

# Postpartum Sequelae of the Hypertensive Diseases of Pregnancy: A Pilot Study

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## Abstract

**Background:** Hypertensive disorders are one of the most common medical conditions that may complicate pregnancy. Postpartum blood pressure (BP) pattern is, however, less clear in affected women and decision to discharge them is usually decided arbitrarily. **Materials and Methods:** A cohort study conducted at Lagos University Teaching Hospital, Lagos, Nigeria, aimed at determining the proportion of pregnant women with pregnancy-induced hypertension (PIH) and preeclampsia (PE) whose BP remains elevated 6 weeks postdelivery and factors associated with the persistent rise. Fifteen women each with PIH and PE were studied in different phases of pregnancy and followed up until 6 weeks postdelivery. Fifteen normotensive pregnant women served as controls. BP patterns were monitored and fasting lipid levels, serum creatinine, fasting glucose profile (FGP), and FGP/insulin ratio were assayed. Data were analyzed with IBM SPSS version 20. **Results:** Proportion of women with PIH or PE who had persistent hypertension at 6 weeks postpartum was 3/29 (10.3%), risk ratio of 1.1. No statistically significant association was found between mean arterial BP at 6 weeks postpartum and age, parity, gestational age at delivery, body mass index, and family history of hypertension. Serum creatinine level showed moderate correlation with persistent hypertension at 6 weeks postpartum ( $r = 0.441$ ,  $P = 0.006$ ), with sensitivity of 100% and specificity of 81.8% at cutoff value of 1.2 mg/dL in detecting pregnant women with hypertensive disorders who will likely remain hypertensive at 6 weeks postpartum. **Conclusion:** There is a need for long-term follow-up of women with PIH/PE beyond puerperium.

**Keywords:** Blood pressure, creatinine, fasting plasma glucose, fasting plasma glucose/insulin ratio, lipid levels, preeclampsia, pregnancy-induced hypertension

## INTRODUCTION

Hypertensive disorders in pregnancy are a major contributor to maternal deaths worldwide, responsible for 5%–15.5% of maternal deaths.<sup>1,2</sup> It has been reported that women with pregnancy-induced hypertension (PIH), whether proteinuric or nonproteinuric, are at risk of cardiovascular diseases later in life, such as essential hypertension, ischemic heart disease, and thromboembolic disease.<sup>3,4</sup> Up to one-third of women with hypertensive disorders in pregnancy may develop hypertension within a decade of an affected pregnancy<sup>5,6</sup> and up to 1 in 5 of these women will be hypertensive 15 years postpartum.<sup>7</sup> It would, thus, be useful to identify which group of women with PIH that has significant risk factors for nonpregnancy cardiovascular disease. Some of these women may then be eligible for preventive intervention using low-dose aspirin and/or statins, based on predetermined criteria.

Hypertensive disorders in pregnancy may also predispose to a number of noncardiovascular events in the long-term and these include Type 2 diabetes mellitus and chronic kidney disease.<sup>3,8-10</sup> In a recent study, it was found that women with a history of the hypertensive disease in pregnancy are four times more likely to develop posttraumatic stress disorders.<sup>11</sup> It is, therefore, important to follow-up women with hypertensive disorders in pregnancy to identify these complications early and commence treatment promptly.

Studies related to the prognosis of hypertensive disorders in pregnancy in our environment are lacking. It becomes

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challenging identifying women with hypertensive disorders in pregnancy who are likely to develop adverse cardiovascular events and other problems later in life following delivery. The issue is further worsened in a low-resource setting like ours where the women have poor health-seeking behavior and are likely to be lost to follow-up.

In a previous study, it was found that the mean interval for blood pressure (BP) to normalize in women with hypertensive disorders in pregnancy was  $24.1 \pm 22.8$  days (median 7 days), whereas 75% of affected women recovered within 6 weeks of delivery and 90% recovered by 60 days postpartum.<sup>12</sup> In our center, we follow-up our postpartum patients routinely until 6 weeks after delivery and hence, we decided to assess the proportion of women in our environment with hypertensive disorders in pregnancy who will remain hypertensive by the end of puerperium (6 weeks) and to identify the risk factors associated with the persistent hypertension and also determine laboratory prognostic factors for the development of nonpregnant cardiovascular disease, such as plasma creatinine, fasting blood sugar, insulin/glucose ratio, and lipid profile [i.e., low-density lipoproteins (LDL), high-density lipoprotein (HDL), cholesterol, and triglycerides (TGs)]. By so doing, we hope to develop protocols as regards risk assessment of our hypertensive pregnant women to minimize complications that may follow unidentified long-term sequelae of hypertensive disorders of pregnancy.

## MATERIALS AND METHODS

### Study design/location

This was a prospective cohort study conducted at Lagos University Teaching Hospital (LUTH) between January and December 2009. Ethical approval was given by the LUTH Health Research and Ethics Committee.

### Subjects

Nonhypertensive women, i.e., normal controls (NC), women with PIH, i.e., BP  $\geq 140/90$  after the 20<sup>th</sup> week of gestation with no previous history of hypertension, preeclampsia (PE), i.e., PIH and proteinuria. These women were recruited into the study after delivery. The NC were the next woman delivering with normal BP recording throughout pregnancy  $\leq 130/80$  mmHg. Pregnant women with the above definitions, between the ages of 20 and 40 were included in this study. Women with known renal, cardiovascular, endocrine (including diabetes) or metabolic disease, chronic liver disease or thromboembolic disease, and known recurrent miscarriage were excluded from the study.

### Sample size

Assuming a prevalence of 17% for hypertensive disorders of pregnancy in a previous study in Northern Nigeria,<sup>13</sup> we estimated a sample size of 217 women with a Type I error of 5% and a power of 80% using the formula:<sup>14</sup>

$$n = \frac{Z^2 pq}{d^2}$$

With a 10% attrition rate of 22, the total sample size required per group (cases and controls) is 239. However, due to a limited fund, we conducted a pilot study comprising 15 women with PIH and 15 women with PE. We also recruited 15 NC with normal BP in pregnancy.

### Intervention

The women with PE and PIH were recruited into the study and asked to come to a designated research room in the college for follow-up at the specified times. They were seen 4 days a week, between 2.00 and 3.00 p.m.

Each woman had a numbered data booklet opened up for her as she was recruited. They were kept in 5 box files– 1 for each group. The codes for the numbers (i.e., the women's names) were kept in a separate file by the principal investigator. Their consent forms were checked and if necessary, they were given another form to sign. A copy of each form was kept in their data booklet while the original was kept in a separate box file. Their weights and heights were measured. These were recorded into their booklets directly. Their BP were measured using the Microlife 3BTO-A BP monitor, blood was taken for lipid profile, fasting blood glucose, serum insulin, and plasma creatinine.

### Standard operating procedure (SOP) for blood pressure measurements and venupuncture

The BP of each woman was taken with the Microlife 3BTO-A<sup>®</sup> digital BP monitor, which has been validated in pregnancy. This was done after the woman had sat down with her feet resting on the floor, for at least 10 min. The BP was taken from the right arm, with the arm supported on a table horizontally and care was taken to ensure that an adequately sized cuff is chosen. After the BP recording, a tourniquet was applied to the woman's arm and 15 ml of blood taken into a 20 ml syringe soon after application of the tourniquet. The blood was put in the bottles as follows:

- 5 ml Lithium heparin
- 2 ml Fluoride oxalate
- 2.5 ml Cold ethylenediaminetetraacetic acid (EDTA)
- 2.5 ml Normal EDTA
- 3 ml Plain bottle.

During this time, her baby was weighed using Seca 384 digital baby weighing scale. The baby's head circumference was also measured. Weights were measured in kg for the babies and rounded off to 1 decimal point and the mother's body mass index (BMI) was calculated. She was given an appointment for her next visit and was called or sent a note to remind her, a week before the appointment was due.

### Data management

Data analysis was performed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Released 2011. The mean BP  $\pm$  standard deviation (SD) was determined for each study group. Each set of BP recordings was compared to the nonpregnant measurements and with each other, using ANOVA with *post hoc* testing by the least significant difference (LSD) test. Spearman's rank correlation analysis

was used in assessing the correlation between serum creatinine levels at recruitment and mean arterial BP (MAP) at 6 weeks postpartum, and also correlation between MAP immediate postdelivery and MAP at 6 weeks postdelivery, after testing for normality of the study population.

Known determinants of BP levels such as age, parity, BMI, and first-degree family history of hypertension were also explored to see what impact they had on the BP levels of women in our environment, using the univariate general linear model (GLM) with *post hoc* testing by the LSD test.

## RESULTS

### Characteristics of participants

The study population comprised 15 normotensive parturient (NC) who served as controls, 15 with -PIH, and 15 with PE. They were all married women. With mean age  $\pm$  SD of  $30.3 \pm 2.3$  years in controls,  $31.8 \pm 4.3$  years in PIH group and  $30.9 \pm 4.9$  years in PE group ( $P = 0.600$ ). The median parity was 1.00 in control and PIH groups and 0.00 in PE group ( $P = 0.494$ ). The mean BMI  $\pm$  SD was  $26.9 \pm 2.9$  kg/m<sup>2</sup> in controls,  $29.4 \pm 3.2$  kg/m<sup>2</sup> in PIH group, and  $30.1 \pm 5.6$  kg/m<sup>2</sup> in PE group ( $P = 0.085$ ). Of the participants, 14 (31.1%) had family history of hypertension, 7 (15.6%) had family history of diabetes mellitus, and none (0.0%) had family history of chronic kidney disease or other cardiovascular disease. Only 1 (2.2%) had a past obstetric history of PIH, one (2.2%) had a past obstetric history of gestational diabetes and 2 (4.4%) had a history of PE. One of the women with PE was lost to follow-up.

### Postpartum blood pressure pattern

Using general linear models (GLM) multivariate analysis, the mean values of systolic BP, diastolic BP (DBP), and MAP immediately after delivery was found to be higher in the PIH group compared to the control group; and women with PE had higher values than those with PIH. This pattern was maintained all through the puerperium [Table 1].

When the different groups were compared with one another using *post hoc* test with LSD, we found that the mean difference

in BP values obtained immediately postpartum between the different groups was statistically significant ( $P < 0.05$ ). At 2-h postpartum, we found statistically significant differences in the mean values of BP readings when the various groups were compared, except for the mean difference in DBP of the PIH versus PE group of 0.20 mmHg ( $P = 0.930$ ) and mean difference in MAP of the PIH versus PE group of 3.94 mmHg ( $P = 0.100$ ). At 6 weeks postpartum, there was statistically significant difference between the DBP and MAP of control versus PE groups only with a mean difference of 12.71 mmHg ( $P = 0.01$ ) and 12.38 mmHg ( $P = 0.001$ ), respectively.

### Factors associated with persistently elevated blood pressure at 6 weeks postpartum

The proportion of women with PIH and PE combined who had persistent hypertension at 6 weeks postpartum was 3 out of 29 (10.3%), with a risk estimate of 1.1 (confidence interval 0.986–1.262). Table 2 summarizes the BP ranges in each study group at 6 weeks postpartum. No statistically significant association was found between MAP at 6 weeks postpartum and age ( $P = 0.320$ ), parity ( $P = 0.215$ ), gestational age at delivery ( $P = 0.591$ ), BMI ( $P = 0.070$ ), and family history of hypertension ( $P = 0.937$ ). Comparison between gestational age groups showed that women with hypertensive disorders in pregnancy necessitating preterm delivery are more likely to have persistent hypertension compared to those delivered at term (15.4% vs. 3.2%), but this finding was not statistically significant ( $P = 0.447$ ). This study also found a moderate positive correlation between MAP at 6 weeks postpartum and MAP immediately after delivery,  $r = 0.472$ ,  $P = 0.001$  [Figure 1].

### Potentially prognostic factors for the development of nonpregnant cardiovascular disease

The serum cholesterol, triglycerides, creatinine, and fasting plasma glucose (FPG) were higher in those who still have BP values  $>140/90$  mmHg at 6 weeks postpartum, but only the serum creatinine showed statistically significant association ( $P = 0.035$ ). When a comparison in the HDL, LDL,

Time of BP recording	NC	PIH	PE	Total
Immediately after delivery (mmHg)				
SBP	120.00 $\pm$ 11.34	137.33 $\pm$ 8.84	154.20 $\pm$ 17.12	137.18 $\pm$ 18.93
DBP	64.67 $\pm$ 7.43	85.33 $\pm$ 8.34	94.07 $\pm$ 12.80	81.36 $\pm$ 15.72
MAP	82.45 $\pm$ 9.21	102.66 $\pm$ 6.34	114.11 $\pm$ 12.78	99.74 $\pm$ 16.34
2 h postpartum (mmHg)				
SBP	119.00 $\pm$ 8.60	141.93 $\pm$ 10.91	154.27 $\pm$ 11.73	138.40 $\pm$ 17.99
DBP	65.00 $\pm$ 4.26	92.47 $\pm$ 4.97	92.27 $\pm$ 8.44	83.24 $\pm$ 14.37
MAP	82.99 $\pm$ 5.06	108.97 $\pm$ 5.99	112.91 $\pm$ 7.89	101.62 $\pm$ 14.81
6 weeks postpartum (mmHg)				
SBP	119.20 $\pm$ 12.26	122.40 $\pm$ 12.08	130.86 $\pm$ 12.53	124.00 $\pm$ 12.97
DBP	66.00 $\pm$ 7.93	71.93 $\pm$ 10.75	78.71 $\pm$ 10.00	72.07 $\pm$ 10.75
MAP	83.73 $\pm$ 8.54	88.77 $\pm$ 10.54	96.11 $\pm$ 9.88	89.39 $\pm$ 10.74

BP readings are presented as mean $\pm$ SD for each study group. BP – Blood pressure; SD – Standard deviation; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; MAP – Mean arterial blood pressure; PIH – Pregnancy-induced hypertension; PE – Preeclampsia; NC – Normal control

and FPG/insulin ratio of women who were normotensive, had prehypertension or hypertension at 6 weeks postpartum was done, we found lower levels of these biochemical substances in those with persistent hypertension at 6 weeks postpartum, but these differences did not show any statistical significance ( $P=0.809$ ,  $P=0.612$ , and  $P=0.861$ , respectively). Table 3 gives a summary of the mean values of these biochemical substances in association with various BP ranges.

Using spearman’s rank correlation analysis after testing for normality of population, we found a moderate correlation,  $r=0.441$ , which was statistically significant,  $P=0.006$  between serum creatinine levels at recruitment and MAP at 6 weeks

postpartum [Figure 2]. At our laboratory’s standardized normal range of  $<1.2$  mg/dL for serum creatinine, we found that the sensitivity of serum creatinine as a prognostic marker in identifying women with hypertensive disorders in pregnancy who are likely to have persistent hypertension was 100% and the specificity was 81.8%.

## DISCUSSION

This study showed that women with PE are more likely to have a higher BP compared to those with PIH. Macdonald-Wallis *et al.* in an earlier study found that women with PE had a more rapid rise in their BP from 30 weeks gestational age onward

**Table 2: Blood pressure pattern in each study group at 6 weeks postpartum**

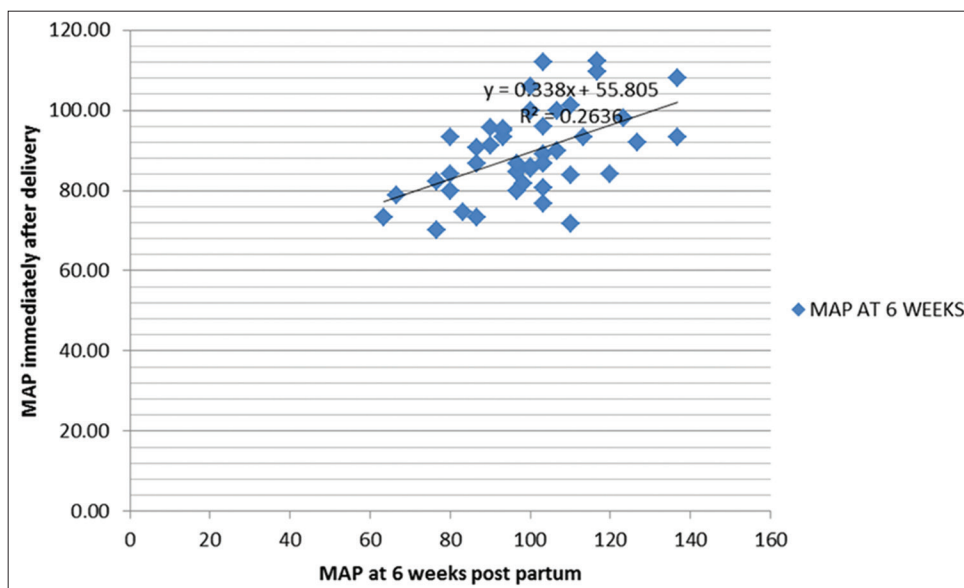
BP range at 6 weeks postpartum	Normal	Prehypertensive	Hypertensive	Total
NC	7 (46.7)	8 (53.3)	0 (0.0)	15 (100.0)
PIH only	7 (46.7)	7 (46.7)	1 (6.7)	15 (100.0)
PE only	4 (28.6)	8 (57.1)	2 (14.3)	14 (100.0)
PIH + PE combined	11 (37.9)	15 (51.7)	3 (10.3)	29 (100.0)
All subjects	18 (40.9)	23 (52.3)	3 (6.8)	44 (100.0)
$\chi^2, P$	5.087, 0.533			

Figures are presented as frequency (percentage). PIH – Pregnancy induced hypertension; PE – Preeclampsia; NC – Normal control; BP – Blood pressure

**Table 3: Mean values of biochemical parameters at diagnosis in association with blood pressure range at 6 weeks after delivery**

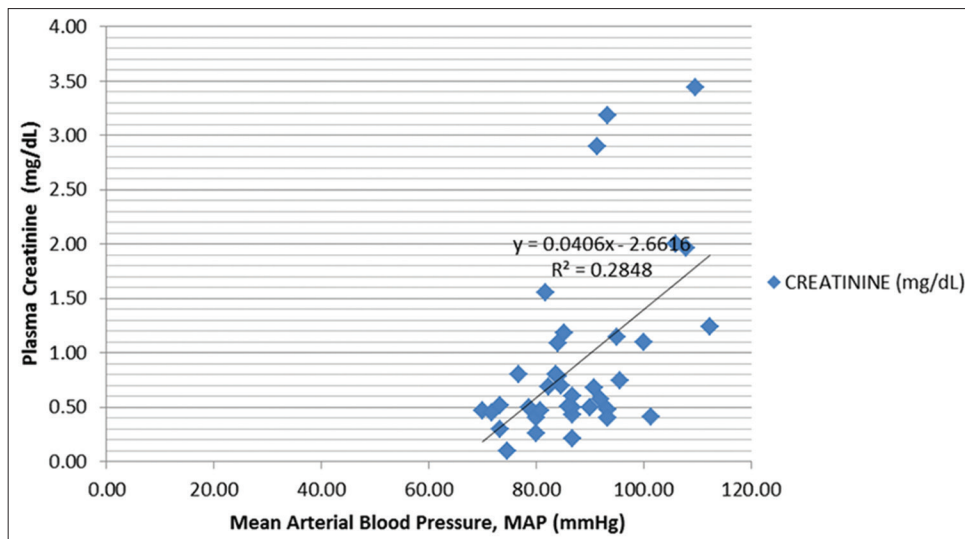
BP range at 6 weeks postpartum	Cholesterol (mmol/L)	TG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	Creatinine (mg/dL)	FPG (mg/dL)	Serum insulin ( $\mu$ IU/mL)	FPG/insulin (mg/ $10^{-4}$ U)
Hypertensive	2.13±1.39	1.02±0.43	0.61±0.69	1.06±0.49	2.34±1.56	115.76±45.74	4.90±4.95	38.60±29.70
Normal	2.95±1.09	0.89±0.50	0.89±0.48	1.65±0.98	0.70±0.72	75.99±44.26	3.00±3.89	76.04±80.86
Prehypertensive	2.67±0.83	0.72±0.44	0.94±0.45	1.40±0.81	0.94±0.67	67.22±26.27	5.05±9.24	68.87±78.87
$P$	0.541	0.548	0.809	0.612	0.035	0.317	0.842	0.861

Values of biochemical parameters are presented as mean±SD. SD – Standard deviation; TG – Triglyceride; HDL – High-density lipoprotein; LDL – Low-density lipoprotein; FPG – Fasting plasma glucose; BP – Blood pressure



**Figure 1: Correlation between mean arterial blood pressure at 6 weeks postpartum and mean arterial blood pressure immediately after delivery**





**Figure 2:** Scatter chart showing correlation between mean arterial blood pressure at 6 weeks postpartum and plasma creatinine level at recruitment

compared to women whose pregnancy is complicated by PIH or essential hypertension.<sup>15</sup> This is not surprising considering the widespread endothelial damage and elaboration of vasoactive substances implicated in the etiopathogenesis of PE. The loss of statistical significance in the mean difference of DBP and MAP when both groups (PIH and PE) were compared may be due to the small sample size used in this study.

The proportion of women with PIH and PE combined in this study that had persistent hypertension at 6 weeks postpartum was 10.3%. This buttresses the need for close monitoring and follow-up postpartum to identify those who will develop hypertension early and institute treatment. Over half of the women diagnosed of hypertension in pregnancy had 6 weeks postpartum BP values within prehypertensive range further emphasizing the need for long-term follow-up in all women with hypertensive disorders in pregnancy considering the greater risk of developing hypertension in prehypertensive women. Prehypertension has also been found to be a predictor of diabetes mellitus and coronary heart disease in women, RR 2.06 and 1.98, respectively, in an earlier study by Onat *et al.*<sup>16</sup> An interesting finding is that even among women who were normotensive in pregnancy, the incidence of prehypertension at 6 weeks postpartum was 53.3%. It therefore follows that we need to emphasize regular BP checks of all postpartum women and follow them up beyond the puerperium, which is 6 weeks postpartum in our environment, to identify early those who will become hypertensive. This finding puts a query as to why the puerperium should last 6 weeks. There may be a need for an extension of the time frame defining puerperium and follow-up of these women to reduce the proportion of women lost to follow-up. Women with a prior history of PE has been found to have a 2-fold increase in the risk of stroke, arrhythmias, and heart failure, and 10-fold increase in the risk of developing chronic kidney disease; and clinic visits in the postpartum period has been identified as a

great opportunity to screen and identify those with chronic hypertension.<sup>3</sup> Postpartum screening of cardiovascular risk factor and subsequent treatment in women with a history of PIH or PE at term was found to be cost-effective in a previous study<sup>17</sup> and this should, thus, be encouraged.

This study also found that the MAP at 6 weeks postpartum was not significantly affected by age, parity, gestational age at delivery, BMI, and family history of hypertension. However, it was observed that women who were delivered preterm were more likely to develop persistent hypertension by 6 weeks postpartum compared to those who were delivered at term. Although this finding was not statistically significant, it may have some clinical relevance because preterm deliveries in women with hypertensive disorders in pregnancy is often related to the early onset and severity of hypertension in this category of women which may become life-threatening to both mother and baby. This assertion is supported by our finding of a positive correlation between MAP immediately after delivery and MAP at 6 weeks postpartum.

Of all the biochemical parameters studied only serum creatinine level at diagnosis was found to have a statistically significant association with persistent hypertension at 6 weeks postpartum. Its use as a prognostic marker in predicting those women with hypertension in pregnancy that are likely to develop persistent hypertension appears promising. This is especially so considering its high sensitivity (100.0%) and high specificity (81.8%) in identifying women at risk of persistent hypertension at a cutoff value of 1.2 mg/dL. This finding is in tandem with what was found by Ayansina *et al.* in an earlier study in Aberdeen, Scotland in which it was found that chronic kidney disease is more prevalent with women with PIH and PE, with women with PE being more susceptible than those with PIH.<sup>18</sup> There is thus a need to conduct further longitudinal study using larger sample size to explore and confirm these findings.

## CONCLUSION

One-tenth of women with the hypertensive disorder in pregnancy have persistent hypertension by 6 weeks postpartum, whereas a large proportion of hypertensive and nonhypertensive pregnant women have BP values within prehypertensive ranges by 6 weeks postpartum. This buttresses the need for long-term follow-up of all women postpartum beyond the puerperium because of the high risk of hypertension in prehypertensive patients. Elevated serum creatinine appears to be a good prognostic marker in predicting those women with hypertensive disorders in pregnancy who will likely become hypertensive by the end of puerperium.

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## Conflicts of interest

There are no conflicts of interest.

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