function and maternal serum potassium. For women of black African or Caribbean family origin with hypertension during the postnatal period, consider antihypertensive treatment with: • nifedipine or amlodipine if the woman has previously used this to successfully control her blood pressure. For women with hypertension in the postnatal period, if blood pressure is not controlled with a single medicine, consider a combination of nifedipine (or amlodipine) and enalapril If this combination is not tolerated or is ineffective, consider either: • adding atenolol or labetalol to the combination treatment or • swapping 1 of the medicines already being used for atenolol or labetalol.
SOMANZ 2015	All agents mentioned earlier (including the ACE inhibitors enalapril, captopril and quinapril) are compatible with breast feeding. Clonidine has been found to accumulate significantly in neonatal serum, although the significance is undetermined

Research priorities

More data on the efficacy and breast-feeding profile of post-partum antihypertensive agents, is required.

At the time of publication, there were 4 RCTs that were examining some of these questions:

- Safest Choice of Antihypertensive Regimen for Postpartum Hypertension (SCARPH) **(https://clinicaltrials.gov/ct2/show/NCT05551104)**
- Comparing Nifedipine and Enalapril in Medical Resources Used in the Postpartum Period **(https://clinicaltrials.gov/ct2/show/NCT04236258)**
- Labetalol or Nifedipine for Control of Postpartum Hypertension: A Randomized Controlled Trial **(https://clinicaltrials.gov/ct2/show/NCT05309460)**
- Comparing the efficacy of oral labetalol with oral amlodipine in achieving blood pressure control in women with postpartum hypertension: randomized controlled trial (HIPPO study—Hypertension In Pregnancy & Postpartum Oral-antihypertensive therapy)
- **(https://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=40435&EncHid=&modid=&compid=%27,%2740435det%27)**

PART 8: Long Term Post-partum Care

Recommendations

8.1 Women should be informed of the long-term risks associated with preeclampsia and the importance of post-partum follow up prior to discharge from hospital (Patient information sheet 8.1). (PP)

8.2 Women should be reviewed by their general practitioner within 1 week of discharge from hospital to ensure stable blood pressure post discharge and titrate medications accordingly. (PP)

8.3 At 3-6 months post-partum, a follow up review of blood pressure (consider a 24-hour blood pressure monitor if not previously done), urine protein assessment (uACR and/or uPCR), BMI and metabolic profile (fasting blood glucose and fasting cholesterol assessment) should be considered. Interventions for any abnormalities (i.e.: further investigations, specialist referral, weight management, lifestyle changes, smoking cessation) should be discussed (Clinician summary sheet 8.1). (PP)

8.4 A yearly follow up of blood pressure, urine protein assessment, BMI and metabolic profile should be considered in identifying early abnormalities in the first 5-10 years post-partum (Clinician summary sheet 8.1). (PP)

8.5 At every review, women should be opportunistically screened for post-partum depression and anxiety. The Edinburgh Postnatal Depression Scale (EPDS) can be used as an initial screening tool (Clinician summary sheet 8.1)). (PP)

8.6 At every review, women should be counselled on the risk of preeclampsia in subsequent pregnancies and the importance of pre-conception medical optimisation, contraception (where indicated) and risk minimisation strategies (i.e. : prophylactic aspirin) (Clinician summary sheet 8.1). (PP)

Description of intervention

The relationship between preeclampsia and long-term cardiovascular risks have been demonstrated in multiple meta-analyses (464-467). The largest meta-analysis of cohort and case-control studies to date (50 studies, >10 million participants)(464)demonstrated that compared to women with normal pregnancies, women with a history of preeclampsia in their first pregnancy were found to have a higher rate of:

- Composite adverse cardiovascular outcome (2.57 versus 0.97 percent; adjusted pooled odds ratio [OR] 1.99, 95% CI 1.79-2.22)
- Cardio or cerebrovascular disease
(1.20 versus 0.56 percent; [OR] 1.79, 95% CI 1.61-2.01)
- Cardiovascular death
(2.39 versus 1.12 percent; [OR] 2.18, 95% CI 1.79-2.66)
- Hypertension
(8.84 versus 3.32 percent; [OR] 3.74, 95% CI 2.87-4.87)
- Type 2 diabetes
(3.55 versus 1.88 percent; [OR] 2.28, 95% CI 1.58-3.28)
- Acute or chronic kidney disease and end-stage kidney disease
(0.38 versus 0.15 percent; [OR] 3.35, 95% CI 2.25-5.00)
- Metabolic syndrome
(20.6 versus 4.2 percent; [OR] 4.05, 95% CI 2.42-6.77)
- Dyslipidaemia
(66.3 versus 54.6 percent; [OR] 2.54, 95% CI 0.81-2.95)

Patients with early-onset preeclampsia (onset <34 weeks of gestation) were found to have higher long-term risks than those with late-onset preeclampsia when compared against controls with previous normal pregnancies:

- Composite adverse cardiovascular outcome:
  - Early onset
  (3.22 versus 1.44 percent; [OR] 3.79, 95% CI 2.70-5.31)
  - Late onset
  (3.77 versus 1.51 percent; [OR] 1.89, 95% CI 1.53-2.33)
- Cardiovascular death:
  - Early onse
  (1.77 versus 0.92 percent; [OR] 5.12, 95% CI 3.22-8.12)
  - Late onset
  (1.06 versus 0.49 percent; [OR] 1.65, 95% CI 1.46-1.86)

Some studies suggest that the observed increased risk of cardiovascular morbidity/mortality in a previously preeclamptic women can be attributed to underlying genetic factors and pre-existing risk factors that are common to both disorders (468, 469). However, it is also possible that the pathophysiology of preeclampsia induces physiologic and metabolic changes associated with endothelial dysfunction, insulin resistance, sympathetic overactivity, proinflammatory activity and abnormal lipid profile, that leads to an increased risk of cardiovascular and cerebrovascular disease (470-475).

Whilst there is good evidence to demonstrate that future risk of cardiovascular, cerebrovascular and renal disease following preeclampsia and the need for follow-up, there remains a significant gap in the data to suggest the appropriate post-partum surveillance program and interventions in minimising these risks.

Rationale for recommendation

At present, there remains a lack of studies to suggest the appropriate and effective post-partum surveillance program and interventions in minimising the risk of cardiovascular, cerebrovascular and renal disease, although trials are underway (476). Given this, the proposed post-partum surveillance and interventions below have been graded as practice points until more rigorous evidence-based data are available.

8.1 Given the significant long-term risks associated with preeclampsia, women should be counselled on the long-term risk associated with preeclampsia at the time of discharge and the importance of post-partum follow up should be emphasised. The 'Patient information sheet 8.1' provided can be used as a supplemental information sheet. Where required and appropriate, this information should be communicated with women's general practitioner through the hospital discharge summary.

8.2 Given the risk of escalation in blood pressure within the first 1-4 weeks post-delivery (477, 478), women should be advised to attend a review with their general practitioner within 1 week of discharge from hospital to ensure stable blood pressure following their discharge.

8.3 Given that most preeclampsia related physiological changes should resolve within 3 months of delivery, a comprehensive review of blood pressure (with a 24-hour blood pressure monitor where feasible, to detect whitecoat or masked hypertension), urine protein assessment (uACR and/or uPCR), renal function and liver function assessment should be done at the 3-6-month mark to ensure normalisation. Further investigation and referral to a specialist should be considered to assess for previously undiagnosed underlying comorbidities where ongoing abnormality is observed (as below).

The 'Clinician summary sheet 8.1' provided can be used as a guidance when conducting the 3-6 month mark assessment.

a) Ongoing antihypertensive requirements

b) 24-hour ABPM (479-481):
- Overall 24-hour of ≥130/80 mmHg
- Daytime average of ≥135/85 mmHg
- Night-time average of ≥120/70 mmHg

Inadequate nocturnal dipping (<10%) is shown to be associated with other medical issues e.g. obstructive sleep apnoea, and in the long term, is associated with an increased cardiovascular morbidity. However, good quality sleep at the time of the ABPM assessment will need to be verified, especially in women with newborns, for this parameter to be validly assessed.

c) Clinical (office) blood pressure of ≥140/90 mmHg (480, 481).A 24-hour ABPM should be conducted to rule out white coat hypertension as elevated office blood pressure readings alone may represent white coat hypertension.

d) Features of early renal impairment with persistent urine albumin to creatinine of >3.5mg/mmol or protein to creatinine ratio of >10mg/mmol or persistent microscopic haematuria with or without abnormal renal function

e) Abnormal liver enzymes and persistent thrombocytopenia

Interventions for any abnormalities (i.e: further investigations, specialist referral, weight management, lifestyle changes, smoking cessation) should be discussed and instituted.

It should be noted that there is emerging evidence that upper limits of post-partum normal blood pressure are approximately 120/80mmHg for both office and ambulatory readings (482), so readings above this should prompt attention to lifestyle behaviour change measures in the first instance. Women with sustained ABPM ≥130/80mmHg or clinic BP ≥140/90mmHg, should be considered for antihypertensive therapy.

8.4 A yearly follow up of blood pressure, urine protein assessment, BMI and metabolic profile should be considered in either following up on identified abnormalities or in identifying early abnormalities in the first 5-10 years post-partum. The need for ongoing lifestyles changes in achieving and maintaining a healthy BMI, smoking cessation and optimisation of known risk should be emphasized.

8.5 Preeclampsia is associated with an increased risk of post-partum depression (483), therefore, where feasible, at every review, women should be opportunistically screened for post-partum depression and anxiety. The Edinburg Postnatal Depression Scale (EPDS) can be utilised as an initial screening tool.

8.6 At every review, women should be counselled on the risk of preeclampsia in subsequent pregnancies and the importance of pre-conception medical optimisation, contraception (where indicated) and risk minimisation strategies (i.e. : prophylactic aspirin) (Clinician summary sheet 8.1).

Recommendation in other guidelines

Guideline	Recommendation
ISSHP 2022	At 3 months postpartum, all women should be reviewed to ensure that BP, urinalysis, and any laboratory abnormalities have normalised. If proteinuria or hypertension persist, then appropriate referral for further investigations should be initiated. At 6 months postpartum, where possible, all women should be reviewed again, at which point we suggest that BP ≥ 120/80 mmHg lead to discussion of lifestyle change Following hypertensive pregnancy, particularly pre-eclampsia, counselling should be provided about the heightened health risks for the mother (particularly cardiovascular) and the offspring We recommend calculating lifetime (not 10-year) cardiovascular risk scores to estimate cardiovascular risk in these women Annual medical review following hypertensive pregnancy is recommended for the first 5 – 10 years postpartum Following hypertensive pregnancy, all women and their offspring should adopt a healthy lifestyle that includes eating well, exercising, aiming for ideal body weight, living smoke-free, and aiming for BP <120/80 mmHg
Australian Pregnancy Care Guidelines 2019	No recommendation made
NICE 2019	Advise women who have had a hypertensive disorder of pregnancy to discuss how to reduce their risk of cardiovascular disease, including hypertensive disorders, with their GP or specialist. This may include: • avoiding smoking • maintaining a healthy lifestyle • maintaining a healthy weight In women who have had pre-eclampsia or hypertension with early birth before 34 weeks, consider pre-pregnancy counselling to discuss possible risks of recurrent hypertensive disorders of pregnancy, and how to lower them for any future pregnancies. Advise women who have had pre-eclampsia to achieve and keep a BMI within the healthy range before their next pregnancy (18.5–24.9 kg/m2)
SOMANZ 2015	No recommendation made

Research priorities

The is a need for more data on the following aspects of the post-partum care of women with a history of preeclampsia

- Cardiovascular risk prediction tool (clinical and biomarkers) specific to women with a history of preeclampsia
- Optimal long term blood pressure target for women with a history of preeclampsia
- Influence of the DASH diet in minimising long term metabolic, cardiovascular and cerebrovascular risks
- Influence of early detection and intervention on metabolic risk factors on long term cardiovascular and cerebrovascular events in women with a history of preeclampsia
- Influence of early statin therapy on cardiovascular and cerebrovascular events in women with a history of preeclampsia
- Influence of early ACE-i or ARB therapy on cardiovascular and cerebrovascular events in women with a history of preeclampsia

< 6 weeks post-partum

- Blood pressure assessment
- Non-steroidal anti-inflammatory avoidance (where possible)
- Adherence to antihypertensives
- Screen for features of post-partum depression and/or anxiety. The Edinburgh Postnatal Depression Scale (EPDS) can be used as an initial screening tool

3-6 months post-partum

- Blood pressure assessment with a 24-hour blood pressure monitor where possible
  - Consider further assessment for a secondary hypertension screen +/- specialist review if blood pressure remains ≥130/80mmHg (ABPM),
  - ≥140/90mmHg (clinic blood pressure assessment) or if remains on antihypertensives
  - Encourage lifestyle measures if BP is noted to be persistently > 120/80mmHg
- Asses for normalisation of abnormal laboratory-based results
  - Consider further assessment +/- specialist review for persistently abnormal renal function, urine microalbumin to creatinine ratio (uACR), urine protein to creatinine ratio (uPCR), liver function or haematological parameters.
- Screen for features of post-partum depression and/or anxiety
  - Consider a combination of non-pharmacological and pharmacological intervention
- Metabolic screen: BMI, fasting cholesterol and fasting blood glucose level assessment
  - Consider a combination non-pharmacological and pharmacological interventions in addressing abnormal metabolic features
  - Discuss future pregnancies: importance of pre-conception care and early preeclampsia prophylactic intervention (i.e: aspirin, regular exercise, dietary +/- supplemental calcium)
- Discuss contraception where relevant (where there is need for medical optimisation) prior to next pregnancy)
- Explain future cardiovascular, metabolic and renal risk factors.

Yearly review

- Reassessment of metabolic, cardiovascular and renal risk factors (BP, weight, lipid and glycaemic profile, urine protein analysis)
  - Discuss future pregnancies: importance of pre-conception care and early preeclampsia prophylactic intervention (i.e. : aspirin, regular exercise, dietary +/- supplemental calcium)
- Explain future cardiovascular, metabolic and renal risk factors

CLICK HERE FOR A PDF COPY **Summary sheet 8.1: Clinician check list for long term post-partum care**

Life after preeclampsia

Pregnancy as a window to your future health

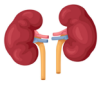
Know your risk: Women who have had preeclampsia in their pregnancy may be at a higher risk of the following later in life:

4x higher risk of developing high blood pressure

2x higher risk of developing heart disease

2-4x higher risk of type 2 diabetes mellitus

2x higher risk of developing stroke



4-8x higher risk of kidney disease

2 in 3 women will die from a cardiac disease

What you can do

You can lower your risk: A history of preeclampsia doesn't have to mean you will develop cardiovascular problems.

You can make a change today for a healthier tomorrow!

Get regular exercise

Take any prescribed medications

Eat a well-balanced, healthy diet

Adopt a healthy lifestyle for yourself and your loved ones

Speak with your doctor before your next pregnancy

Maintain a healthy weight

Stop smoking

See your doctor for a regular health check

CLICK HERE FOR A PDF COPY **Patient information sheet 8.1 : Life after preeclampsia**

Committee Member Profile and Declaration

Prof Angela Makris
MBBS, FRACP, PhD, MMed
Nephrologist & Obstetric Medicine Physician
Chair, Guidelines Development Group

Prof. Angela Makris is a clinician researcher. She is a Renal and Obstetric Physician at South West Sydney based at Liverpool Hospital and undertakes research at the University of Western Sydney and Heart Research Institute. She is co-director of the Vascular Immunology Laboratory. Her research interests include therapies for the treatment and prevention of preeclampsia as well as post-partum management and assessment. She is also the co-Editor of Hypertension in Pregnancy Journal.

Declared conflict of interest: None

Dr Renuka Shanmugalingam
MBBS (Hons), FRACP, PhD
Nephrologist & Obstetric Medicine Physician
Lead, Guidelines Development Group

Dr Shanmugalingam is a nephrologist and obstetric medicine physician at Liverpool Hospital, Sydney. Dr Shanmugalingam has completed a PhD in Hypertensive Disorders of Pregnancy and has a clinical and research interest in renal obstetrics. She also has a strong passion for teaching and is currently the clinic sub-dean at Western Sydney University's school of Medicine. Dr Shanmugalingam is an executive council member of SOMANZ and heads the Education Committee at SOMANZ.

Declared conflict of interest: None

A/Prof Helen L Barrett
BSc (Hons) MBBS (Hons) FRACP MHA PhD
Endocrinologist & Obstetric Medicine Physician

A/Prof Helen Barrett is Director of Obstetric Medicine at the Royal Hospital for Women, Randwick NSW and a conjoint Associate Professor, UNSW Medicine. Dr Barrett undertakes clinical care for women with high-risk complex pregnancy across the breadth of Obstetric Medicine. Her research focuses on understanding maternal, placental metabolism in complex pregnancy and how they relate to the microbiota. Dr Barrett has been an investigator in many observational and randomised controlled trials of management in pregnancy.

At the time of publication of this document, A/Prof Barrett was the Immediate Past President of SOMANZ

Declared conflict of interest: None

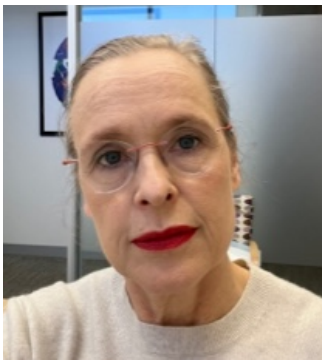
Dr Amanda Beech
PHED Bsc, MBBS (Hons), FRACP
Endocrinologist & Obstetric Medicine Physician

Amanda Beech is an Obstetric Medicine Physician and Endocrinologist at the Royal Hospital for Women, Randwick, and holds a conjoint Senior Lecturer position at the University of New South Wales. She has a breadth of clinical experience in preconception counselling, managing medical disorders of pregnancy including hypertension and pre-eclampsia, gestational and pre-existing diabetes, thyroid disease and hyperemesis, as well as a focus on women's health across all ages, particularly reproductive endocrinology, menopause and osteoporosis.

Amanda is a current representative on both the SOMANZ and ISOM Councils and is actively involved in research areas of hypertension in pregnancy and postnatal risk following pregnancies complicated by hypertensive disorders and gestational diabetes (BP2 and DIVINE). Having previously worked as a teacher, Amanda has a passion for medical education, and along with her lecturing, she is the Clinical Lead for the Simulation and Integrative Learning Centre at the Royal Hospital for Women.

Declared conflict of interest: None

Committee Member Profile and Declaration



Dr Lucy Bowyer
MBBS BMedSci MD FRCOG FRANZCOG DDU CMFM
Obstetrician and Gynaecologist

Dr Lucy Bowyer is an Obstetrician and Gynaecologist also sub-specialising in maternal fetal medicine. She has had a career-long interest in distilling clinical data into accessible information both for front line clinicians and women with medical complications of pregnancy. She has co-authored several SOMANZ guidelines including the first guidelines on sepsis and hyperemesis and previous drafts of the hypertension guideline. She has a strong belief that clinical research should be distilled and translated into clear information for the consumer, be that patient or health care practitioner. She works at the Royal hospital for Women in Sydney, is a conjoint lecturer at UNSW and a partner of Ultrasound Care, private O & G ultrasound.

Declared conflict of interest: None

Dr Tim Crozier
MBBS (Hons) FRACP FCICM PGCertClinUS MPH
Intensivist and Critical Care Physician

Dr Tim Crozier is a physician intensivist with a particular interest in obstetric intensive care and maternal critical illness. This interest began during his ICU training and after gaining Fellowship in 2007 he has gained extensive experience in Obstetric Critical Care. He has published in peer reviewed journals as well as authoring and co-authoring book chapters and has been an invited speaker both in Australia and internationally. He was the Intensive Care member of the working party for the 2017 SOMANZ Guidelines on Sepsis in Pregnancy. He is involved in international collaborations in Obstetric Critical Care and is a Foundation member of the World Obstetric Critical Care Society.

Declared conflict of interest: None

Ms Amanda Davidson
LLB/BCom
Consumer and patient representative

Amanda is an Australian lawyer with over 30 years' senior leadership experience in Australia and Asia whose coreprofessional expertise is in major infrastructure, construction and engineering projects. Past roles have included as senior partner in Australian and International first tier law firms. An innovator with significant commercial acumen, Amanda's professional career has included her role as Chair of PEARLS (Preeclampsia Research Laboratories within the Heart Research Institute), a non-profit established in 2002 to raise awareness of and support research into preeclampsia, in relation to which she was awarded the Order of Australia in 2015. Through her work related to preeclampsia over the past 20 years Amanda understands the importance of medical research and has a demonstrated ability to advocate for increased investment in research. Amanda has a deep interest in the furtherance of medical research in Australia, and is a co-founder and director of Australian Pregnancy Hypertension Foundation Limited, a new company established to further investment, collaboration and advocacy for preeclampsia research.

Declared conflict of interest: None

A/Prof Marloes Dekker Nitert
MSc, PhD, PG Cert Clinical Trials
Scientist

A/Prof Marloes Dekker Nitert is a Senior Lecturer in Metabolism at the University of Queensland. She has a MSc in Medical Cell Biology from the University of Amsterdam, The Netherlands and a PhD in Experimental Medical Science from Lund University, Sweden. She has a long-standing interest in the role of metabolism and the microbiome on health disease in pregnancy. Marloes works closely together with clinician scientists to identify and test new strategies for improving pregnancy outcomes for mother and baby.

Declared conflict of interest:

1) Abbott Nutrition Conference 2017, Columbus Ohio
   Payment For Lectures: money paid to the individual (Conference on maternal and infant microbiota in 2017)

Committee Member Profile and Declaration

Prof Aunty Kerrie Doyle
Indigenous health academic

Aunty Kerrie is the inaugural professor and associate dean on Indigenous Health in the School of Medicine at Western Sydney University. She is the Chair of the Indigenous subcommittee for WHTRN, and the academic lead of the Aboriginal Health and Wellbeing clinical academic group of Maridjulu Budyari Gumal. An Aboriginal woman from Winninninni/Budjeri and Cadigal/Irish heritage, she is married to a chiefly Tuhoe kaumatua, has one son and 2 poodles. She has no grannies, and hope is fast fading.

Declared conflict of interest: None

A/Prof Luke Grzeskowiak
BPharm (Hons), GCertClinEpid, PhD, AdvPracPharm, FSHP
Academic Pharmacist

Associate Professor Luke Grzeskowiak is a Practitioner Fellow at Flinders University and the South Australian Health and Medical Research Institute, and a practicing clinical pharmacist in SA Pharmacy within the Southern Adelaide Local Health Network. He leads an active research program focused on improving health outcomes for women and newborns through supporting quality use of medicines and the development and promotion of more efficacious, safer, and personalised approaches towards medication use in pregnancy and lactation. He was a founding member of the Society of Hospital Pharmacists of Australia Women and Newborn Health Leadership Group and is actively involved in clinician education & training as well as consumer engagement activities related to medication use in pregnancy and lactation.

Declared conflict of interest: None

Dr. Nicole Hall
General Practitioner and primary health representative
MBBS, FRACGP

Dr Nicole Hall is a general practitioner and a GP VMO in high-risk Antenatal Care at Liverpool hospital. She is the RACGP representative on the stillbirth Centre for Research Excellence and the Centre of Perinatal Excellence.

Declared conflict of interest: None

A/Prof Hicham Cheikh Hassan
BSc (Med), MBBS (Hons), FRACP, MMed (ClinEpi), FASN
Nephrologist

A/Prof Hicham C. Hassan is a Senior Staff Specialist at the Illawarra Shoalhaven Local Health District and Associate Professor with the University of Wollongong. His interests include clinical epidemiology, cardiovascular disease in patients with kidney disease and acute kidney injury.

He received his medical degree in Ireland, completed Nephrology training in Australia and underwent a Clinical and Research fellowship with the University of British Columbia, Canada. He also holds a Master of Clinical epidemiology through the University of Sydney.

Hicham has published numerous original research in international nephrology journals. He is currently the chair of the AKTN CKD Working Group and co-chair of the CARI kidney stone guideline working group.

Declared conflict of interest: None

Committee Member Profile and Declaration

Prof Annemarie Hennessy
MBBS, FRACP, PhD, MBA
Nephrologist and Obstetric Physician

Annemarie Hennessy (AM) is a renal and Obstetric Physician. She is the Dean of the School of Medicine and the Foundation Chair of Medicine at Western Sydney University. She is the Executive Dean of the Joint programme in Medicine with the Charles Sturt University, and currently the Pro-Vice Chancellor Heath and Medicine at Western Sydney University. She is the Co-director of the Vascular Immunology Group at the Heart Research Institute (HRI). She is an active physician caring for women with preeclampsia, hypertension, and vascular and kidney diseases at Campbelltown Hospital for SWSLHD. Annemarie is a Board Member of the Ingham Institute for applied Medical Research and represents WSU on the Maridulu Budyari Gumul (SPHERE alliance) Board.

Distinguished Prof. Hennessy has a research interest in high blood pressure in pregnancy and has active research collaborations with Universities and hospitals in Sydney, Sweden and the USA, with numerous publications in peer-reviewed journals. She is also the Managing Director of PEARLS, a non-profit organisation established under the auspices of the Heart Research Institute, Royal Prince Alfred Hospital and Campbelltown Hospital to raise funds to support ongoing research into the cause of preeclampsia in pregnancy.

Declared conflict of interest: None

A/Prof Amanda Henry
PhD MPH FRANZCOG B.Med. (Hons 1), B.Med.Sci (Hons 1), DDU (O&G)
Academic Obstetrician

Associate Professor Amanda Henry is an academic obstetrician at UNSW Sydney and St George Hospital. Her research focus is on complications of pregnancy, particularly hypertensive disorders of pregnancy, and their impact on a woman's lifelong health. A/Prof Henry leads a NSW Health and NHMRC funded program of work centred on improving women's cardiovascular health after hypertensive pregnancy, including the early-intervention Blood Pressure Postpartum (BP2) randomised trial, and Closing Knowledge Gaps after Hypertensive Pregnancy project. She is also a committed collaborative researcher, supervisor, and educator in the area of perinatal trials and improving pregnancy and birth care more generally. A/Prof Henry is passionate about professional advocacy to improve women's health, and holds professional leadership roles including as SOMANZ Councillor, RANZCOG Councillor, and Medical Advisor for consumer organisation Australian Action on Preeclampsia (AAPEC).

Declared conflicts of interest:

- NSW Health Translational Research Grants Scheme
- Grants Pending: money paid to the institution (Joint CIA on this project - subject/grant topic (Blood Pressure Postpartum BP2 trial) overlaps with the proposed work)
- National Health and Medical Research Council (Australia)
- Grants Pending: money paid to the institution (Recipient of Early Career Fellowship (1141570) on "Adverse Cardiovascular outcomes after hypertensive pregnancy: altering this trajectory" - subject matter relevant to proposed work)

Dr. David Langsford
MBBS (Hons), PhD, FRACP
Nephrologist and Obstetric Physician

Dr Langsford is a nephrologist, director of physician training and head of obstetric medicine at Northern Health. He is also an honorary senior clinical fellow at the University of Melbourne.

Declared conflict of interest: None

A/Prof Vincent Lee
MBBS (Hons 1), FRACP, PhD
Nephrologist

A/Prof Lee is a clinician-scientist (Nephrologist) at Westmead Hospital (Sydney), Clinical Associate Professor, Academic Lead (Medicine) at Westmead Clinical School, and Principal Investigator of the Westmead Applied Research Centre, The University of Sydney. His research interests include the prevention, management and future long term health effects of hypertensive disorders in pregnancy. He leads the renal pregnancy service at Westmead Hospital, Sydney.

Declared conflict of interest: None

Committee Member Profile and Declaration

Prof Zachary Munn
GradDip HlthSc, BMedRed, PhD
Methodologist

Professor Zachary Munn is an advocate for evidence-based healthcare and for ensuring policy and practice is based on the best available evidence. Professor Munn is the Director of Health Evidence Synthesis, Recommendations and Impact (HESRI) in the School of Public Health at the University of Adelaide; Head of the Evidence Synthesis Taxonomy Initiative (ESTI); Founding Director of the JBI Adelaide GRADE Centre; Chair of the Guidelines International Network (GIN) and a National Health and Medical Research Council (NHMRC) Investigator. He is a systematic review, evidence implementation and guideline development methodologist.

Declared conflict of interest:

Guidelines International Network. Board Membership: money paid to the individual

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Prof. Michael Peek
MB BS BSc (Med) PhD FRANZCOG FRCOG CMFM DDU
Obstetrician

Professor Michael Peek is Director of Research Development and Professor of Obstetrics and Gynaecology at the Australian National University and a subspecialist in Maternal Fetal Medicine at the Centenary Hospital for Women and Children in Canberra.

Professor Peek is a Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) certified Maternal Fetal Medicine Subspecialist with a thirty-year career nationally and internationally in clinical service, research and education into medical disorders in pregnancy. He also has close ties to rural Australia running high-risk obstetric outreach clinics in rural NSW. His research into medical disorders in pregnancy is both clinical (including obstetric ultrasound) and laboratory based. This has led to over 170 peer reviewed publications and chapters in obstetric medicine textbooks.

Declared conflict of interest: None

A/Prof. Joanne Said
MBBS, FRANZCOG, CMFM, PGrad Dip Epid, PhD
MFM Obstetrician

A/Prof Joanne Said is the Head of Maternal Fetal Medicine (MFM) at Joan Kirner Women's and Children's at Sunshine Hospital, Western Health and a clinician researcher with the Department of Obstetrics and Gynaecology at The University of Melbourne. She is the Chair of the Pregnancy working group for GenV - a whole of state birth cohort currently recruiting in Victoria and a former president of the Society of Obstetric Medicine Australia and New Zealand. She currently leads an international randomised trial investigating antenatal corticosteroids prior to caesarean section in women with diabetes (the PRECeDe trial) as well as the Australian arm of the international C*STEROID trial investigating antenatal corticosteroids prior to caesarean section in women without diabetes.

Declared Conflicts of interest:

1) Western Imaging for Women
   Board Membership: money paid to the individual (Medical Director. Private Ultrasound practice. I receive a share of profit distributions)
   Service in Victoria Fee for sonologist services provided)

Dr. Helen Tanner
MBBS, FRACP
Internalist and Obstetric Physician

Helen Tanner is an obstetric and general physician. She is based in Queensland and is the clinical director of obstetric medicine at the Royal Brisbane and Women's Hospital. Helen completed her PhD in 2022 on the prevalence and management of maternal ketones in pregnancy. She continues to have a research interest in the field of maternal metabolism and its effect on obstetric outcomes. Helen has previously been on the SOMANZ council and currently represents SOMANZ on the executive council of ISOM.

Declared conflict of interest: None

Committee Member Profile and Declaration

Ms. Rachel Taylor
B.Mid/PG Cert Critical & Complex Care/PG Cert TERTL/Master of MidProfPractice
Midwifery representative and consumer/patient representative

Rachel Taylor is currently employed as a midwifery clinical coach at Whatu Ora Waikato where she is also the regional GAP research champion. She is additionally involved with the Taonga Tuku Iho Knowledge Translation for Equity in Pre-term Birth Care research project through her role as co-director of NZ Action on Preeclampsia, as well as the Pacific Collaboration Forum assessing the long-term effects of childbirth trauma and loss among women/wahine. Rachel is the current editor of the Midwifery Research Review, a chapter editor for Elsevier and a professional supervisor for the Midwifery Council of NZ. Previous to her role at Whatu Ora Waikato, she was a senior lecturer of midwifery at Te Pukenga (Wintec) Waikato. She is currently embarking on her research journey examining the links between socio-economic deprivation, environmental pollution and preeclampsia, while working ever so slowly towards her first publication. Rachel's favourite things are her family, friends, fresh air and sunshine and going away on holiday.

Declared conflict of interest: None

Dr. Meredith Ward
MBBS FRACP PhD
Neonatologist

Dr Meredith Ward is a senior medical specialist in Neonatology and Paediatrics, who has practised at Royal Hospital for Women and Prince of Wales Private Hospital in Randwick since 2003. Her clinical interests include the holistic care of preterm infants, including peri-operative care, long-term follow up, neuroprotection of vulnerable neonates and care of infants exposed to drugs and alcohol in pregnancy. Dr Ward completed a PhD studying endogenous neural stem cells, and their potential neuroprotective role, through the School of Medical Sciences, University of New South Wales, in 2018. Dr Ward supervises students engaged in medical research and supports multi-centre clinical trials related to neonatal research.

Declared conflict of interest: None

A/Prof Jason Waugh
BSc (hons),MB BS, DA, CCST (Obstet Gyn),FRCOG, FRANZCOG
Clinical Director / Obstetrician

A/Prof Waugh trained in the UK and New Zealand and worked as a consultant and Clinical Director in the UK for 16 years before moving to Auckland where he has been Clinical Director and high risk obstetrician for 5 years. Jason's research interests are all translational with a focus on preeclampsia and point of care testing with an emphasis on proteinuria measurement. He has over 100 publications including publishing an Obstetric Medicine textbook for midwives and has had over 4 million dollars of grant funding. He is past president of the Macdonald UK Obstetric Medicine Society and the British Maternal and Fetal Medicine Society and is currently on SOMANZ council.

Declared conflict of interest: None

Dr. Linda Yen
MBChB, FRACP
Rheumatologist and Obstetric Physician

Dr Linda (Lu-Yin) Yen MBChB (University of Otago, NZ) FRACP, and has had obstetric medicine training at National Women's Health Auckland City Hospital. She is currently working as a rheumatologist and a general physician at Te Whatu Ora Counties Manukau. She also does obstetric medicine clinics to care for high-risk maternity patients.

Declared conflict of interest: None

Committee Member Profile and Declaration

Diagnostic tool Analysis (DTA) team

Dr Deonna Ackermann
MBBS, MPH

Dr Deonna Ackermann is a Lecturer in Clinical Epidemiology at the University of Sydney where she is involved with teaching evidence-based medicine and research methods to graduate medical students. She has a background in general practice, a Master of Public Health and is currently enrolled in a PhD which is focused on embedding methodological research to support decision making in clinical trials and translation of research results into practice.

Declared conflict of interest: None

A/Prof Katy Bell
MBChB, MMed (Clin Epi, merit), PhD
Methodologist

Associate Professor Katy Bell is a clinical epidemiologist in the Sydney School of Public Health at the University of Sydney. She holds NHMRC Investigator (Emerging Leadership Level 2) and Project grants supporting research on sustainable models of health care that benefit health, and do not cause harm. Clinical Epidemiology applies epidemiology principles and methods to the clinical setting, with a focus on improving clinical decisions and patient outcomes, and it is the science that underpins evidence-based practice. As a clinical epidemiologist, Katy is expert in the evaluation of clinical effectiveness and safety of healthcare, with a particular interest in the benefits and harms of medical tests for screening, diagnosis, and monitoring of disease. Her research includes primary studies such as randomised controlled trials and cohort studies, and evidence reviews including meta-analysis. Her research is multidisciplinary and co-designed with end-users (patients, clinicians, policy makers) to ensure direct relevance of the evidence generated.

Katy is involved in health policy as a Clinical Discussant member for the Australian Government Medical Services Advisory Committee Evaluation Subcommittee. In this role she provides advice on the quality, validity, and relevance of internal and external assessments for applications being considered for government funding on the Medical Benefits Scheme (MBS). She also has strong public engagement, providing regular interviews about her research for international and national media and articles for The Conversation to empower citizens to ask about the potential harms, as well as benefits, of medical tests.

Declared conflict of interest: None

Prof Robin Turner
Bsc (Hons), PhD, MBiostat
Biostatistician

Professor Robin Turner is Director of the Biostatistics Centre at the University of Otago, New Zealand. Robin is a biostatistician who specialises in the application of biostatistical methods to health-related research. Her research covers a wide range of health-related areas including understanding the burden of influenza and other respiratory viruses, improving follow-up and monitoring after treatment for cancer and estimating the prevalence and risk factors for chronic diseases. She is involved in research into improved biostatistical methods for risk prediction modelling and she has expertise in the methods and analysis of diagnostic test accuracy reviews. As the methods expert she ensures research studies are designed and analysed properly and uses a range of complex biostatistical methods to do this.

Declared conflict of interest: None

Ms Ellie Medcalf
BA, MPH

Ellie Medcalf holds a Master in Public Health and is a PhD Student and research assistant at the School of Public Health, The University of Sydney. Her research focuses on applying innovative statistical and epidemiological methods to improve the translational gains from randomised controlled trials (RCTs). In particular, she is interested in using advanced missing data and causal inference methods to address methodological issues in RCTs and thus maximise the use of trial evidence in clinical practice.

Declared conflict of interest: None

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