Variations in guideline recommendations on dose of aspirin for the prevention of preeclampsia and fetal growth restriction in Aotearoa New Zealand, 100 mg or 150 mg.

Statement from the Chairperson of Guideline Development Panel for Small for gestational age and fetal growth restriction in Aotearoa New Zealand He Aratohu Ritenga Haumanu mō te Tōhuatanga Kōpiri me te Pakupaku Rawa - a clinical practice guideline and Co-Lead Author Taonga Tuku Iho, national best practice guide for preterm birth (and Chairperson of the Carosika Collaborative).

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Several national, bi-national and international bodies responsible for pregnancy healthcare guidelines applicable at a population level for Aotearoa New Zealand provide recommendations and practice advice on the use of 'low dose' aspirin (considered as 50-150 mg) for the prevention of preeclampsia and fetal growth restriction.[1-7] These guidelines have been informed by a large number and wide variety of randomised trials across varying populations and at-risk groups exploring the potential benefits of aspirin treatment. Several meta-analyses have assimilated the results of these trials and explored differences by factors such as gestational age of commencing treatment, timing of administration, as well as, by dose of drug used.

A 2017 systematic review and meta-analysis of 45 randomised controlled trials including over 20 000 participants using between 50-150 mg of aspirin daily, suggested a dose-response effect when treatment was commenced <16 weeks,[8] favouring the highest dose (150 mg) although with significant effects seen on rates of preeclampsia, severe preeclampsia and fetal growth at doses of 75 mg and 100 mg, but not at 80 mg (Figure 1). At the same time the Perinatal Antiplatelet Review of International Studies (PARIS) Collaboration published findings of a secondary analysis of a meta-analysis of individual participant data, including over 32 000 participants in 31 randomised trials.[9] This analysis was focused on gestational age of commencing treatment, however, sensitivity analysis explored dose effect and did not suggest differences for dose ≤75 mg compared with >75 mg daily dose (Figure 2). More recent clinical trials including the large multicentre Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial have focussed on the higher 150 mg dose of aspirin.

Despite a lack of head-to-head trials of different doses of aspirin, recent international guidelines from organisations considered applicable to an Aotearoa New Zealand population have been updated and include recommendations for use of a 150mg dose of aspirin. This includes from the International Society for the Study of Hypertension in Pregnancy (ISSHP),[5] the International Federation of Gynecology and Obstetrics (FIGO)[6] and the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ).[4] Te Whatu Ora national guidelines for preeclampsia and hypertension in pregnancy[1] and fetal growth restriction[2] have been updated within the last two years and continue to recommend a 100 mg dose (Table 1).

Although a change in aspirin dose recommendation from 100 mg to 150 mg may seem relatively straightforward, it poses some challenges in Aotearoa New Zealand. In particular, the lack of an available, funded and enteric-coated 150 mg dose preparation. The only two preparations currently available on the Pharmac Community Schedule are 100mg enteric-coated (code 2184273) and 300 mg dispersible (code 2184338). It has been suggested to recommend that women/pregnant people are prescribed the 300 mg dispersible tablet and advised to cut the

tablet in half, discarding the unused half. Alternatively, prescribing two 100mg tablets with advice to cut one tablet in half (enteric-coated medication should not be cut). This additional end-user preparation is likely to lead to variations in dose received and a significant reduction in compliance and hence effectiveness. ISSHP and FIGO acknowledge limitations for some countries in sourcing the 150 mg dose and the challenges of cutting enteric-coated tablets. FIGO makes a pragmatic practice recommendation in these situations for a minimum dose of 100 mg to be prescribed.

Given the international, evidence-informed move to a recommended dose of 150 mg aspirin for the prevention of preeclampsia and fetal growth restriction, we believe Aotearoa New Zealand should source and fund an enteric-coated 150mg aspirin for this indication. This provides practitioners with the opportunity to consider prescribing it and for the appropriate national guideline groups to consider the evidence regarding aspirin dose in an Aotearoa context and update guideline recommendations appropriately with the knowledge that any change would be implementable. Previous co-ordinated action from the New Zealand Committee of Royal Australian and New Zealand College of Obstetricians and Gynaecologists and New Zealand College of Midwives was successful in producing a combined statement to promote clinical risk screening and aspirin use in 2015 (updated in 2018).[3] Once a funded and easily accessible supply of a 150mg dose of aspirin is available, similar initiatives could be included to enable equitable implementation.

Until an appropriate 150mg dose preparation of aspirin is available, we recommend that 100 mg aspirin for the prevention of preeclampsia and fetal growth restriction in Aotearoa New Zealand continues to be the preferred dose.

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Figure 1. The effect of aspirin use from ≤16 weeks on perinatal outcomes according to dose of aspirin (systematic review and meta-analysis).[8]

Outcome ≤16 wk	No. of trials	No. of participants	Relative risk (95% confidence interval) random effect	*P* value	I^2	Dose-response correlation	
						Adjusted R^2	*P* value
Preeclampsia							
50 mg	1	66	0.33 (0.04–3.04)	.33	n/a	44%	.036
60 mg	4	3326	0.93 (0.75–1.15)	.49	0%		
75 mg	2	373	0.42 (0.25–0.70)	.001	72%		
80 mg	4	270	0.52 (0.26–1.01)	.06	1%		
100 mg	7	985	0.48 (0.31–0.74)	.0009	0%		
150 mg	1	93	0.07 (0.00–1.25)	.07	n/a		
Total	19	5113	0.57 (0.43–0.75)	<.001	52%		
Severe preeclampsia							
60 mg	3	3279	0.96 (0.71–1.28)	.77	0%	100%	.008
75 mg	2	373	0.24 (0.09–0.65)	.005	9%		
100 mg	3	334	0.23 (0.08–0.64)	.005	0%		
150 mg	1	93	0.07 (0.00–1.25)	.07	n/a		
Total	9	4079	0.47 (0.26–0.83)	.009	60%		
Fetal growth restriction							
50 mg	1	46	1.00 (0.22–4.45)	1.00	n/a	100%	.044
60 mg	3	1378	0.78 (0.53–1.16)	.22	0%		
75 mg	2	373	0.48 (0.32–0.72)	.0004	0%		
80 mg	3	180	0.64 (0.11–3.74)	.62	0%		
100 mg	7	869	0.45 (0.28–0.71)	.0007	0%		
150 mg	1	93	0.29 (0.10–0.82)	.02	n/a		
Total	17	2939	0.56 (0.44–0.70)	<.001	0%		

n/a, not applicable.

Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. AJOG 2017 http://dx.doi.org/10.1016/j.ajog.2016.09.076

Figure 2. Sensitivity analysis for outcomes of preeclampsia based on trials characteristic (individual participant data meta-analysis).[9]

Characteristics	RR (95% CI)	Subgroup interaction test
Relative risk of preeclampsia in main analysis	0.90 (0.84–0.97)	
PARIS definition of preeclampsia (SBP ≥140 mm Hg or DBP ≥90 mm Hg and trialist-defined proteinuria)	0.90 (0.83–0.97)	Sensitivity analysis only
Trialists' own definition of preeclampsia	0.88 (0.81–0.96)	
Placebo-controlled studies	0.90 (0.84–0.97)	$P = .52$
No placebo	0.71 (0.41–1.25)	
Aspirin dose ≤75 mg	0.92 (0.85–0.99)	$P = .23$
Aspirin dose >75 mg	0.77 (0.61–0.97)	

CI, confidence interval; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure; *PARIS*, Perinatal Antiplatelet Review of International Studies; *RR*, relative risk.

Meher S, Duley L, Hunter K, Askie L. Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis. AJOG 2017 http://dx.doi.org/10.1016/j.ajog.2016.10.016

Table 1. Summary of aspirin dose recommendations from pregnancy healthcare guidelines applicable at a population level for Aotearoa New Zealand.

Guideline name and author	Year of publication	Audience	Aspirin dose recommendation
Te Whatu Ora – Health New Zealand Small for gestational age and fetal growth restriction in Aotearoa New Zealand He Aratohu Ritenga Haumanu mō te Tōhuatanga Kōpiri me te Pakupaku Rawa. A clinical practice guideline	2023	national	100mg
Te Whatu Ora – Health New Zealand. Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in Aotearoa New Zealand: Te Tautohu, Te Tumahu i te Toto Pōrutu me te Pēhanga Toto Kaha i te Hapūtanga ki Aotearoa: A clinical practice guideline	2022	national	100mg
International Society for the Study of Hypertension in Pregnancy (ISSHP) The 2021 ISHHP classification, diagnosis & management recommendations for international practice	2021	international	150mg after multivariable screening 100-162mg after clinical/BP screening
International Federation of Gynecology and Obstetrics (FIGO) The FIGO initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention	2019	international	150mg
New Zealand Committee of Royal Australian and New Zealand College of Obstetricians and Gynaecologists and New Zealand College of Midwives Guidance regarding the use of low dose aspirin in the prevention of pre-eclampsia in high-risk women	2015 (2018 update)	national	100mg
Royal Australian and New Zealand College of Obstetricians and Gynaecologists Early pregnancy screening and prevention of preterm preeclampsia and related complications	2024	bi-national	At least 100mg
Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) SOMANZ Guideline for the Management of Hypertensive Disorders of Pregnancy 2014 (updated 2015, 2023)	2014 (2023 update)	bi-national	150mg
World Health Organization (WHO) WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia	2011	international	75mg

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2. Te Whatu Ora – Health New Zealand. 2023. *Small for gestational age and fetal growth restriction in Aotearoa New Zealand He Aratohu Ritenga Haumanu mō te Tōhuatanga Kōpiri me te Pakupaku Rawa. A clinical practice guideline.* Wellington: Te Whatu Ora – Health New Zealand https://www.tewhatuora.govt.nz/publications/small-for-gestational-age-fetal-growth-restriction-guidelines/ accessed 22nd Jan 2025

3. Guidance regarding the use of low dose aspirin in the prevention of pre-eclampsia in high risk women 2015 (updated 2018). New Zealand Committee of Royal Australian and New Zealand College of Obstetricians and Gynaecologists and New Zealand College of Midwives.

4. SOMANZ Hypertension in Pregnancy Guideline 2023 https://somanz.org/hypertension-in-pregnancy-guideline-2023/ accessed 22nd Jan 2025

5. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertension 27 (2022) 148–169 https://doi.org/10.1016/j.preghy.2021.09.008

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8. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. AJOG 2017 http://dx.doi.org/10.1016/j.ajog.2016.09.076

9. Meher S, Duley L, Hunter K, Askie L. Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis. AJOG 2017 http://dx.doi.org/10.1016/j.ajog.2016.10.016