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Impact of the ACOG guideline regarding low dose aspirin for prevention of superimposed preeclampsia in women with chronic hypertension

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Abstract

Background: Patients with chronic hypertension are at increased risk for superimposed preeclampsia. The 2016 American College of Obstetricians and Gynecologists (ACOG) guideline recommended initiating 81 mg daily aspirin for all pregnant women with chronic hypertension to prevent superimposed preeclampsia.

Objective: 1) To evaluate the rates of implementation of the 2016 ACOG guideline over time; 2) To evaluate the effectiveness of aspirin for the prevention of superimposed preeclampsia and other adverse maternal and neonatal outcomes in women with chronic hypertension before and after this guideline.

Study design: This is a retrospective study of women with chronic hypertension who delivered at Thomas Jefferson University Hospital from 1/2014 through 6/2018. This cohort of women with chronic hypertension was divided into 2 groups, before and after the ACOG recommendation published in 7/2016. Daily 81 mg aspirin was initiated between 12 to 16 weeks. We excluded multiple gestations and incomplete records. The primary outcome was incidence of superimposed

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preeclampsia, and secondary outcomes were incidence of superimposed preeclampsia with or without severe features, small for gestational age, and preterm birth <37 weeks. Subgroup analysis based on risk stratification was evaluated in women with chronic hypertension requiring antihypertensive medication, history of preeclampsia and pre-gestational diabetes.

Results: We identified 457 pregnant women with chronic hypertension, 203 in the post-ACOG group and 254 in the pre-ACOG group. Aspirin 81 mg was offered to 142 (70%) in the post-ACOG group and 18 (7.0%) in the pre-ACOG group. Maternal demographics were not significantly different. The overall incidence of superimposed preeclampsia was not significantly different: 87 (34.3%) vs. 72 (35.5%), $p=0.79$ in the pre and post ACOG guideline groups, respectively. Superimposed preeclampsia with severe features significantly increased: 32 (12.6%) vs 9 (4.4%), $p<0.01$ while superimposed preeclampsia without severe features significantly decreased: 55 (21.7%) vs 63 (31.0%) $p=0.03$. There were no significant differences in small for gestational age neonates or preterm birth <37 weeks incidences between groups. There were no significant differences in the subgroup analysis based on the severity of chronic hypertension requiring antihypertensive medication, history of preeclampsia, or pregestational diabetes.

Conclusion: After the adoption of the ACOG guidelines in 70% of the cohort, superimposed preeclampsia, small for gestational age, and preterm birth were not significantly decreased after implementation of aspirin 81mg initiated between 12 to 16 weeks of gestation.

Condensation:

Low dose aspirin does not prevent superimposed preeclampsia in women with chronic hypertension.

Keywords

Low dose aspirin; aspirin; superimposed preeclampsia; preeclampsia; chronic hypertension; ACOG; small for gestational age; preterm birth

INTRODUCTION

Preeclampsia is a hypertensive disorder that affects millions of pregnant women on a global scale. It increases the risk of preterm birth (PTB), end-organ damage, maternal mortality, and future cardiovascular disease such as coronary artery disease and stroke.¹ Hypertensive disorder in pregnancy is the second most common direct cause of maternal mortality worldwide (14%).² Superimposed preeclampsia occurs when women with chronic hypertension (CHTN) develop preeclampsia. It is characterized by worsening or uncontrollable hypertension, new onset of proteinuria, or significantly increased preexistent proteinuria.³

The pathophysiology underlying preeclampsia is not fully defined.^{4, 5} It has been theorized that there are two stages of preeclampsia: 1) inadequate placental implantation^{6, 7} and 2) a maternal hypertensive state resulting from placental hypoxia, oxidative stress, and inflammation.^{8, 9} In normal pregnancy, trophoblasts invade the myometrium and induce remodeling of the uterine spiral arteries to low resistance vessels, allowing for enhanced uteroplacental blood flow.^{4, 10} In preeclampsia, shallow invasion of the myometrium causes

poor remodeling of the spiral arteries, leading to reduced uteroplacental perfusion.^{7, 10} The metabolic stress results in the release of secondary inflammatory mediators such as thromboxane A2 into the maternal bloodstream, which causes endothelial dysfunction and reduces endothelial-derived vasodilator properties, leading to vasoconstriction and increased maternal blood pressure (BP).¹¹ Release of other mediators such as soluble receptor (sFLT) for vascular endothelial growth factors (VEGF), placental growth factor (PlGF), type 1 angiotensin II receptor antibodies, hypoxia inducible factors (HIF) have all been implicated in multiple pathophysiological mechanisms to produce the clinical syndrome preeclampsia.^{10, 12} Pre-existing conditions such as hypertension, diabetes, and inflammatory states such as autoimmune disease are believed to contribute to poor placentation, decreased uteroplacental perfusion, and overall level of inflammation^{4-8, 11}. Low dose aspirin has been proposed to decrease the risk of preeclampsia, through inhibition of cyclooxygenase-1 in the arachidonic acid pathway, decreasing thromboxane A2 production.¹³

In September 2014, the United States Preventative Services Task Force (USPSTF)¹⁴ conducted a systematic review to identify the risk factors for which physicians should recommend low dose aspirin to prevent the incidence of preeclampsia: history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or type 2 diabetes, renal disease, or autoimmune disease. In July 2016, the American College of Obstetricians and Gynecologists (ACOG) endorsed the USPSTF recommendation in offering 81 mg low dose aspirin for patients with these high risk factors between 12 and 28 weeks of gestation.¹⁵ Guidelines in multiple countries now recommend that low-dose aspirin prophylaxis should be considered for women with more than one of several moderate risk factors for preeclampsia.^{1, 15-18}

The objective of this study was to evaluate 1) the implementation of 2016 ACOG guideline recommending low dose aspirin in high-risk patients over time and 2) the effectiveness of aspirin in preventing superimposed preeclampsia and adverse maternal and neonatal outcomes in women with CHTN.

METHODS

Study and Population

This is a retrospective cohort study of all patients with singleton gestation and diagnosis of CHTN who had prenatal care since the first trimester and delivered at Thomas Jefferson University Hospital from January 2014 to June 2018. The diagnosis of CHTN was made by patient history, current prescription of antihypertensive medication, or elevated BP defined as 140 mmHg systolic or 90 mmHg diastolic identified on two occasions before 20 weeks of gestation. Pregnancy dating was confirmed by ultrasound before 20 weeks of gestation. We divided this cohort of women with CHTN into two groups: pre-ACOG guideline and post-ACOG guideline. The post-ACOG group consisted of women who were less than 16 weeks after the ACOG guideline was issued in July 2016. Our practice recommended daily low dose 81 mg aspirin to start between 12 to 16 weeks of gestation to patients with CHTN, and it was continued until delivery. Patients with multiple gestations, major fetal malformations, known genetic conditions, incomplete medical records or incomplete delivery data were excluded from the study. The Institutional Review Board at Thomas

Jefferson University Hospital approved this study; IRB # 14D.96 was first approved on 03/15/2014, reviewed annually, and last approved on 5/23/2019.

Variables

All data was obtained from electronic medical records, including demographic data such as age, race, body mass index (BMI, kg/m²), obesity (BMI > 30 kg/m²), nulliparity, and smoking during pregnancy. Diagnosis of pre-gestational diabetes, history of preeclampsia, and other chronic medical conditions were also recorded. Data regarding prescription of aspirin including date and gestational age at starting date were collected. Patient adherence to aspirin was collected through prenatal visit documentation from patient self-reporting. Tablet count was not feasible.

Diagnostic criteria for superimposed preeclampsia with and without severe features were based on the 2013 ACOG Hypertension in Pregnancy Task Force.³ Superimposed preeclampsia was diagnosed by a sudden increase in previously well-controlled BP or escalation of antihypertensive medications to control BP, new onset of proteinuria or a sudden increase in known proteinuria prior to or early in pregnancy. Sudden increases in BP or proteinuria were not well defined by the 2013 ACOG Hypertension in Pregnancy guideline. In our practice, we defined sudden increase in BP as previously well-controlled BP: normal (<140 mmHg systolic or <90 mmHg diastolic) or mild range BP (140–159 mmHg systolic or 90–104 mmHg diastolic) in clinic and by self-monitoring at home that subsequently worsened to severe range BP (≥ 160 mmHg systolic or ≥ 105 mmHg diastolic) as confirmed by the clinic or hospital, requiring initiation or escalation of antihypertensive medications to achieve a goal of mild range BP's. Escalation of medication was defined as the initiation of antihypertensive medication, increase in prior antihypertensive medication or addition of a second antihypertensive agent in order to meet the goal of mild range BP's. The treating provider determined the choice of antihypertensive. Sudden increase in proteinuria was defined as a 50% increase in proteinuria compared to baseline pre-pregnancy or first trimester proteinuria. In the absence of a 24-hour urine protein collection, often due to non-compliance, a urine protein/creatinine ratio (UPC) was obtained. A sudden increase in proteinuria was also defined as a UPC ≥ 0.5 with a baseline UPC < 0.3.

Superimposed preeclampsia with severe features was diagnosed when any of the following were present: severe range of BP (≥ 160 mmHg systolic or ≥ 105 mmHg diastolic despite escalation of antihypertensive therapy (uncontrolled severe BP), platelet count <100,000/microliter, elevated liver transaminases (two times the upper limit of normal concentration according to institutional laboratory), new onset or worsening renal insufficiency (creatinine ≥ 1.1 mg/dL or twice the baseline value), pulmonary edema or severe persistent right upper quadrant/epigastric pain or cerebral/visual disturbances unresponsive to medication.³

Indications for delivery, delivery information, maternal complications and neonatal outcomes such as birthweight in grams, small for gestational age (SGA) defined as less than 10th percentile according to Fenton growth chart,¹⁹ Apgar at 5 minutes, neonatal intensive care unit (NICU) admission rates, and incidence of mechanical ventilation, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage or sepsis were also collected.

Our institutional practice regarding management of patients with CHTN included increasing the frequency of prenatal visits to every 2–4 weeks and prescribing automated home blood pressure devices for self-monitoring and reporting at prenatal visits. Blood pressure devices were not standardized as the brand was determined by insurance coverage or out of pocket payment. Patients brought them to the clinic for teaching as needed. We emphasized the importance of appropriate cuff size given the high incidence of obesity in our population. Patients notified physicians of elevated blood pressures by phone or electronic message which were used to triage for further clinical evaluation. All decisions regarding diagnoses, interventions, and medications were based on blood pressure readings confirmed by standardized instruments in the clinic, emergency room, or labor and delivery unit. Chronic antihypertensive medication was continued if patients were taking them prior to the first prenatal visit. Medications with potential fetal adverse effects were substituted. Medication was initiated if BP was ≥ 160 mmHg systolic or ≥ 105 mmHg diastolic as recommended by ACOG. Baseline labs were requested at the first prenatal visit to evaluate for end-organ damage; these included complete blood count, electrolytes, liver function tests, creatinine, 24-hour urine protein, EKG, HbA1c or early 1-hour glucose test if not already diagnosed with diabetes mellitus, and an ophthalmology consultation. Reports of dating and anatomy ultrasounds were reviewed for gestational age, major fetal malformations, and intrauterine growth restriction (IUGR). Serial fetal growth evaluations were done every 4 weeks for patients with CHTN per TJUH protocol. IUGR was defined by estimated fetal weight less than 10th percentile on the Hadlock et al growth curve.²⁰ Patients diagnosed with IUGR were followed by non-stress tests (NST) twice a week and weekly umbilical artery Doppler and amniotic fluid index. Women diagnosed with superimposed preeclampsia without severe features continued outpatient observation with weekly visits, laboratories and twice a week NSTs, while those with severe features were admitted to the hospital for daily surveillance to determine the appropriate time for delivery. Indications for delivery were ≥ 37 weeks for those with superimposed preeclampsia without severe features and ≥ 34 weeks for those with superimposed preeclampsia with severe features according to the 2013 ACOG Hypertension in Pregnancy Task Force.³ The primary outcome was the overall incidence of superimposed preeclampsia compared in the pre and post ACOG groups and the implementation of the low dose aspirin guideline. Secondary outcomes were incidence of superimposed preeclampsia with and without severe features, gestational age at diagnosis of preeclampsia, gestational age at delivery, and incidence of preterm delivery before 37, 34, and 28 weeks of gestation.

Analysis of incidence of superimposed preeclampsia with and without severe features pre and post ACOG guidelines was conducted in the following subgroups: 1) Only CHTN without other risk factors, 2) Severe CHTN requiring antihypertensive medications, 3) CHTN and history of preeclampsia, and 4) CHTN and pre-gestational diabetes.

Statistics

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version. 22 (IBM Inc., Armonk, NY, USA). Data are shown as means \pm standard deviation (SD) or number (percentage). Differences between pre-ACOG group and post-ACOG groups were analyzed using Chi-square test or Fisher's exact test for categorical variables.

Results of primary and secondary outcomes were presented as odds ratio (OR) or as mean difference with 95% of confidence interval (CI). In the presence of any significant demographic confounders, adjusted ORs (aOR) were calculated after adjusting for the confounders. Sub-group analysis by risk factors and nonparametric data were compared using Wilcoxon and Mann-Whitney tests. P value < 0.05 was considered statistically significant.

RESULTS

Eight thousand one hundred and eighty women with singleton pregnancy delivered at TJUH between January 2014 and June 2018. Among them, 652 (8.03%) had a diagnosis of CHTN at discharge, and 457 (70%) of them had complete records for analysis. The pre-ACOG group had 254 (55.5%) patients and the post-ACOG group had 203 (44.5%) patients.

Maternal Demographics

There were no statistically significant differences in the demographic characteristics between the pre- and post-ACOG groups. (Table 1). As a result, we did not need to adjust for any confounders in the main outcomes. Dating ultrasound by crown rump length before 14 weeks was done in 388 (85%) of women, and all women had anatomy ultrasound and serial fetal growth evaluations.

ACOG Guideline Implementation

Aspirin was offered to 142/203 (70%) women post-ACOG and 18/254 (7%) pre-ACOG. Implementation of the guideline increased over time from 24.2% in 2016 to 82.6% in 2018, (Figure 1). After the ACOG guideline was released, patients with CHTN and history of preeclampsia were more likely to be prescribed aspirin than patients with only CHTN 48/55 (87.3%) vs 72/114 (63.3%), $p<0.01$) and had better documentation regarding adherence to the prescribed aspirin than patients with only CHTN 45/55 (81.8%) vs 65/114 (57.0%), $p<0.01$). (Figure 2)

Maternal Outcomes

The overall incidence of superimposed preeclampsia was unchanged 87/254 (34.3%) vs 72/203 (35.5%), $p=0.79$ when the pre-ACOG and post-ACOG groups were compared. The incidence of superimposed preeclampsia without severe features was significantly decreased 32/254 (12.6%) vs 9/203 (4.4%), $p<0.01$ while the incidence of superimposed preeclampsia with severe features was significantly increased 55/254 (21.7%) vs 63/203 (31.0%), $p=0.02$ in the pre and post ACOG groups, respectively. There were no differences regarding gestational age at diagnosis of superimposed preeclampsia, indications of delivery, mode of delivery, maternal or fetal complications. There were seven cases of stillbirths in both groups and no maternal or neonatal deaths (Table 2). Even when evaluating only women who were offered aspirin in the post-ACOG group 142 (70%) vs the pre-ACOG group, the incidence of superimposed preeclampsia: 57/142 (40.1%) vs. 87/254 (34.3%); odds ratio (OR) 1.3, 95% confidence interval (CI): 0.84 to 1.9), $p=0.27$, remained not significantly different while superimposed preeclampsia with severe features was again significantly increased in the post-ACOG group 52/142 (36.6%) vs 55/254 (21.6%) OR 2.1 (1.3 – 3.3), $p=0.002$.

Women who were prescribed aspirin in the post-ACOG group (70%) vs women who were not prescribed aspirin in the post-ACOG group (30%) were more likely to be older and have a history of preeclampsia. After adjusting for these confounding factors (age and history of preeclampsia), there was no difference in overall incidence of superimposed preeclampsia 15/61 (24.6%) vs 57/142 (40.1%), aOR 1.81 (0.90 – 3.64), but there was a significant increase in superimposed preeclampsia with severe features in patients who were prescribed aspirin 11/61 (18.0%) vs 52/142 (36.6%), aOR 2.36 (1.10–5.06). (Supplementary Material Table 2)

Women who developed superimposed preeclampsia with severe features were evaluated separately to compare patients pre-ACOG and post-ACOG. While there were no differences in inherent maternal demographics, post-ACOG patients were less likely to be on antihypertensive medication 35/55 (63.6%) vs 19/63 (30.2%). After adjusting for this, there were no differences in gestational age at delivery or adverse perinatal outcomes when the pre-ACOG and post-ACOG groups were compared. (Supplementary Material Table 3 and 4)

There were no differences in the overall incidence of superimposed preeclampsia or presence of severe features when the subgroups were analyzed: history of preeclampsia, pre-gestational diabetes, or severity of hypertension based on the need for antihypertensive medication (Table 3).

When analyzing both pre and post-ACOG cohorts combined, the incidence of overall superimposed preeclampsia women with both CHTN and history of preeclampsia was significantly increased when compared with women with only CHTN: 53/116 (45.7%) vs. 87/289 (30.1%) OR 1.9; (95%CI: 1.25–3.0). The incidence of superimposed preeclampsia with severe features was also increased in patients with both CHTN and history of preeclampsia: 40/116 (34.4%) vs. 65/289 (22.5%) OR 1.8; (95%CI: 1.12–2.9) respectively.

Preterm Birth and Neonatal Outcomes

There were no significant differences in the overall gestational age at delivery, incidence of PTB at <37, <34 or <28 weeks when comparing the post-ACOG and pre-ACOG groups. There were no significant differences in neonatal outcomes before and after the ACOG guideline (Table 4). The findings in gestational age and preterm birth remained non-significant even when patients were subdivided by the presence of superimposed preeclampsia with severe features, (Supplementary Material Table 4).

In both pre and post-ACOG groups combined, the incidence of preterm birth < 37 weeks in the entire cohort was 113/457 (24.7%). Women with CHTN and superimposed preeclampsia had an increased incidence of preterm birth <37 weeks 74/159 (46.5%) vs 39/298 (13.1%) $p < 0.0001$; OR 5.7; (95% CI, 3.6–9.1) when compared with women with CHTN without superimposed preeclampsia. There was even higher risk if diagnosed with superimposed preeclampsia with severe features: 68/118 (57.6%) vs 39/298 (13.1%) $p < 0.0001$; OR 9.0; (95% CI, 5.5–14.8).

COMMENT

Principal Findings

The overall implementation rate of the 2016 ACOG guideline for preeclampsia prevention with low dose aspirin 81mg before 16 weeks to women with singleton pregnancy and CHTN was 70%. During 2018, it increased to 82%. The overall incidence of superimposed preeclampsia was unchanged before and after the ACOG guideline; moreover, the incidence of superimposed preeclampsia with severe features was significantly increased. There were no differences in the gestational age at diagnosis of superimposed preeclampsia, PTB by gestational age or SGA.

Results

Our cohort seems to have a high incidence of overall superimposed preeclampsia (35%), recurrent superimposed preeclampsia (45.7%), superimposed preeclampsia with severe features (25%) and perinatal complications, but despite the differences in population and diagnostic criteria over time, our results are consistent with other publications. In an individual participant data (IPD) meta-analysis to calculate the recurrence risk of hypertensive disorders of pregnancy (HDP), 236/581 (41%) women with CHTN developed recurrence of HDP.²¹ In a prospective cohort from United Kingdom, 180/822 (22%) of women with CHTN developed superimposed preeclampsia; half of them had early-onset of superimposed preeclampsia (<34 weeks) with 48% incidence of IUGR and 51% of preterm delivery among them.²² In a retrospective cohort of women with CHTN from Thailand, 130/300 (43.3%) developed superimposed preeclampsia with significantly increased incidence of SGA, low birth weight, asphyxia, and neonatal intensive care unit admission.²³ In a retrospective cohort of 447 women with CHTN from Dallas, Texas; women with baseline proteinuria >300 mg/24 hours were statistically significantly more likely to develop superimposed preeclampsia 44/56 (79%) when compared with women with CHTN and negative proteinuria 193/391 (49%) aOR, 4.22; (95% CI, 2.8–8.5 p<0.001) with increased risk of PTB and SGA.²⁴ These studies indicate that patients with CHTN have a significant risk for developing superimposed preeclampsia and associated complications, requiring much attention and intervention.

We also noticed an increased incidence of superimposed preeclampsia with severe features in the post-ACOG group. After further analysis, we believe this is secondary to a learning curve after the publication of the 2013 ACOG guidelines with new diagnostic criteria and management for superimposed preeclampsia and superimposed preeclampsia with severe features. We hypothesize possible underdiagnosis in the subsequent few years (pre-ACOG group). Some diagnostic parameters such as the definition of sudden increase in blood pressure, indications for initiation or escalation of antihypertensive medications, and the definition of significant increase of proteinuria were unclear, requiring the creation of internal guidelines.

The novelty of this retrospective study is that it evaluated rates of superimposed preeclampsia in a singular high-risk cohort with CHTN and analyzed sub-groups with additional risk factors. The USPSTF performed a systematic review of randomized control

RR, 0.97; (95% CI, 0.84–1.12 p=0.28).⁴⁴ No significant difference was found when women were randomized to initiating aspirin before 16–20 weeks' gestation compared with those randomized at or after 16–20 weeks. They reported a 10% reduction in the incidence of preeclampsia.^{43, 44}

Our findings are consistent with RCTs and IPD meta-analysis reporting that low dose aspirin may not be sufficient for preeclampsia prevention in patients with chronic hypertension.^{25, 38}

The mechanism for the lack of efficacy of low dose aspirin in preeclampsia prevention for certain subgroups of women has been proposed. Broadly, aspirin is required at higher concentrations in pregnancy. Evaluation of different doses of aspirin (100mg vs 150mg) showed that there was a reduction in the total drug metabolite concentration in pregnant vs. non-pregnant women, likely due to altered pharmacokinetics and increased clearance.⁴⁵ Obesity has been implicated as a factor in poor response to low dose aspirin. Obesity limits the absorption of aspirin, and platelet regeneration occurs at a higher rate. This allows for increased renewal of cyclooxygenase-1, decreasing the time-dependent effect of aspirin.⁴⁶ In a secondary analysis of the MFMU RCT,^{25, 47} maternal serum thromboxane B2 (TXB2) (an indirect measure of thromboxane A2) levels were drawn at three different times of pregnancy and stratified by BMI. Obese women, especially those with BMI > 40 kg/m², had higher median TXB2 levels in both the second and third trimesters, and lower rates of complete TXB2 inhibition by aspirin when compared with non-obese women. Chronic diseases as CHTN, diabetes, lupus, renal disease, antiphospholipid syndrome have an increased risk of preeclampsia, likely due to inflammatory factors that may affect the endometrium and uterine and ovarian vasculature prior to pregnancy, altering the implantation process and placentation in the first trimester.⁶ The trophoblastic invasion occurs in two waves; the first wave is decidual invasion of spiral arteries at 8 to 10 weeks and the second wave invasion into myometrial segments at 16 to 18 weeks.⁴⁸ Changes in the timing of aspirin initiation could be an option. Studies in women that underwent in vitro fertilization have shown that preconception low dose aspirin is associated with improved implantation rates, and increased blood flow velocity in the uterine and ovarian arteries with lower pulsatility index values.⁴⁹ RCTs have shown that preconception initiation of 75–100 mg aspirin is safe in pregnancy,^{50–52} A systematic review evaluating low dose aspirin initiated prior to conception or before 11 weeks⁵³ in women with infertility, or recurrent pregnancy loss showed no difference in the incidence of preeclampsia 11/404 (2.7%) vs. 25/415 (6%) RR 0.52 (CI: 0.23–1.17, p=0.12), but showed a significant decrease in PTB < 37 weeks: 35/657 (5.3%) vs. 65/659 (10%) RR 0.52 (CI: 0.27–0.97, p=0.04). These studies have a low incidence of preeclampsia, as this question was not in their original design. A recent multicenter double blinded placebo control trial in low risk nulliparous women, prescribed 81 mg aspirin between 6 0/7 and 13 6/7 weeks of pregnancy. It not only showed a significantly decreased in overall PTB <37 weeks but showed also significantly decreased PTB < 34 weeks with hypertensive disorders of pregnancy: 8/5780 (0.1%) vs. 21/5764 (0.4%) RR: 0.38 (0.17–0.85) p=0.015.⁵⁴ Timing in aspirin initiation needs to be factored in when evaluating low dose aspirin efficacy in preeclampsia prevention.

The Fetal Medicine Foundation (FMF) has developed a prediction model for preeclampsia based on maternal risk factors, uterine artery pulsatility index, mean arterial pressure

(MAP), serum pregnancy-associated plasma protein-A, and placental growth factor multiple of the median values.^{55, 56} After screening 35,948 singleton pregnancies, 1058 (2.9%) experienced preeclampsia. This algorithm predicted 75% (95% CI, 70–80%) of preterm-preeclampsia and 47% (95% CI, 44–51%) of term-preeclampsia, at a false positive rate of 10%. This prediction model, validated in Asia,⁵⁷ Australia,⁵⁸ and the United States,⁵⁹ was compared with the United Kingdom NICE guidelines¹⁶ and ACOG recommendations,¹⁵ demonstrating that the FMF screening performance to predict preterm preeclampsia was far superior than the traditional approach with the use of maternal factors.⁶⁰ This prediction model may assist with better candidate selection for preeclampsia prevention medications in women with CHTN.

Strengths and Limitations

Our study has a number of strengths. We evaluated the implementation of the ACOG guideline recommending low dose of aspirin for preeclampsia prevention in one of the populations at highest risk for preeclampsia, those with CHTN, and evaluated the effect of additional risk factors, such as severity of disease based on use of antihypertensive medication, history of preeclampsia and pre-gestational diabetes on rates of superimposed preeclampsia with and without severe features. The single institution design of the study allows for standardized diagnostic criteria and practice management in accordance with the ACOG Task Force on Hypertension in Pregnancy.³ Another strength of the study is the selection of high-risk patients based only on past medical history rather than biomarkers or uterine artery Doppler and can be replicated in other communities where those biomarkers are not available.⁶¹

Our study does have some limitations. It is a retrospective cohort, and therefore we are unable to make conclusions regarding causality. The sample size is small and maybe underpowered to detect a small clinical difference in the two groups. Due to lack of clarity of diagnostic criteria for superimposed preeclampsia from the ACOG recommendations, we developed institutional guidelines to define sudden increase of hypertension and proteinuria, which may differ slightly from other institutional interpretations. We did not collect MAP information at the first prenatal visit. The home BP monitoring was not standardized and was self-reported. Very few women brought their devices for calibration. We did not have the funding for standardized BP devices or monitoring systems. However, self-reported measurements were used to screen women for further evaluation, and clinical decisions were only made after confirming BP using a standardized BP device in a clinical setting. Adherence to aspirin could not be reported with complete accuracy, as it was based on patient report and chart documentation, and we were not able to monitor pill intake. Our patient population includes patients with multiple risk factors for preeclampsia including African American race, multiple comorbidities, and obesity, and thus, our results may not be universally applicable. We did not include other well-known risk factors of preeclampsia as family history of preeclampsia or conception by in vitro fertilization.

Research Implications

Further studies on the dosing, timing, and evaluation of the efficacy of aspirin in preeclampsia prevention are needed on women with chronic hypertension, as they have a

significant risk of developing superimposed preeclampsia and adverse outcomes. Using a higher dose of aspirin, 150mg, or 162mg (2 tablets), as suggested by the International Federation of Gynecology and Obstetrics (FIGO) recommendation, may be an option.⁶² The efficacy of preconception initiation of aspirin at different doses needs to be studied in high-risk population. The impact of maternal BMI on the appropriate dose of aspirin requires pharmacokinetic studies. Lastly, evaluation of lower goals for BP control in women with CHTN (<140 or <90 mmHg) vs. (<150 or <100 mmHg) and their effect on the incidence of superimposed preeclampsia and severe features.⁶³ Evaluation of other high-risk subgroups including women with history of preeclampsia, diabetes mellitus, multiple pregnancies, renal disease or autoimmune disease needs to be studied independently. If an RCT studying women with CHTN and low dose aspirin for superimposed preeclampsia prevention is planned, enrollment of 3400 women will be needed to decrease the risk from 30% to 25.5% (by 15%) with an 80% power and 95% confidence interval.

Conclusions

Our findings showed an overall 70% institutional adherence to the 2016 ACOG recommendation of 81mg aspirin in patients with CHTN for superimposed preeclampsia prevention. However, the daily 81 mg of aspirin initiated between 12 to 16 weeks of pregnancy did not decrease the incidence of superimposed preeclampsia, severe features, SGA or PTB in patients with CHTN.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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American Journal of Obstetrics and Gynecology at a Glance:

- a. **Why was the study conducted?**
 - To evaluate the ACOG recommendation of low dose aspirin 81mg for pregnant women with chronic hypertension
- b. **What are the key findings?**
 - Superimposed preeclampsia, small for gestational age, and preterm birth were not significantly decreased after implementation of daily 81 mg aspirin initiated between 12 to 16 weeks of gestation.
- c. **What does this study add to what is already known?**
 - Low dose aspirin for women with chronic hypertension as recommended by ACOG or USPSTF does not prevent superimposed preeclampsia or other adverse maternal and neonatal outcomes.
 - Further studies on the dosing, timing, and efficacy of aspirin in preeclampsia prevention are needed for women with specific risk factors.

Incidence of Superimposed Preeclampsia and Aspirin Use

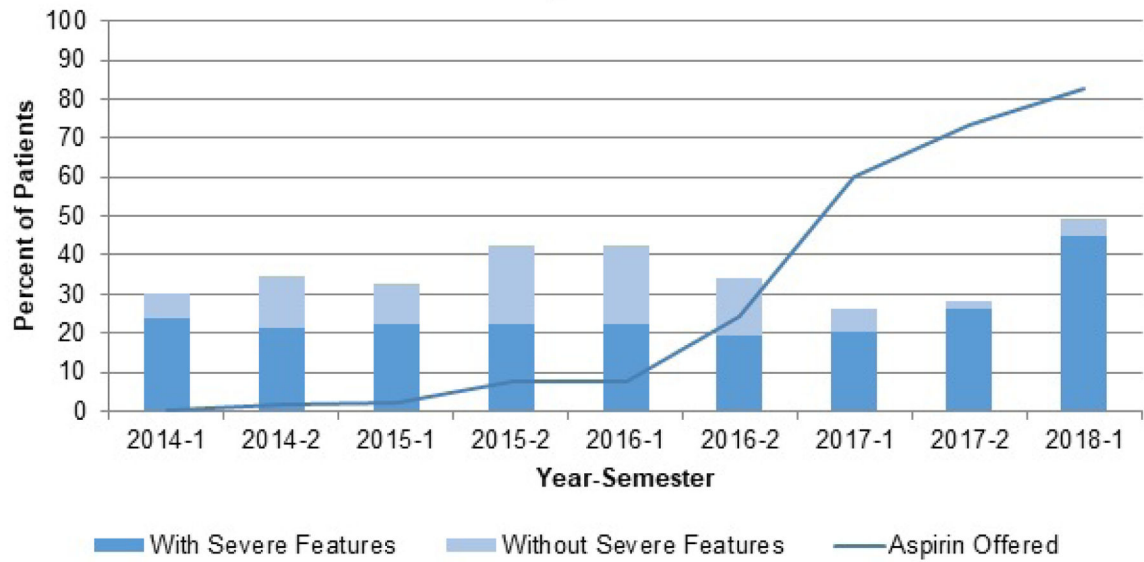


Figure 1.
 Incidence of Superimposed Preeclampsia and Aspirin Use
 Percent of patients who developed superimposed preeclampsia with and without severe features and percent of patients who were offered aspirin over time. Time presented as year-semester.

Implementation of ACOG Guideline by Risk Factor

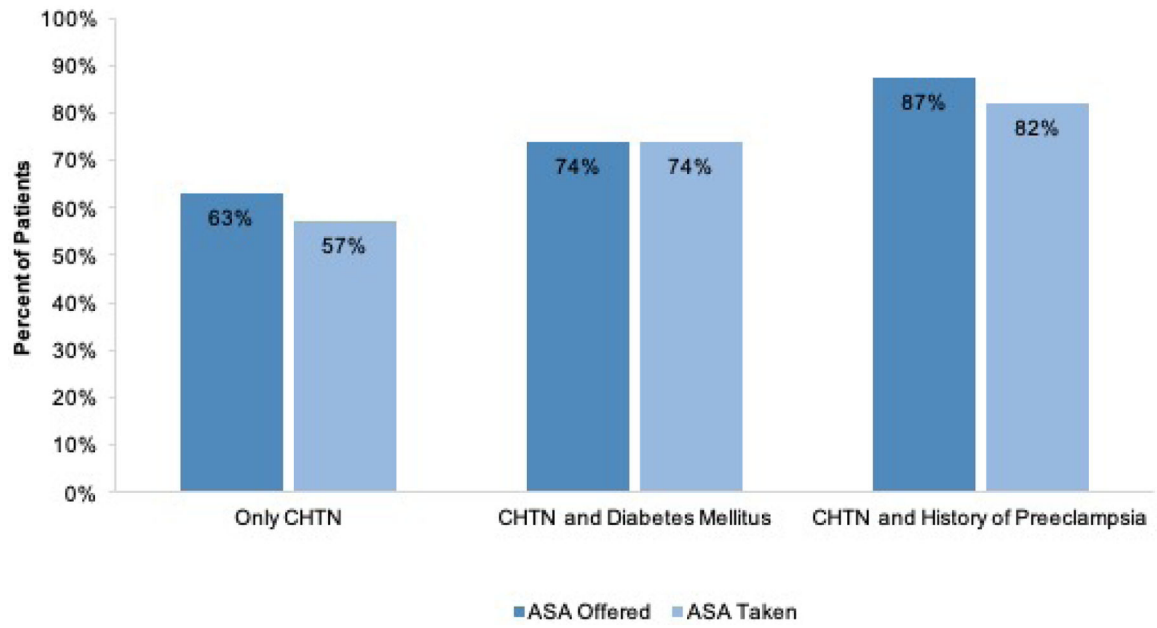


Figure 2.
 Implementation of ACOG Guideline
 Percent of patients who were offered aspirin and taking aspirin by subgroup.

Table 1.

Maternal Demographics

Characteristic	Pre ACOG N=254	Post ACOG N=203	P - value
Maternal age	32.7±5.4	31.9±6.2	0.12
Race			
African American	160 (63.0)	128 (63.1)	1.0
White	62 (24.4)	46 (22.7)	0.74
Hispanic	12 (4.7)	13 (6.4)	0.53
Asian	12 (4.7)	7 (3.4)	0.64
Other	8 (3.15)	9 (4.4)	0.62
Gravida	3.9±2.6	3.99±2.7	0.98
Nulliparous	77 (30.3)	53 (26.1)	0.34
History of Preterm birth	66 (26.0)	60 (29.5)	0.4
BMI	35.0±9.3	34.89±8.3	0.84
Obesity BMI >30	169 (66.5)	141 (69.45)	0.54
History of Preeclampsia	55 (21.7)	61 (30.1)	0.051
Pregestational diabetes	35 (13.8)	29 (14.3)	0.23
Gestational diabetes	37 (14.6)	26 (12.8)	0.64
Thyroid disorders	10 (4.92)	10 (3.93)	0.29
Antiphospholipid syndrome	1 (0.4)	0 (0)	0.69
Autoimmune disorder	11 (4.3)	5 (2.4)	0.31
Vascular disease	4 (1.57)	1 (0.4)	0.38
Sickle cell disease	4 (1.57)	1 (0.5)	0.38
Thromboembolism	11 (4.33)	2 (0.98)	0.10
Renal disease	16 (6.3)	5 (2.4)	0.16
Smoking	34 (16.74)	52 (20.47)	0.85
Substance abuse	20 (7.87)	15 (7.39)	0.59
Antihypertensive medication	117 (46.06)	61 (30.04)	0.11
Prescribed aspirin	18 (7.0)	142 (70.0)	<0.01
Verbally reported taking aspirin	15 (5.9)	135 (66.5)	<0.01
Gestational age at aspirin prescription	14.94 ±6.3	14.97 ±4.3	0.98

Values reported as n (%) or mean ± standard.

ACOG: American College of Obstetricians and Gynecologist

BMI: Body mass index

Table 2.

Maternal Outcomes

Maternal Outcomes	Pre ACOG N=254	Post ACOG N =203	P - value
Superimposed preeclampsia	87 (34.3)	72 (35.5)	0.79
Without severe features	32 (12.6)	9 (4.4)	<0.01
With severe features	55 (21.7)	63 (31.0)	0.02
GA at diagnosis of superimposed preeclampsia	34.1±4.0	33.8±4.1	0.65
Mode of delivery			
Caesarean	102 (40.16)	94 (46.3)	0.19
Indication for delivery			
Completed 37 weeks	159 (62.6)	131 (64.53)	0.69
Fetal indication	30 (11.81)	30 (14.78)	0.4
Lab abnormalities	7 (2.76)	13 (6.4)	0.06
Uncontrolled severe BP ^a	28 (11.02)	36 (17.73)	0.04
Persistent maternal symptoms	17 (6.69)	14 (6.9)	1.0
Spontaneous onset of labor	46 (18.11)	31 (15.27)	0.45
Placental abruption	5 (1.97)	4 (1.97)	1.0
Eclampsia	0 (0)	0 (0)	-
HELLP Syndrome	0 (0)	3 (1.48)	0.25
Pulmonary edema	2 (0.7)	1 (0.4)	1.0
Magnesium at delivery	53 (20.87)	48 (23.65)	0.5
Maternal complications			
Postpartum hemorrhage	27 (10.63)	32 (15.8)	0.11
Maternal ICU admission	4 (1.57)	2 (1.0)	0.59
Maternal brain imaging	1 (0.39)	4 (2.0)	0.19
Maternal mortality	0 (0)	0 (0)	-
Fetal complications			
Antenatal steroids	41 (16.14)	39 (19.21)	0.45
Intrauterine growth restriction	21 (8.3)	17 (8.4)	0.92
Abnormal umbilical artery Doppler	10 (3.9)	6 (3.0)	0.57
Stillbirth	2 (0.99)	7 (2.7)	0.19

Values reported as n (%) or mean ± standard

ACOG: American College of Obstetricians and Gynecologist; BP: Blood pressure; HELLP: hemolysis, elevated liver enzymes, low platelet count; ICU Intensive care unit.

^aUncontrolled severe blood pressure (BP) is defined as BP not controlled after several intravenous doses of antihypertensive medications.

Table 3.

Subgroup analysis. Incidence of Superimposed Preeclampsia without and with Severe Features

	Pre ACOG N=254	Post ACOG N=203	P-value
Incidence of Superimposed Preeclampsia without Severe Features			
ONLY CHTN ^a	53/170 (31.2)	34/119 (28.6)	0.70
CHTN with Anti-hypertensive Meds	46/117 (39.3)	22/61 (36.1)	0.75
CHTN and History of Preeclampsia	25/55 (45.4)	28/61 (45.9)	1.0
CHTN and Pre-gestational Diabetes	13/35 (37.1)	12/29 (41.4)	0.8
Incidence of Superimposed Preeclampsia with Severe Features			
Only CHTN ^a	34/170 (20.0)	31/119 (26.0)	0.25
CHTN with Antihypertensive Meds	35/117 (29.9)	19/61 (31.1)	0.87
CHTN and History of Preeclampsia	15/55 (27.3)	25/61 (40.9)	0.17
CHTN and Pre-gestational Diabetes	8/35 (22.8)	9/29 (31.0)	0.57

Values reported as n (%).

ACOG: American College of Obstetricians and Gynecologists

CHTN: Chronic hypertension

^aOnly CHTN group (women with history of preeclampsia, or medical conditions as pregestational diabetes, renal disease, vascular disease, antiphospholipid syndrome, autoimmune disorder, sickle cell disease were excluded)

Table 4.

Neonatal Outcomes

	Pre ACOG N=254	Post ACOG N=203	P-value
Gestational age at delivery (weeks)	36.8±9.1	36.9±3.2	0.29
PTD <37 weeks	60 (23.62)	53 (26.11)	0.54
PTD <34 weeks	28 (11.02)	25 (12.32)	0.67
PTD <28 weeks	9 (3.54)	6 (2.96)	0.73
Birthweight (g)	2880±808	3040±2188	0.32
Small for gestational age	32 (12.6)	19 (9.36)	0.29
Apgar at 5 minutes <7	14 (5.5)	13 (6.4)	0.69
NICU admission	84 (33.07)	69 (33.99)	0.84
RDS	26 (10.24)	25 (12.32)	0.55
Ventilator required	15 (5.91)	20 (9.85)	0.16
IVH Grade 3,4	2 (0.8)	1 (0.5)	1.0
NEC	4 (1.57)	1 (0.5)	0.38
Sepsis	3 (1.18)	3 (1.48)	0.1

Values reported as n (%) or mean ± standard.

ACOG: American College of Obstetricians and Gynecologists; PTD: Incidence of preterm delivery, NICU: Neonatal intensive care unit. RDS: Respiratory distress syndrome; IVH: Intraventricular hemorrhage; NEC: Necrotizing enterocolitis.

Table 5.

Randomized control trials using aspirin for preeclampsia prevention that included women with chronic hypertension.

Included in USPSTF Review	Author	ASA Dosage (mg daily)	Preeclampsia in ASA group	Preeclampsia in Placebo group	OR	P value	% of patients with CHTN	Incidence of Preeclampsia in CHTN patients	GA at ASA initiation (weeks)
Yes	Viimikka 1993 ³⁰	50	9/97	11/100	0.83 (0.33 – 2.10)	0.82	83%	No data	15–16
Yes	CLASP 1994 ²⁶	60	257/3449	290/3437	0.87 (0.73 – 1.04)	0.14	20%	No data	12 – 32
Yes	MFMU 1998 ²⁵	60	229/1273	253/1266	0.88 (0.72 – 1.07)	0.21	30%	26% ASA vs 25% placebo (p = 0.66)	13–26
Yes	Ayala 2013 ²⁷	100	11/176	22/174	0.49 (0.25– 0.99)		N/A	No data	12–16
Yes	Grab 2000 ²⁸	100	3/22	2/21	1.50 (0.23 – 10.02)	1.00	44%	No data	18
Yes	Hermida 1997 ²⁹	100	3/50	7/50	0.43 (0.12– 1.56)		N/A	No data	12–16
Yes	Villa 2012 ³¹	100	8/61	11/60	0.67 (0.25 – 1.81)	0.46	17%	No data	12–13
No	ECPPA 1996 ³²	60	32/496	30/494	1.07 (0.64 – 1.78)	0.90	47%	No data	12–32
No	Byaruhanga 1998 ³³	75	17/113	23/117	0.72 (0.36 – 1.44)	0.39	16%	No data	20–28
No	Vainio 2002 ³⁴	86	2/43	10/43	0.2 (0.05– 0.86)		34%	No data	12–14
No	Ebrashy 2005 ³⁵	75	26/74	40/65	-	-	35%	No data	14–16
No	Zhao, 2012 ⁶⁴	75	22/120	64/122	-	-	N/A	No data	13–16
No	Odibo 2015 ³⁶	81	3/16	3/14	0.85 (0.14 – 5.07)	1.00	53%	No data	18–32
No	Stanescu 2015 ⁶⁵	150	0/100	2/50	0.96 (0.91 – 1.02)	0.11	N/A	No data	11–14
No	ASPRE 2017 ³⁷	150	66/798	94/822	0.70 (0.50 – 0.97)	0.04	7%	5/49 ASA vs 5/61 placebo 1.22 (0.33 – 4.49) P = 1.0	11–14
Total			688/6888	862/6835					

USPSTF: United States Preventative Services Task Force; ECPPA: randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnant women. ECPPA (Estudo Colaborativo para Prevencao da Pre-eclampsia com Aspirina) Collaborative Group; CHTN: chronic hypertension; MFMU: Maternal Fetal Medicine Units network; ASPRE: Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia; N/A: not available; ASA: aspirin; GA: gestational age; OR: odds ratio.

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