Low Dose Aspirin

I. **Definition:** For the purpose of this protocol, low-dose aspirin will be defined as a dose of 81 mg, as defined by the American College of Gynecology Committee Opinion No. 743.
   a. Higher doses (150mg) have been studied, but utilized a screening strategy that is not widely performed in the United States (serum analytes and uterine artery Doppler), limiting the generalizability of the findings.

II. **Background:** Preeclampsia is a common complication of pregnancy associated with severe morbidity and mortality for both the mother and the neonate, especially when early onset and severe in nature. Thus, a challenge of modern obstetrics becomes identifying women at high risk for development of early onset, severe pre-eclampsia and taking measures to prevent this diagnosis. Importantly, low dose aspirin has been used during pregnancy to prevent or delay the onset of preeclampsia. Aspirin is a cyclooxygenase inhibitor with mild anti-inflammatory and antiplatelet properties that has been investigated as a preventative measure for preeclampsia since the 1970's. A meta-analysis of more than 30 trials investigating dosages of 50-150mg of aspirin for the prevention of pre-eclampsia showed a 10 percent lower incidence of preeclampsia in this population. Mixed data was reported as to whether gestational age of initiation affects the strength of this finding. The ASPRE trial confirmed a significantly lower incidence of the primary outcome of preeclampsia <37 weeks in high risk women who took aspirin vs. placebo.

III. **Pathophysiology:** Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits COX-1 and COX-2 enzymes, which are necessary for prostaglandin biosynthesis. The COX-1 isoform is present on vascular endothelium and regulates production of thromboxane A2 and prostacyclin. Prostacyclin is a vasodilator and inhibitor of platelet aggregation, while thromboxane A2 is a vasoconstrictor and promotes platelet aggregation. Aspirins effect on COX- dependent prostaglandin synthesis is dose dependent. At lower doses, aspirin preferentially inhibits thromboxane A2. This is thought to improve early placental perfusion, but the exact mechanism of action is unknown.

IV. **Safety Profile:**
   a. Maternal Risks: no increased risk of hemorrhagic complications associated with low dose aspirin use during pregnancy
   b. Fetal Risks: no increased risk of ductal closure in large RCT's, no increased risk of neonatal intracranial hemorrhage or other neonatal hemorrhagic complications, no increased risk of fetal anomalies, including gastroschisis.
   c. Exclusion criteria:
      i. Allergy to aspirin/NSAID's
      ii. Hx of nasal polyps (can cause life-threatening bronchospasm)

iii. Hx of GI bleed
iv. Severe hepatic dysfunction
v. Hx of hemorrhagic stroke
vi. Obstetric bleeding—decisions made on case-by-case basis

d. Safety profile of low dose aspirin is supported by Society for Maternal Fetal Medicine (SMFM), American College of Obstetrics and Gynecologists (ACOG), and U.S. Preventative Services Task Force

V. Recommendations:

a. We recommend low dose aspirin (81 mg) for women at high risk for preeclampsia based on criteria from **EITHER** ASPRE risk calculator **OR** risk factors discussed in table in VI (borrowed from American College of Gynecology Committee Opinion No. 743)
b. Low dose aspirin should be initiated between 12-28 weeks (optimally before 16 weeks) and continued daily until delivery
c. Low dose aspirin should be initiated based on a "increased risk" result from ASPRE fetal medicine calculator OR 1 high or 2 or more moderate risk factors from Medical Risk Assessment Table (VI).
d. Low dose aspirin is currently NOT recommended solely for indication of prior unexplained stillbirth, prevention of fetal growth restriction, prevention of spontaneous preterm birth, or prevention of early pregnancy loss.
e. Risk calculator utilized by ASPRE Trial: https://fetalmedicine.org/research/assess/preeclampsia/first-trimester

VI. Medical Risk Assessment:

Table 1. Clinical Risk Assessment for Preeclampsia*

Risk Level	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	• Nulliparity • Obesity (body mass index greater than 30) • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age 35 years or older • Personal history factors (eg, low birthweight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

*Includes only risk factors that can be obtained from the patient's medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.

†Single risk factors that are consistently associated with the greatest risk of preeclampsia. The preeclampsia incidence rate would be approximately 8% or more in a pregnant woman with one or more of these risk factors.

‡A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk of preeclampsia. These risk factors are independently associated with moderate risk of preeclampsia, some more consistently than others.

§Moderate-risk factors vary in their association with increased risk of preeclampsia.

Modified from LeFevre, ML. 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 2014;161:819–26.

VII. References

1. ACOG Committee Opinion No. 743: Low-Dose Aspirin Use During Pregnancy.Obstet Gynecol. 2018; 132(1): e44—e52. doi: 10.1097/ AOG.0000000000002708
2. Daniel L. Rolnik, David Wright, Liona C. Poon, Neil O'Gorman, Argyro Syngelaki, Catalina de Paco Matallana, Ranjit Akolekar, Simona Cicero, Deepa Janga, Mandeep Singh, *et al.* "Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia." *New England Journal of Medicine.* 2017. doi: 10.1056/NEJMoa1704559