

Guidance regarding the use of low-dose aspirin in the prevention of pre-eclampsia in high-risk women.

MARCH 2015

Developed By:

**NEW ZEALAND COMMITTEE OF
THE ROYAL AUSTRALIAN & NEW
ZEALAND COLLEGE OF
OBSTETRICIANS &
GYNAECOLOGISTS (RANZCOG)**

**NEW ZEALAND COLLEGE OF
MIDWIVES ((NZCOM)**



1.0 Executive Summary

- All women presenting for maternity care need a comprehensive general and obstetric history at initial presentation, including assessment of pre-eclampsia risk factors
- Major risk factors for preeclampsia include:
 - previous pre-eclampsia requiring delivery before 37 weeks or with haemolysis, elevated liver enzymes, and/or low platelets (HELLP) syndrome
 - Predisposing medical conditions
 - Autoimmune e.g.
 - Systemic Lupus Erythematosus
 - Scleroderma
 - Anti-phospholipid syndrome
 - Chronic hypertension
 - Diabetes type 1 and 2
 - Any chronic kidney disease
- Women with major risk factors have a risk of pre-eclampsia of about 20%
- All women with major risk factors for pre-eclampsia require specialist consultation as per “Guidelines for Consultation with Obstetric and Related Medical Services”.
- Low dose aspirin (LDA) commenced before 16-20 weeks reduces the risk of preeclampsia in women with major risk factors
- It is recommended that LDA is prescribed by the General Practitioner or the obstetric service whenever possible
- Initiation of LDA treatment is recommended at 12 weeks and discontinued at 36 weeks
- At the specialist consultation calcium, which also reduces the risk of pre-eclampsia in women at high risk, may be prescribed.

2.0 Introduction

The New Zealand Committee of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and the New Zealand College of Midwives (NZCOM) developed this guidance for their respective professions regarding the use of Low Dose Aspirin 100mg (LDA) and Calcium for the prevention of pre-eclampsia and to clarify respective roles and responsibilities when providing collaborative care for women who are at increased risk.

3.0 Background

Pre-eclampsia is characterized by defective placentation leading to insufficient placental perfusion and ischaemia with resultant endothelial dysfunction, which results in the clinical syndrome of pre-eclampsia. Trophoblast invasion of the spiral arteries occurs from 8 weeks and is completed by 20 weeks gestation. It is thought that anti-platelet agents, (such as LDA), taken in early pregnancy may reduce pathological coagulation and vasoconstriction in the placental circulation and also promote placental growth thereby reducing the incidence of pre-eclampsia ^{1,2}.

Meta-analyses have demonstrated that LDA commenced prior to 20 weeks of gestation, in all women with known risk factors, reduces the likelihood of the development of pre-eclampsia [RR 0.83 (95% CI 0.77 to 0.89)] ^{1,2,3,4}. Importantly, there was also a 14% reduction in fetal and neonatal deaths [RR 0.86 (95% CI 0.76 to 0.98)] ¹. This risk reduction was greater in women at high risk of pre-eclampsia [RR 0.54 (95% CI 0.41 to 0.70)] as opposed to those at moderate risk [RR 0.86 (95% CI (0.79 to 0.95)] ¹. The benefit was confined to women in whom LDA was commenced before 16-20 weeks of gestation ^{1,2,3}. Studies have assessed the effect of a range of doses of LDA and the beneficial effect appears greater with doses >75 milligram ³. In New Zealand 100 milligram enteric coated Aspirin tablets are available and subsidized by Pharmac and this is the recommended dose ⁵. Enteric-coated tablets reduce the risk of gastric side effects.

4.0 Advice to practitioners

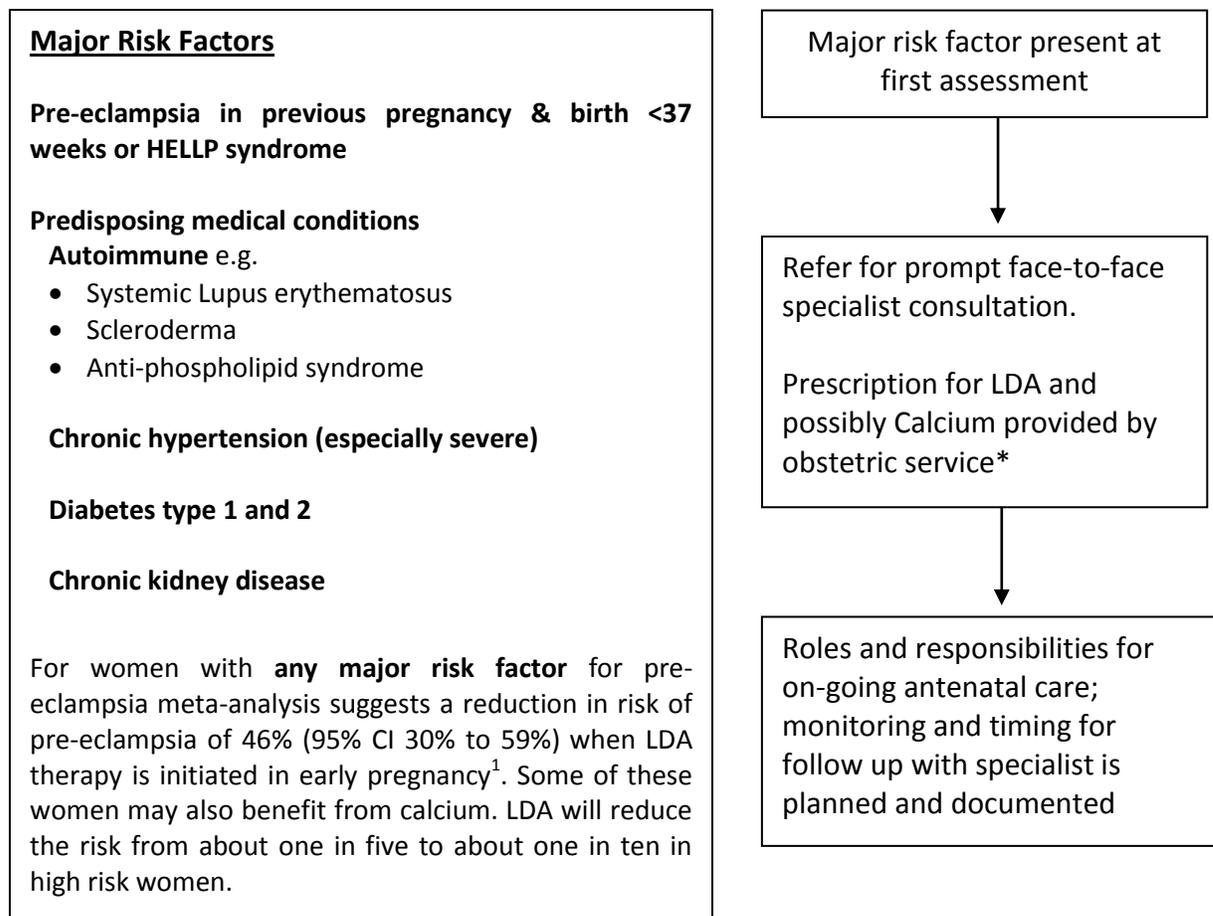
All women presenting for maternity care need a comprehensive general and obstetric history at initial presentation, including assessment of pre-eclampsia risk factors (see Figure 1). Ongoing antenatal care will be individualized.

When assessing risk factors practitioners should refer to the “Guidelines for Consultation with Obstetric and Related Medical Services” ⁶ for guidance about ongoing care arrangements.

4.0 Early access to LDA will provide the most protection

Women with major risk factors for pre-eclampsia should be offered LDA commencing before 20 weeks whilst placental development is occurring. There is no evidence for any teratogenic effect from treatment with LDA, but as LDA was initiated at 12 weeks in a number of the large randomised studies ^{1,2,3} this appears to be both a safe and effective gestation at which to initiate treatment.

Figure 1: Risk assessment and prevention of pre-eclampsia – major risk factors



***GP may prescribe LDA when pregnancy confirmed to commence at 12 weeks**

5.0 Major risk factors for pre-eclampsia

The background risk for preeclampsia in low risk pregnant women is 1-2% in multipara and approximately 5% in nullipara.² Women with major risk factors for pre-eclampsia, as defined below, have an approximately 20% risk of developing pre-eclampsia and LDA prophylaxis is recommended⁷. These conditions are also major risk factors for small for gestational age (SGA) infants.

Major risk factors are defined as:

- Pre-eclampsia in a previous pregnancy resulting in birth <37 weeks or with haemolysis, elevated liver enzymes, and/or low platelets (HELLP syndrome)
- Predisposing medical conditions
 - Autoimmune e.g.
 - Systemic Lupus Erythematosus
 - Scleroderma
 - Anti-phospholipid syndrome
 - Chronic hypertension
 - Diabetes type 1 and 2
 - Any chronic kidney disease

When a major risk factor is identified at first assessment, prompt referral for obstetric assessment and care planning is recommended as per the Referral Guidelines⁶. Practitioners may highlight on the referral that the woman needs prompt assessment / treatment for prevention of pre-eclampsia so that the obstetric services prioritise the referral. These women require a face-to-face obstetric assessment preferably in the first trimester. It is recommended that the prescription of LDA 100mg for women with major risk factors for pre-eclampsia is provided by the general practitioner or by the obstetric service whenever possible. LDA 100mg will usually be commenced at 12 weeks.

6.0 Role of calcium

A large systematic review reported that calcium supplementation (1.5-2 gram/day of elemental calcium) started in the first half of pregnancy reduced the risk of pre-eclampsia especially in women at high risk [RR 0.22 (95% CI 0.12 to 0.42)], and also in women with low calcium intake in their diets [RR 0.36 (95% CI 0.20 to 0.65)]⁸. Most of these studies were carried out in women at low risk of pre-eclampsia with low calcium diets and the generalisability of these findings to other settings is unclear. Taking a history of dietary calcium intake may help to decide who will benefit. Calcium did not reduce the rate of SGA infants in the above studies and should not be prescribed for prevention of SGA alone. A decision regarding a recommendation for calcium supplementation will be made at the time of specialist consultation in women with major risk factors, and the prescription provided by the obstetrician at that time. Calcium treatment is normally continued until the birth of the baby. A recent systematic review has suggested that a lower dose of daily calcium (500mg) may also reduce pre-eclampsia⁹ and results of a large study are awaited.

7.0 Discharge from maternity care

Women who have had pre-eclampsia in the recent pregnancy should be advised at discharge from maternity services:

- to be aware that they have an increased risk of developing pre-eclampsia in future pregnancies
- to seek care at an early gestation for any future pregnancies in order to access preventative treatment (LDA and possibly calcium) and other advice especially if the pre-eclampsia was early onset or complicated by HELLP syndrome
- to address other modifiable risk factors for pre-eclampsia such as obesity and postpartum weight retention.

8.0 Informed consent requirements

Women need a full discussion regarding the benefits versus risks / side-effects of the treatment in order to give informed consent. (See Right 6 of the Code of Health and Disability Services Consumer's Rights). Although there is clear evidence of benefit for the prophylactic use of LDA in the prevention of pre-eclampsia aspirin is classified as a category C medicine (Australian Government, Dept of Health, Therapeutic Goods Administration)¹⁰.

8.1 Contraindications to LDA (rare in women of reproductive age)

- Previous peptic ulcer
- Asthma induced by Non-Steroidal Anti Inflammatory Drugs
- Allergy to aspirin

8.2 What dose?

- 100 milligram enteric coated tablet of aspirin is recommended as LDA >75 milligrams may have slightly better effects compared with LDA <75 milligrams².
- Take with food

8.3 Bleeding in early pregnancy

- Approximately 20% of women who have ongoing pregnancies will experience vaginal bleeding before 20 weeks'
- Aspirin has anti-platelet effects by inhibiting the production of thromboxane, which binds platelets together to create a patch over damaged walls of blood vessels
- Women taking LDA who experience bleeding should be advised to contact their midwife or maternity care provider
- LDA can be continued if spotting or light vaginal bleeding occurs in early pregnancy, however specialist advice is recommended for all women with moderate to heavy bleeding (bleeding like a period or with blood clots)

- If moderate to heavy bleeding occurs discontinue aspirin and arrange specialist consultation

8.4 When should LDA be stopped?

- 36-37 weeks is the usual time to stop, but there are no major concerns if women give birth taking LDA.

References

1. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD004659. DOI: 10.1002/14651858.CD004659.pub2.
2. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, Forest J-C Giguere Y. Prevention of pre-eclampsia and intrauterine growth restriction with aspirin started in early pregnancy- a meta-analysis. *Obstet Gynecol* 2010;116:402-14.
3. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA, on behalf of the PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet* May 2007 DOI:10.1016/S0140-6736(07)60712-0
4. LeFevre ML on behalf of the U.S. Preventive Services Task Force. Low-Dose Aspirin Use for the Prevention of Morbidity and Mortality From Preeclampsia: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. [Epub ahead of print 9 September 2014] doi:10.7326/M14-1884.
5. http://www.nzf.org.nz/nzf_1529.html
6. Guidelines for Consultation with Obstetric and Related Medical Services. Ministry of Health 2012. Retrieved December 2013 from <http://www.health.govt.nz/publication/guidelines-consultation-obstetric-and-related-medical-services-referral-guidelines>
7. National Institute for Health and Clinical Excellence. (NICE) Hypertension in pregnancy. The management of hypertensive disorders during pregnancy. August 2010
8. Hofmeyr GJ, Lawrie TA, Atallah ÁN, Duley L. Calcium supplementation during pregnancy for preventing hypertensivedisorders and related problems. *Cochrane Database of Systematic Reviews* 2010, Issue 8. Art. No.: CD001059. DOI: 10.1002/14651858.CD001059.pub3.
9. Hofmeyr GJ, Belizán JM, von Dadelszen P; Calcium and Pre-eclampsia (CAP) Study Group. Low-dose calcium supplementation for preventing pre-eclampsia: a systematic review and commentary. *BJOG*. 2014 Jul;121(8):951-7. doi: 10.1111/1471-0528.12613.
10. <https://www.tga.gov.au/prescribing-medicines-pregnancy-database#searchname>

Cover Image courtesy of David Castillo Dominici at FreeDigitalPhotos.net