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Use of Daily Low-Dose Aspirin in Pregnancy for Women at High Risk of Preeclampsia at Georgetown Public Hospital Corporation

Dr. Sabrina Gittens[1], Dr. Janie Pak[2]

[1]Georgetown Public Hospital Corporation, East and New Market Street Georgetown, Guyana
[2]Kaiser Permanente San Diego Medical Center, 9455 Clairemont Mesa Blvd, San Diego, California, United States

Corresponding Author: Dr. Sabrina Gittens

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ABSTRACT

Objective: To Determine what proportion of eligible high-risk women diagnosed with preeclampsia received low dose aspirin during antepartum care.

Design & Methods: This was a retrospective chart review of all patients who delivered at Georgetown Public Hospital Corporation between September to December 2017 and were diagnosed with a hypertensive disorder in pregnancy. The primary outcome was the fraction of women diagnosed with preeclampsia, eclampsia or HELLP syndrome who met the U.S. Preventive Task Force criteria to be started on aspirin and were started on aspirin between 12 and 28 weeks of gestation. Maternal secondary outcomes included: Intensive care unit admissions, end organ injury, placental abruption and death. Neonatal secondary outcomes included: Neonatal intensive care unit admissions, fetal growth restriction, preterm births, stillbirths and neonatal death. Data was organised and analysed in Microsoft Excel 2016.

Results: Of the 2,452 deliveries, 2,160 (88%) charts were found and reviewed. 14.3% were diagnosed with a hypertensive disorder in pregnancy. Of these, 37% had preeclampsia, eclampsia or HELLP syndrome. Among these, 36.8% met criteria to receive low dose aspirin antepartum but only 4.8% received aspirin. Of the secondary outcomes, one death occurred because of a haemorrhagic CVA. 42.1% of neonates were born prematurely of which 4 were stillbirths and 4 were neonatal deaths.

Conclusions; The routine use of a low dose of aspirin among pregnant women who met the criteria to be started on was low.

Recommendations: All women should be screened for the risk of developing preeclampsia and if needed, aspirin should be started between 12-28 weeks of gestation to get the best effects.

Key Words: preeclampsia, aspirin in pregnancy, GPHC

INTRODUCTION

Hypertensive disorders in pregnancy is one of the leading cause of maternal deaths with 99% of them occurring in developing countries.[1,2] Risk factors strongly predisposing pregnant women to developing preeclampsia include: history of preeclampsia, multifetal gestation, chronic hypertension, Type 1 or 2 diabetes, renal disease, and autoimmune diseases.[3-7] A wide array of serious complications can arise from preeclampsia including HELLP syndrome (**H**emolysis, **E**levated **L**iver enzymes and **L**ow Platelets), cerebrovascular accident (CVA), kidney injury, pulmonary oedema, placental abruption, intrauterine growth restriction (IUGR), fetal and maternal demise.[2,7] Daily use of low dose aspirin has been shown to significantly decrease the risk of developing preeclampsia, preterm birth, and IUGR in women at high risk for preeclampsia and should be offered to them in their second

trimester. [8-14] Unlike prior belief, the daily use of a low dose of an antiplatelet agent (aspirin) has not been shown to cause any significant change or abnormal bleeding time values. [15] Although preeclampsia is a leading cause of maternal morbidity and mortality in Guyana, many high-risk women are not offered aspirin in their second trimester despite its benefits. Low dose aspirin is easily accessible and affordable but the lack of knowledge or fear of its use during pregnancy may be barriers to providers prescribing it to high risk women. The impact of these missed opportunities is largely unknown as no studies have been done to measure it.

Having a knowledge of baseline practices at the Georgetown Public Hospital Corporation (GPHC), the primary referral hospital, can guide interventions focused on educating health care professionals to help reduce the risk of one of the most serious and common disorders in pregnancy for both mother and baby. The objective of this study was to determine the proportion of eligible high-risk women diagnosed with preeclampsia who received low dose of aspirin during their antepartum care using the US Preventive Services Task Force criteria (USPSTF) (Table 9).

MATERIALS AND METHODS

This was a retrospective, observational descriptive study involving a chart review of all patients who delivered at GPHC from September 1st to December 31st 2017. The charts of all patients who were diagnosed with a hypertensive disorder in pregnancy including preeclampsia, eclampsia or HELLP syndrome, gestational hypertension (GHTN), chronic hypertension (CHTN) and chronic hypertension with superimposed preeclampsia (CHTN with SIP) were included in this study. All other charts were excluded. Basic demographic information including age, race, marital status, region of residence (the 10 administrative regions are depicted below with an arrow focusing on the region with most of the population and the capital city - region 4), antenatal clinic (ANC), gestational age at diagnosis, referral information, and gestational age on admission to GPHC were collected.

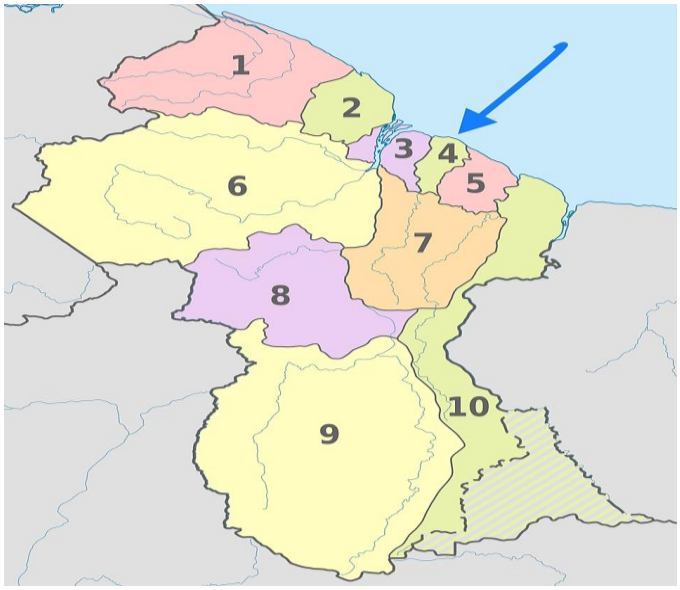

Figure 1: Map of Administrative Division of Guyana

https://commons.wikimedia.org/wiki/File:Guyana,_administrative_divisions_-_Nmbrs_-_colored.svg
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There was a total of 2,452 deliveries between September 1st, 2017 and December 31st, 2017 at GPHC. 2,160 of the 2,452 (88.1%) were reviewed. The remainder of the charts could not be located. Of the 2,160 patients, 308 (14.3%) were diagnosed with a hypertensive disorder of pregnancy and included in this study.

The medical charts were reviewed to determine how many of these women were eligible to receive prenatal aspirin by either having at least one strong risk factor or more than or equal to three moderate risk factors for preeclampsia according to the USPSTF criteria. Strong risk factors included: history of preeclampsia especially when accompanied by an adverse outcome, multifetal gestation, chronic hypertension, Type 1 or 2 diabetes, renal disease, or autoimmune diseases. Moderate risk factors included: nulliparity, obesity (body mass index (BMI) >30 kg/m2), family history of preeclampsia (mother or sister), sociodemographic characteristics, more than or equal to 35 years of age, personal history factors (Table *9*).

The primary outcome of interest was to determine the proportion of eligible women diagnosed with preeclampsia, eclampsia or HELLP syndrome who met USPSTF criteria to start prenatal low-dose aspirin and actually received this therapy between 12 and 28 weeks of gestation. Secondary maternal outcomes of interest included: maternal intensive care unit (ICU) admissions, end organ injury, abruption and death. Secondary neonatal outcomes included: intrauterine fetal demise (IUFD), IUGR, preterm birth and associated early neonatal comorbidities and stillbirths among women diagnosed with preeclampsia. This study was approved by the Institutional Review Board within the Ministry of Public Health of Guyana and by the research committee at GPHC. Data was collected and analyzed using Microsoft Excel 2016.

STATISTICAL METHODS

Being a descriptive observational study, measures of frequency (count and percent) and central tendency (mean and mode) were described.

RESULTS

Table 1 summarizes the demographic information for the 308 of the 2,160 patients diagnosed with a hypertensive disorder. Ages ranged from 14 to 42 with an average of 27. The most prevalent race was African at 37.7% (n = 43). 41.2% (n = 47) were in a Common-law relationship and more than half (54.39 %, n=62) resided in region 4 [Figure *1*].

	Number	Percentage
Age group		
18 and under	10	8.8%
19-25	46	40.4%
26-30	16	14.0%
31-34	18	15.8%
>/= to 35	24	21.1%
Total	114	100.0%
Race		
African	43	37.7%
Mixed	34	29.8%
East Indian	18	15.8%
Amerindian	18	15.8%
Not stated	1	0.9%
Total	114	100.00%
Marital status		
Common-Law	47	41.2%
Single	33	29.0%
Married	30	26.3%
Not stated	4	3.5%
Total	114	100.00%
Region		
4	62	54.4%
3	21	18.4%
1	11	9.7%
6	7	6.1%
10	3	2.6%
5	3	2.6%
7	3	2.6%
2	2	1.8%
8	1	0.9%
9	1	0.9%
Total	114	100.00%

Table 1: Demographic information of all patients diagnosed with a hypertensive disorder in pregnancy

Table *2* shows the gestational ages at the first ANC visit. Of the 114 patients with preeclampsia, eclampsia or HELLP syndrome, 40 patients' antenatal history was not found or recorded. The remaining 74 patients had an average of 7.3 antenatal visits. 78.1% (n = 89) were referred to GPHC, at an average gestational age of 35 weeks. At the time of referral, 88.8% (n=79) were after 28 weeks of gestation, beyond the

gestational age at which guidelines recommend starting aspirin.

Gestational Age	GA at first ANC	
	Number	%
< 12 weeks*	18	15.8%
12 0/7 to 19 6/7	35	30.7%
20 0/7 to 27 6/7	13	11.4%
28 0/7 to 33 6/7	4	3.5%
34 0/7 to 36 6/7	3	2.6%
37 and above	-	-
Post-partum	-	-
Not seen	41	36%
Grand Total	114	100%

Table 2: Gestational age at diagnosis and first antenatal clinic visit

GA - gestational age
ANC - antenatal clinic

36.8% (n=42) of the women diagnosed with a hypertensive disorder were candidates for low dose aspirin based on varying risk factors (Table *3*) of which only two actually received aspirin (4.8%). The most common strong risk factors were CHTN (18.4%, n=21) and a history of preeclampsia (15.8%, n=18). The most common moderate risk factors were nulliparity (38.6%, n=44), African race (37.7%, n=43), age equal to or above 35 years (21%, n=24) and obesity (15.8%, n=18). Of the two women who received aspirin, one was started at 22 weeks 3 days and the other at 33 weeks 6 days. These findings reflect the primary outcome of the study.

	Number	Percentage
High Risk factors		
Chronic hypertension	21	18.4 %
History of preeclampsia	18	15.8 %
Renal disease	1 (CRF)	0.9 %
Autoimmune disease	1 (Goitre)	0.9 %
Multifetal gestation	0	0.0 %
Type 1 or 2 diabetes	0	0.0 %
Moderate risk factors		
Nulliparity	44	38.6 %
Sociodemographic characteristics	43 (African)	37.7 %
Age ≥35 years	24	21 %
Obesity (BMI > 30kg/m2)	18 §	15.8 %
Personal history factors	8 PTD (7 died)	7 % (6.1% died)
Family history of preeclampsia	2	1.6 %

Table 3: Risk factors for Preeclampsia

BMI - body mass index calculated as Kg per m^2 - § for 64 patients was not recorded/done.
CRF - chronic renal failure
PTD - preterm delivery

The average gestational age at delivery was 37 weeks. The average weight at delivery was 2622g (Table *4*). A 5- minute APGAR score of 7 or less was seen in 14.9% (n = 17) neonates of which only two were at term. The APGAR score was unknown for 3 patients due to inability to find the charts. There was a total of 4 neonatal deaths and 4 stillbirths (3.5% each). 6.1% (n = 7) neonatal outcomes were unknown due to the inability to find the charts. All but one of these deaths were in preterm neonates. The cause of death was documented for only one of the neonates and was noted to be as a result of haemorrhagic shock. Of the 86.8% (n=99) neonates that were alive with a documented chart, 36.6% (n = 36) had more than or equal to one of the following: respiratory distress syndrome, sepsis and pneumonia.

Gestational age	Number	%
Less than 28	2	1.8%
Between 28 and 32	8	7%
Between 32 and 34	9	7.9%
Between 34 and 37	29	25.4%
> 37	65	57%
GA unknown	1	0.9%
Grand Total	114	100%
Neonatal Weight		
Less than 1000g	4	3.5%
Between 1000 and 1500g	6	5.3%
Between 1500 and 2000g	8	7%
Between 2000 and 2500g	20	17.5%
Between 2500 and 3000g	28	24.6%
Over 3000g	38	33.3%
Unknown	10	8.8%
Grand Total	114	100%
Days of admission		
1 to 3 days	74	65%
4 to 6 days	12	10.5%
7 to 9 days	6	5.3%
10 to 14 days	5	4.4%
>/= 15 days	9	7.9%
Unknown	8	7%
Grand Total	114	100%

Table 4: Neonatal outcomes

54.4% (n = 62) of the women delivered vaginally and 45.6% (n = 52) by cesarean delivery. 27.2% (n = 31) with the hypertensive diagnosis within the indication for cesarean. 54.4% (n = 62) had induction or augmentation of labour. Table *5* shows details of labour induction and delivery details including mode and estimated blood loss (EBL) and days of admission.

Indication for CD	**Number**	**%**
NRFHT	15	13.2%
Eclampsia	4	3.5%
Failed IOL (HTN)	4	3.5%
HTN	8	7%
HTN & Breech	1	0.9%
HTN & NRFHT	5	4.4%
HTN & LSCS	8	7%
HTN & ROM-(Mec)	1	0.9%
LSCS	1	0.9%
LSCS & Other	2	1.8%
Other	3	2.6%
Total	52	45.6%
Induction or Augmentation of labour		
IOL/AOL	Number	%
AOL	4	3.5%
IOL	49	43%
IOL + AOL	9	7.9%
No	51	44.7%
Unknown	1	0.9%
Total	114	100%
Indication for IOL/AOL	Number	%
CHTN	1	0.9%
CHTN r/o SIP	3	2.6%
CHTN+SIP	6	5.3%
Eclampsia	3	2.6%
GHTN	6	5.3%
GHTN r/o PEC	1	0.9%
MPEC	9	7.9%
PROM	1	0.9%
SPEC	36	31.6%
N/A	47	41.3%
Unknown	1	0.9%
Total	114	100%
EBL	Number	%
>/=1000	6	5.3%
500 to 1000	14	12.3%
Less than 500	94	82.5%
Total	114	100%
Days of admission	Number	%
>/=21 days	3	2.6%
1 to 5 days	67	58.8%
11 to 15 days	6	5.3%
16 to 20 days	2	1.8%
6 to 10 days	29	25.4%
Unknown	7	6.1%
Total	114	100%

Table 5: Maternal outcome and delivery details

CD - cesarean delivery
LSCS -lower segment cesarean section
IOL - induction of labour
AOL - augmentation of labour
NRFHT - non-reassuring fetal heart tracing
ROM - rupture of membranes: Mec - meconium
PROM - prelabour/premature rupture of membranes
EBL - estimated blood loss
IOL – induction of labour
AOL – augmentation of labour
CHTN - chronic hypertension
CHTN r/o SIP - chronic hypertension rule out superimposed preeclampsia
GHTN - gestational hypertension
MPEC - mild preeclampsia (preeclampsia without severe features)
SPEC - severe preeclampsia (preeclampsia with severe features)
N/A - not applicable

Table *6*, *7* and 8 summarises the maternal complications, blood pressure ranges and. abnormal laboratory results respectively. 1.8% (n = 2) were diagnosed with HELLP

syndrome. 7.9% (n = 9) were admitted to the Intensive care unit (ICU), 3.5% (n = 4) with eclampsia, 3.5% (n = 4) with preeclampsia with severe features and 0.9% (n = 1) with CHTN with SIP. One of the patients admitted to ICU died on post-partum day 5 secondary to haemorrhagic CVA (one with eclampsia). 52.6% (n = 60) required the use of antihypertensives during the antepartum period (51 with single drug use and 9 with use of two drugs).

Admitted to ICU		
Complication	**Number**	**Percentage**
ARDS secondary to CAP	1	0.9%
Bilateral mild uretero-hydronephrosis	1	0.9%
Haemorrhagic CVA = died	1	0.9%
Pleural effusion, pericardial effusion	1	0.9%
Pulmonary embolism, atypical pneumonia	1	0.9%
Pulmonary edema	1	0.9%
R/o Cardiomyopathy, hyperkalemia, AKI	1	0.9%
R/o Intracranial hemorrhage	1	0.9%
Total	8	7.2%
Not admitted to ICU		
Complication	**Number**	**Percentage**
AVM	1	0.9%
PPH	1	0.9%
PPH - cervical laceration	1	0.9%
R/o intracranial hemorrhage	1	0.9%
Total	4	3.6%

Table 6: Maternal Complications for patients that were and were not admitted to ICU

ARDS - acute respiratory distress syndrome.
CAP -community acquired pneumonia
CVA - cerebrovascular accident
AKI - acute kidney injury
AVM - arterio-venous malformation
PPH – post-partum haemorrhage

	Number	**Percentage**
Severe range: >/= 160 systolic or >/=110 diastolic	93	81.6%
Mild to moderate range: 140-149 systolic or 90-99 diastolic	19	16.7%

Table 7: Blood Pressure Ranges

Parameter	**Number**	**Percentage**
Hb < 7mg/dL	3	2.6%
PLT < 150 10^9/L	3	2.6%
PLT < 100 10^9/L	1	0.9%
PLT < 50 10^9/L	2	1.8%
LDH> 500	1	0.9%
LDH> 1000	1	0.9%
AST/ALT > double upper limit	4	3.5%
Creatinine > 1.1 mg/dL	35	30.7%

Table 8: Laboratory Findings

Hb - haemoglobin.
PLT - platelet
LDH - lactate dehydrogenase.
AST/ALT - aspartate aminotransferase/ alanine aminotransferase

DISCUSSION

The updated USPSTF guidelines now recommends starting a low-dose of aspirin after 12 weeks but before 28 weeks of gestation for eligible high-risk patients. [10,11] Daily use of low dose aspirin has been shown to significantly decrease the risk of preeclampsia, preterm birth, and IUGR in women at high risk for preeclampsia and should be offered to them in their second trimester. [11,12,13] The daily use of a low dose of an antiplatelet agent (aspirin) has not been shown to cause any significant change or abnormal bleeding time values unlike prior belief. [15] Daily use of low dose aspirin is also recommended by the Royal College of Obstetricians and Gynaecologists (RCOG). [16]

The prevalence of hypertensive disorder in pregnancy for this time period of four months was above the worldwide prevalence (14.3% vs 5.2-8.2%), [6] however that of preeclampsia (5.3%) was consistent with reported global prevalence of 0.2-9.2%. [6] The vast majority of the women (95.2%, n = 40) that should have been started on a daily low dose of aspirin were

not started. Most (88.8%) of the women referred to GPHC - the main referral hospital located in the capital city of Georgetown in region 4 [Figure *1*] - were referred after the gestational age at which aspirin should be started. And 1 of the 2 patients who were started on aspirin was actually started later than the recommended 28 weeks upper limit. This could be due to inadequate knowledge about the current and updated guidelines, mostly in the outlying regions. The majority of patients seen first join an antenatal clinic with an advanced gestational age, above the time for aspirin to have the best effect (between 12 to 28 weeks of gestation). This should indicate the need for continued education and updating of our health care professionals on new practices mostly at the primary health care facilities, but also for new and rotating staff at the secondary and tertiary systems.

The strengths of the study included that the information was collected from the period of the year with the most deliveries which gives a general representation of the hospital as well as Guyana. The time period of the study was only 4 months due to a time constraint, and the incidences were only for that period. These 4 months however, corresponded to the "peak" season. (Deliveries for 2017 total-6164 and deliveries corresponding to these 4 months - 2452 [39.8%]). Also, a good idea of the kinds of, and most prevalent risk factors present among our population was obtained. This was the first study of it's kind in Guyana.

Limitations included that only the information for 2160 of the 2542 deliveries for this period was collected. This was because of the inability to find the medical charts. Hence, the incidence of preeclampsia and hypertensive disorders in pregnancy on a whole was not truly reflected. On this same note all the information for some of the neonates were not seen because the charts were not found, as well as some of the information from the chart of one of the mothers. Documentation in terms of antenatal clinic visits were not copied or recorded in all charts, hence the details related to time of diagnosis and number of clinic visits could not be found. All of this information could not be gathered for one patient because these details were not seen in the chart. Documentation of other information such as BMI parameters was not done for all patients and others such as vital records as well as drug records were not seen.

Women should be encouraged to join ANC early in pregnancy, not only to be screened for risk of developing preeclampsia, but for other health concerns in order to optimize their health in pregnancy and after as well. And for this same reason obtain routine ANC visits in an adequate amount. Because of the prevalence and consequences of preeclampsia, all women should be screened and if needed, aspirin started between 12-28 to get the best effects. Continuous medical education and updates on high risk pathologies, should be routinely performed for the staff at GPHC as well as, and especially for the outlying regions.

CONCLUSIONS

The most common high risk factors that were found included CHTN and a history of preeclampsia, while the most common moderate risk factors were nulliparity, African race, age equal to or above 35 years and obesity. The use of aspirin to reduce the risk of developing preeclampsia for these patients was insufficient at only 4.8%. Both cases were started beyond the recommended initial gestational age to have the best effect. A large part of this could possibly be attributed to the lack of knowledge of this practice, principally among the outlying regions.

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APPENDIX

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 erythematous, antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has ≥1 of these high-risk factors
Moderate‡	Nulliparity; Obesity (body mass index >30 kg/m^2); Family history of preeclampsia (mother or sister); Sociodemographic characteristics (African American race, low socioeconomic status); Age ≥35 years; Personal history factors (e.g., low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval)	Consider low-dose aspirin if the patient has several of these moderate-risk factors§
Low	Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

Table 9: Clinical Risk Assessment for Preeclampsia*USPSTF Criteria

* Includes only risk factors that can be obtained from the patient medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.
† Single risk factors that are consistently associated with the greatest risk for preeclampsia. The preeclampsia incidence rate would be approximately ≥8% in a pregnant woman with ≥1 of these risk factors.
‡ A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk for preeclampsia. These risk factors are independently associated with moderate risk for preeclampsia, some more consistently than others1.
§ Moderate-risk factors vary in their association with increased risk for preeclampsia.

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