South African National Essential Medicine List
Primary Health Care Level Medication Review Process
Component: Obstetrics & Gynaecology

EVIDENCE SUMMARY

Date: 2 May 2024
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QUESTION: Initiation of aspirin at primary health care (PHC) level for reducing the risk of early onset pre-eclampsia in pregnant women with risk factors for the development of early onset pre-eclampsia (e.g. pre-eclampsia in a previous pregnancy, chronic hypertension, diabetes, antiphospholipid syndrome, or systemic lupus erythematosus (SLE)), as a nurse-initiated prescription prior to referral to secondary level of care.

Background

Hypertensive disorders of pregnancy (HDP) are the most common direct cause of maternal mortality and account for 18% of all maternal deaths in South Africa (SA). [1] In SA, most pregnant women book for basic antenatal care at community health clinics. If the patient is identified as high risk, the patient is referred to the next level of care. This referral may be immediate or take days to weeks depending on the individual patient risk profile and health system challenges. There is a risk that the appointment at the district level will only be at >20 weeks gestation which is too late to initiate aspirin. Therefore, it is crucial that the patient starts aspirin prophylaxis timeously for the prophylaxis to be effective in reducing the risk of early onset pre-eclampsia.

Currently, aspirin, oral, 150 mg daily until 36 weeks is recommended for prevention of pre-eclampsia in the Adult Hospital Level (AHL) Standard Treatment Guidelines (STGs), for women at high risk of pre-eclampsia, e.g. pre-eclampsia in a previous pregnancy, chronic hypertension, diabetes, antiphospholipid syndrome, or systemic lupus erythematosus (SLE). The guidance in the AHL STGs stipulates that prophylaxis should be initiated from 6 weeks' gestation onwards, preferably starting before 16 weeks' gestation.[2]

As detailed in the current AHL STG for the prevention of pre-eclampsia, aspirin, oral can only be initiated at secondary level of care. Historically, the National Essential Medicines List Committee retained aspirin for secondary level initiation in all women with chronic hypertension, who are pregnant as the patient would require referral to the secondary level of care for evaluation and management.[3,4,5]NEMLC highlighted that pregnant women with chronic hypertension may have been on complex and teratogenic antihypertensive medication and ultrasound scanning to evaluate the foetus for abnormalities, and/or switching to safer medication would be appropriate for secondary level and therefore initiation of prophylactic aspirin and calcium for pre-eclampsia would also only be appropriate for secondary level of care. Expert opinion was cited as the evidence for strict secondary level aspirin initiation for prevention of pre-eclampsia.[6] However, this expert opinion neglected to recognise that the women who are currently well, but have historical risk factors (e.g. previous history of pre-eclampsia) might not be referred immediately to secondary care, but only at a scheduled appointment, which may be a few weeks later. These patients will then potentially miss out on the benefit of early initiation of aspirin prophylaxis.

Other Guidelines

The updated maternity guidelines (2024)[7] recommend Aspirin 150mg taken at bedtime (at night to prevent gastric irritation) from 6 weeks of gestation (but preferably before 16 weeks) until 36 weeks to reduce the risk of early onset pre-eclampsia. This is based on the 2018 International Society for the Study of Hypertension in Pregnancy (ISSHP) guideline, which was adopted for use in SA.[8] The ISSHP was updated in 2021, and cites the evidence for use of aspirin in women at increased risk of pre-eclampsia as strong (ISSHP 2021).[9]

The national hypertension in pregnancy guidelines (2018/2019) recommend that aspirin should be started for all women with risk factors for early onset pre-eclampsia (prior pre-eclampsia, chronic hypertension, multiple gestation, pre-gestational diabetes, maternal body mass index >33, anti-phospholipid syndrome/systemic lupus erythematosus (SLE), and assisted reproduction therapies) but only if the woman books early enough to start aspirin (ideally 12 to 14 weeks) but can be up to 20 weeks' gestation (with 75 – 162 mg/day aspirin – a quarter or half an aspirin tablet). Aspirin should be stopped at 36 weeks to reduce the risk of bleeding at delivery. It should be noted that aspirin is also not successful in reducing the risk of term pre-eclampsia.[9]

External Comment & Alignment to NDOH Guidelines
External comment advocating for the initiation of aspirin at PHC has recently been received by the NDOH. Furthermore, alignment with the NDOH program guidelines would be ideal.

Summary of Evidence
The evidence for the use of aspirin in women at risk for early-onset pre-eclampsia is regarded as strong[10] and well documented.

Efficacy
Ngene & Moodley[10] provide a summary regarding evidence for preventing maternal morbidity and mortality from preeclampsia and eclampsia particularly in low- and middle-income countries as follows (Taken from Ngene & Moodley):

- ***Cochrane review (2019):*** % reduction in pre-eclampsia as a result of aspirin prophylaxis with most trials using a dose of 50–75 mg/day was 18%, risk ratio 0.82 (36,716 women, 60 trials, RR 0.82, 95% CI 0.77 to 0.88; high-quality evidence). NNT =61 for one woman to benefit.
- ***National Institute for Health and Care Excellence (NICE)***: recommends aspirin for women with one major risk factor (hypertension in prior pregnancy, chronic renal diseases, diabetes, chronic hypertension, autoimmune diseases (e.g., antiphospholipid syndrome and systemic lupus erythematosus) or two moderate risk factors (nulliparity, age ≥40 years, family history, body mass index ≥35 kg/m2 at first antenatal visit, pregnancy interval >10 years, multifetal pregnancy) for pre-eclampsia.
- ***Low dose aspirin:*** clinical trials showed greater reduction of pre-eclampsia recurrence in women who had a prior history of preterm pre-eclampsia than in those with a previous pre-eclampsia at term.
- In ***ASPRIN trial*** that investigated nulliparous women in low- and middle-income countries, the effectiveness of aspirin (initiated between 6- and 13-weeks' gestation) in preventing preterm birth was greatest in births at <34 than <37 weeks' gestational age: RR 0·75, (95% CI: 0·61 - 0·93), p = 0·039 vs RR 0·89, (95% CI: 0·81 to 0·98), p = 0·012. Preterm birth before 37 weeks occurred in 668 (11·6%) of the women who took aspirin and 754 (13·1%) of those who took placebo.
- The Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial confirmed a significant reduction in risk when aspirin was used following screening with a multimodal algorithm which included maternal risk factors.

Safety
The literature shows[10] low-dose aspirin has been widely regarded as safe in pregnancy, although there are small increases in bleeding risk; mostly intrapartum and postpartum bleeding and a small (0.06%) increase in neonatal intracranial bleeds. Most of these risks can be mitigated by discontinuing aspirin by 36 weeks, based on the lack of effectiveness for prevention of term pre-eclampsia.

Primary Health Care
Ngene & Moodley[10] acknowledge that in low- and middle-income countries especially at primary health care level, diagnosis of preeclampsia might be limited due to financial costs and technological challenges. In such settings, recognising signs and symptoms as well as risk factors associated with preeclampsia, would be important. Initiation of timeous prophylaxis with aspirin would therefore be vital.

Cost Considerations

At March 2024 tender prices,[11] a 28-day supply of aspirin of 150mg ranges from R2.55 to R5.74, assuming half of the scored 300mg tablet will be used.

Medicine Pack short Description	Pack Size	Supplier Name	Price	Approximate Price Per Tablet*	Approximate Month Supply (28 Days)*
Aspirin; 300mg; tablet, scored; 14 Tablets	14	Ipharma (Pty) Ltd	5.74	0.41	5.74
Aspirin; 300mg; tablet, scored; 14 Tablets	14	Resmed Healthcare Cc	4.27	0.31	4.27
Aspirin; 300mg; tablet, scored; 14 Tablets	14	Unimed Healthcare (Pty) Ltd	4.08	0.29	4.08
Aspirin; 300mg; Tablet; 96 Tablets**	96	Resmed Healthcare Cc	17.5	0.18	2.55

*Rounded to 2 decimal places

** Not listed as scored – assumption that patient can break tablet

Conclusion

Aspirin is widely available, inexpensive and has a favourable fetal and maternal safety profile and research shows that aspirin prophylaxis for women at risk of hypertensive related diseases of pregnancy particularly in low- and middle-income countries results in reduction in the risk of early onset preeclampsia.

Proposal

To alter prescribing level of aspirin, 150mg, oral for reduction in the risk of early onset pre-eclampsia in pregnancy to PHC level for nurse initiation, in alignment with NDOH maternity and hypertension in pregnancy guidelines.

PHC/Adult ERC Recommendation: 2 May 2024

The PHC /AHL ERC supports the use of aspirin 150mg oral, until 36 weeks of pregnancy, for prevention of pre-eclampsia for all levels of care.

NEMLC Recommendation: 16 May 2024

NEMLC accepted the proposal as recommended by the PHC/Adult ERC (see above)

[1] South African National Department of Health (NDoH). The 2017 Annual Saving Mothers Report. Pretoria: NDoH; 2017:5.

[2] National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2020. http://www.health.gov.za/

[3] Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2019 Oct 30;2019(10):CD004659. https://pubmed.ncbi.nlm.nih.gov/31684684/

[4] Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannavar M, Okitawutshu J et al; ASPIRIN Study Group. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. Lancet. 2020 Jan 25;395(10220):285-293. https://www.ncbi.nlm.nih.gov/pubmed/31982074

[5] National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Review: Safety of aspirin in pregnancy, February 2020. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[6] National Department of Health. South African Primary Healthcare Level Essential Medicines List Chapter 6: Obstetrics & Gynaecology Conditions. National Essential Medicines List Committee (NEMLC) Recommendations for Medicine Management (2016 – 2018)

[7] NDOH. National Maternity Care Guidelines. Updated 2024.

[8] Moodley J, Soma-Pillay P, Buchmann E, Pattinson RC. Hypertensive disorders in pregnancy: 2019 National guideline. S Afr Med J. 2019 Sep 13;109(9):12723. PMID: 31635598.

[9] Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, Kenny LC, McCarthy F, Myers J, Poon LC, Rana S, Saito S, Staff AC, Tsigas E, von Dadelszen P. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2022 Mar;27:148-169. doi: 10.1016/j.preghy.2021.09.008. Epub 2021 Oct 9. PMID: 35066406.

[10] Ngene NC, Moodley J. Preventing maternal morbidity and mortality from preeclampsia and eclampsia particularly in low- and middle-income countries. Best Pract Res Clin Obstet Gynaecol. 2024 Feb 15;94:102473. doi: 10.1016/j.bpobgyn.2024.102473. Epub ahead of print. PMID: 38513504.

[11] NDOH Tenders, available from https://www.health.gov.za/tenders/ (accessed 18 April 2024).