New Zealand College of Midwives

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

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Developed by:

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

NEW ZEALAND COLLEGE OF MIDWIVES (NZCOM)

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1. 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 pre-eclampsia include:
  - Previous pre-eclampsia requiring delivery before 37weeks
    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
  - Assisted conception with oocyte donation
  - Family history of pre-eclampsia (mother and/or sister)
- Women with major risk factors have a risk of pre-eclampsia of about 20%.
- All women with major **medical** risk factors for pre-eclampsia require specialist consultation as per "Guidelines for Consultation with Obstetric and Related Medical Services", as used in conjunction with Section 88.
- It is recommended that midwives make contact with the obstetric service before prescribing low dose aspirin (LDA).
- Early referral is advised to facilitate timely access to obstetric assessment and advice. A telephone or 'virtual' consultation should ideally be an adjunct to referral for face-to-face consultation, but referral processes and management pathways vary between DHBs.
- LDA commenced before 16 – 20 weeks reduces the risk of pre- eclampsia in women with major risk factors.
- The optimum timing for administration of LDA is in the evening or at bedtime and the optimum dosage is 100 milligrams.
- It is recommended that LDA is prescribed by the obstetric service whenever possible.
- Initiation of LDA treatment is recommended at 12 weeks and discontinued at 36 weeks.
- Women with major risk factors for pre-eclampsia will also benefit from calcium supplementation during pregnancy.
- At the specialist consultation calcium, which also reduces the risk of pre-eclampsia in women at high risk, may be prescribed.

2. 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. Background

Pre-eclampsia is characterised 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 of 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]

A Cochrane systematic review has 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] 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] Importantly, a 14% reduction in fetal and neonatal deaths was also reported [RR 0.86 (95% CI 0.76 to 0.98)]. Some systematic reviews have demonstrated a greater benefit when aspirin is started at ≤16 week's [3 4] but others have reported efficacy when LDA is commenced after 16 weeks'.[1 5 6] It is therefore considered ideal to commence LDA at ≤16 weeks' but there may still be benefit in commencing after 16 weeks'.

Studies have assessed the effect of a range of doses of LDA and the beneficial effect appears greater with doses >75 milligram.[5] In New Zealand 100 milligram enteric coated Aspirin tablets are available and subsidised by Pharmac and this is the recommended dose.[7] Enteric-coated tablets reduce the risk of gastric side effects.

4. Advice to practitioners

All women presenting for maternity care need a comprehensive general and obstetric history and assessment 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" [8] for guidance about ongoing care arrangements.

5. 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 5] 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

Major Risk Factors

Pre-eclampsia in previous pregnancy & birth <37 weeks or HELLP syndrome

Predisposing medical conditions Autoimmune eg.

- Systemic Lupus erythematosus
- Scleroderma
- Anti-phospholipid syndrome

Chronic hypertension (especially severe)

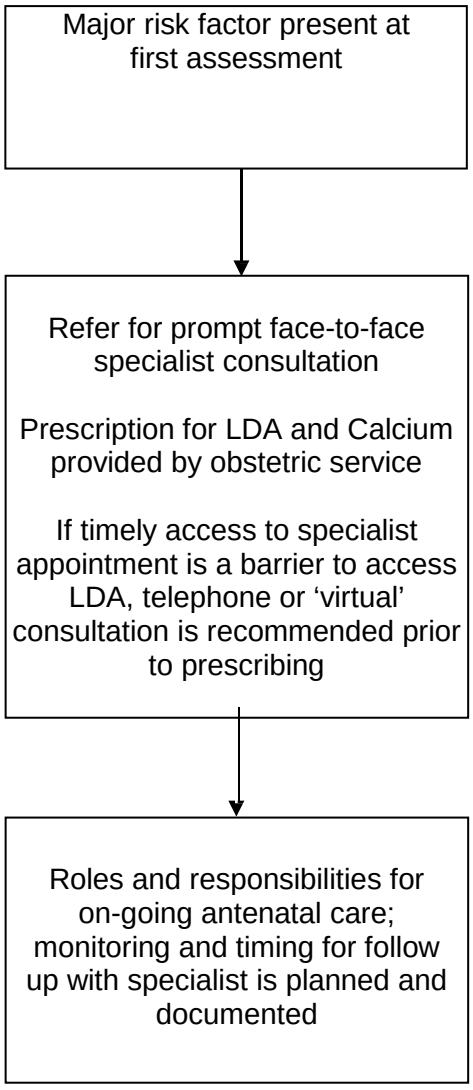
Diabetes type 1 and 2

Chronic kidney disease

Assisted conception with oocyte donation[9]

Family history of pre-eclampsia (mother and/or sister)

For women with any major risk factor for pre-eclampsia, meta-analysis suggests a reduction in risk of pre-eclampsia of 46% (95% CI 30% to 59%) when LDA therapy is initiated in early pregnancy.[1] These women may also benefit from calcium. LDA will reduce the risk from about one in five to about one in ten in high risk women.



6. Major risk factors for pre-eclampsia

The background risk for pre-eclampsia 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 approximate 20% risk of developing pre-eclampsia and LDA prophylaxis is recommended.[6] These conditions are also major risk factors for small for gestational age (SGA) infants.

Major risk factors are identified in Figure 1.

When a major risk factor is identified at first assessment, prompt referral for obstetric assessment and care planning is recommended as per the Referral Guidelines.[8] 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 obstetric service whenever possible. LDA 100mg will usually be commenced at 12 weeks'.

7. 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)].[10]

The Cochrane review demonstrated that calcium supplementation also reduces the overall risk of pre-eclampsia, [RR 0.45 (95% CI 0.31 to 0.65); I^2 = 70%]. As above the effect was greatest for women with low calcium diets and women at high risk of pre-eclampsia. Importantly calcium supplementation also reduced the risk of preterm birth [RR 0.76 (95% CI 0.60 to 0.97); I^2 = 60%], maternal death or serious maternal morbidity [RR 0.80 (95% CI 0.65 to 0.97); I^2 = 0%].[11] Calcium did not reduce the rate of SGA infants and should not be prescribed for prevention of SGA alone. A decision regarding calcium supplementation will be made at the time of specialist consultation in women with major risk factors, and the prescription provided by the obstetric service 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-eclampsia [12] and results of a large study are awaited.

8.0 Informed consent requirements

Women need a full discussion regarding the benefits versus risks / side-effects of LDA treatment in order to give informed consent. (See Right 6 of the Code of Health and Disability Services Consumer's Rights).[13] 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.[14]

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 and when to take?

- A daily 100 milligram enteric coated tablet of aspirin is recommended.[1]
- Take at bedtime or after the evening meal – evening administration appears to be associated with greater protection from pre-eclampsia and SGA compared with administration in the morning.[15]

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.

9. 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.

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