All Hypertensive Disorders of Pregnancy Increase the Risk of Future Cardiovascular Disease

Jane Tooher, Charlene Thornton, Angela Makris, Robert Ogle, Andrew Korda, Annemarie Hennessy

Abstract—Hypertensive disorders of pregnancy are associated with vascular dysfunction in the pregnancy and an increased risk of long-term cardiovascular disease (CVD) in the mother. What remains to be understood is whether the length, severity of the disease, the treatment of hypertension in pregnancy, or the subtype of hypertensive disorders of pregnancy are significant predictors of future CVD. We undertook a retrospective cohort study to review all women who gave birth at a tertiary hospital in Sydney between the years 1980 and 1989 (n=31 656). A cohort of women was further defined by having hypertension during the antenatal, intrapartum, or postnatal periods (n=4387). Randomly selected records of women (n=1158) with a hypertensive disorder of pregnancy were individually reviewed to collect data on their pregnancy and pregnancy outcomes. The entire cohort then underwent linkage analysis to future CVDs. Women who presented with gestational hypertension were at greater risk of future hypertension and ischemic heart disease compared with the women who were diagnosed with preeclampsia. There was no significant difference between the women who were treated with antihypertensive medication and the women who did not receive antihypertensive medication or the duration of hypertensive disorders of pregnancy and future admission for CVD, although severity of hypertension tracked with increased risk of future hypertension in all groups. This study demonstrated that all women who present with any of the subtypes of hypertensive disorders in pregnancy are at significant risk of future CVD compared with women who remain normotensive during their pregnancy. (*Hypertension.* 2017;70:798-803. DOI: 10.1161/HYPERTENSIONAHA.117.09246.)

Key Words: blood pressure ■ cardiovascular diseases ■ hypertension ■ preeclampsia ■ proteinuria

Hypertensive disorders of pregnancy (HDP) affect 5% to 10% of all pregnancies worldwide.[1] Women who have a history of HDP have an increased risk of future cardiovascular disease (CVD) compared with women who remained normotensive in their pregnancy.[2] The most serious of these disorders is preeclampsia. Other forms of hypertension during pregnancy include gestational hypertension (hypertension alone without evidence of end-organ damage or proteinuria), chronic hypertension, and preeclampsia superimposed on chronic hypertension.[3]

The severity of the preeclampsia has been shown to have an association with the magnitude of future cardiovascular risk[2] as women who developed severe preeclampsia have a greater risk of future CVD compared with women with a milder form of the disease.[2] The risk of future CVD also increases with preterm delivery.[2] However, there is a poor understanding of the effect on the duration the woman had preeclampsia or the usage of antihypertensives medications on the future health consequences and whether risk is mitigated by such treatment.

The majority of the currently available data is based on linkages performed with registry or database data defining the pregnancy and its outcomes. There is a scarcity of analyses based on pregnancy outcomes sourced from reliable primary sources such as review of medical records which obtains information directly from the medical event. It has been shown previously that registry data are inaccurate to varying degrees as there may be information missing, the data may lack the necessary information, or there may be coding errors. However, it does provide access to increasing large numbers of patients for review.[4]

The aim of the current study was to examine whether the clinical course of women affected by HDP, such as maximum blood pressure, use of antihypertensive medication, and duration of disease, impacted independently on the women's future cardiovascular health status.

Methods

A retrospective cohort analysis of women delivering between January 1, 1980, and December 31, 1989, at a metropolitan tertiary hospital in Sydney, Australia, was undertaken. Women who had been diagnosed with an HDP in the antenatal, intrapartum, or postnatal period were identified using the *International Statistical Classification of Diseases and Related Health Problems*, Ninth Revision, Australian Modification available through the hospital's databases. Of all the women identified with an HDP, the medical record of every fourth woman was selected for individual medical record analysis. The data were extracted by 2 registered midwives with individual experience >15 years each. The reliability between the 2 data collectors was

established by taking a random sample of the records (10%) and calculating the Cohen κ coefficient.

The medical records of all the women were reviewed using individual patient data methodology to collect data pertaining to pregnancy events, outcomes, and disease classification. Hypertension in pregnancy classification was undertaken using the Society of Obstetric Medicine of Australia and New Zealand definition.[3] Gestational hypertension was defined as an increase in systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or both, after 20 weeks gestation which resolves, and where there was no previous history of renal disease or hypertension before the pregnancy.[3] Preeclampsia was defined as an increase in blood pressure after 20 weeks of gestation associated with the involvement of at least one other organ manifestation.[3] Chronic hypertension was defined as a systolic blood pressure elevated ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg, or both, preconception and not associated with additional systemic features of preeclampsia.[3] Women who presented with hypertension before 20 weeks gestation were said to have chronic hypertension. Chronic hypertension with superimposed preeclampsia was defined when ≥1 of the systemic features of preeclampsia develop in women with chronic hypertension.[3] Severity of blood pressure was categorized with a systolic blood pressure ≥170 mm Hg and a diastolic blood pressure of ≥110 mm Hg.[3]

Subsequently, this entire cohort of women was then provided to the Centre for Health Record Linkage (CHeReL, Sydney, Australia) allowing for linking of this patient group with the database of Admitted Patient Data Collection. The Admitted Patient Data Collection is administered by the New South Wales Health Ministry (New South Wales, Australia) and is a census of all admitted patient activity across all hospitals within New South Wales. The outcomes of interest were admissions for stroke, heart disease, renal disease, or hypertension. The *International Statistical Classification of Diseases and Related Health Problems*, 9th and 10th Revisions, Australian Modification, were used to identify women who were admitted for CVD, renal disease, and hypertension. Women who were identified as having hypertension or renal disease were not necessarily hospitalized for this disease, but the coding was able to indicate that they either have a history of hypertension or renal disease or have been newly diagnosed. The study was approved by the Sydney South Western Area Health Service Ethics Review Committee (Royal Prince Alfred Hospital Zone). Individual consent was not required by the Ethics Review Committee as this is a large retrospective population study. All procedures followed were in accordance with institutional guidelines.

Student *t* tests and ANOVA were used to compare results between the 4 diagnostic groups as the data were normally distributed and the data are expressed as the mean (±SD). Nonparametric data were analyzed using a Mann–Whitney *U* and Kruskal–Wallis tests as appropriate and data reported as the median+interquartile range (25th and 75th percentiles). Contingency tables were compared using χ^2 analysis, and a *P* value <0.05 was considered significant with Bonferroni correction made for multiple testing. Cox regression hazard models were used to do time-to-event analyses. Multivariate models included age, gestation at delivery, and parity. All analysis used IBM SPSS v.23 statistical software (SPSS Inc, Chicago, IL).

Results

A total of 31 656 women delivered at the institution between the years 1980 and 1989. From this cohort, HDP was diagnosed in 4387 (13.8%) women, whereas 27 262 (86.2%) of the women remained normotensive in their pregnancy (seven of the women were unable to be provided with a diagnosis and were excluded from the study). Results from the linked data showed that a total of 12 118 (38.3%) women within this cohort have had at least 1 admission to a hospital within New South Wales. Of these women, 1739 previously had HDP, and 10 379 had remained normotensive in their pregnancy.

Of the women (n=4387) who were coded as having hypertension in their pregnancy, the medical records of 1158 (26%)

were randomly selected and reviewed to determine the correct diagnosis and delivery outcomes. As some of the women had >1 affected pregnancy, there were a total of 1364 pregnancy events. Three women were unable to be classified as their medical records could not be located and were excluded from the study. Of the 1158 medical records that were reviewed, 583 of these women had had an admission to a hospital. From this cohort of women who had had an admission, 162 had preeclampsia, 322 had gestational hypertension, 56 had chronic hypertension, and 43 had preeclampsia superimposed on chronic hypertension (Figure 1). The interobserver reliability between the 2 clinicians collecting the data was high with a Cohen κ coefficient value of 0.91. In this cohort, in which the medical records were reviewed, it is noteworthy that the reliability of *International Statistical Classification of Diseases and Related Health Problems*, Ninth Revision, coding was high as only 8% of the women being over coded for HDP.

It was demonstrated that there was a significant difference between the women who had newly diagnosed hypertension in their pregnancy (preeclampsia and gestational hypertension) compared with the women who remained normotensive in their pregnancy and future admission for hypertension, ischemic heart disease (IHD), and renal disease. The results for the increased risk of CVD for preeclampsia, gestational hypertension, and all women with HDP are shown in Table 1.

In the validated cohort, there was no significant difference between the women with preeclampsia and those with gestational hypertension and admission to hospital for IHD (odds ratio [OR], 1.18; 95% confidence interval [CI], 0.59–2.38), stroke (OR, 0.28; 95% CI, 0.05–1.53), or renal disease (OR, 0.72; 95% CI, 0.27–1.95). The women who had chronic hypertension and superimposed preeclampsia had an increased risk of admission for IHD, with an OR of 2.84 (95% CI, 1.44–5.57) and 2.96 (95% CI, 1.44–6.11), respectively, compared with women who had gestational hypertension. The women who developed superimposed preeclampsia had an increased risk of a future admission for IHD (OR, 3.85; 95% CI, 1.56–9.52) but no difference in admission for stroke or renal disease.

A total of 462 (34%) women in the validated cohort were identified as having severe hypertension. Of the women diagnosed with preeclampsia, gestational hypertension, chronic hypertension, and preeclampsia superimposed on chronic hypertension 52%, 19%, 39%, and 67%, respectively, were identified as developing severe hypertension. The women who had severe blood pressure were more likely to be older, deliver at an earlier gestation, and have smaller babies compared with the women who did not have severe blood pressure (Table 2).

From the validated cohort, the risk of future admissions between the women who remained normotensive and those women who had severe blood pressure is shown in Table 3. The women with severe blood pressure in their pregnancy were at an increased risk of admission for future hypertension, IHD, stroke, and renal disease compared with the women who remained normotensive in their pregnancy.

In the validated cohort, the women who had HDP with severe blood pressure compared with those who had HDP without severe blood pressure demonstrated a significant difference in relation to future admissions for hypertension with an OR of 1.39 (95% CI, 1.01–1.93). There was no significant
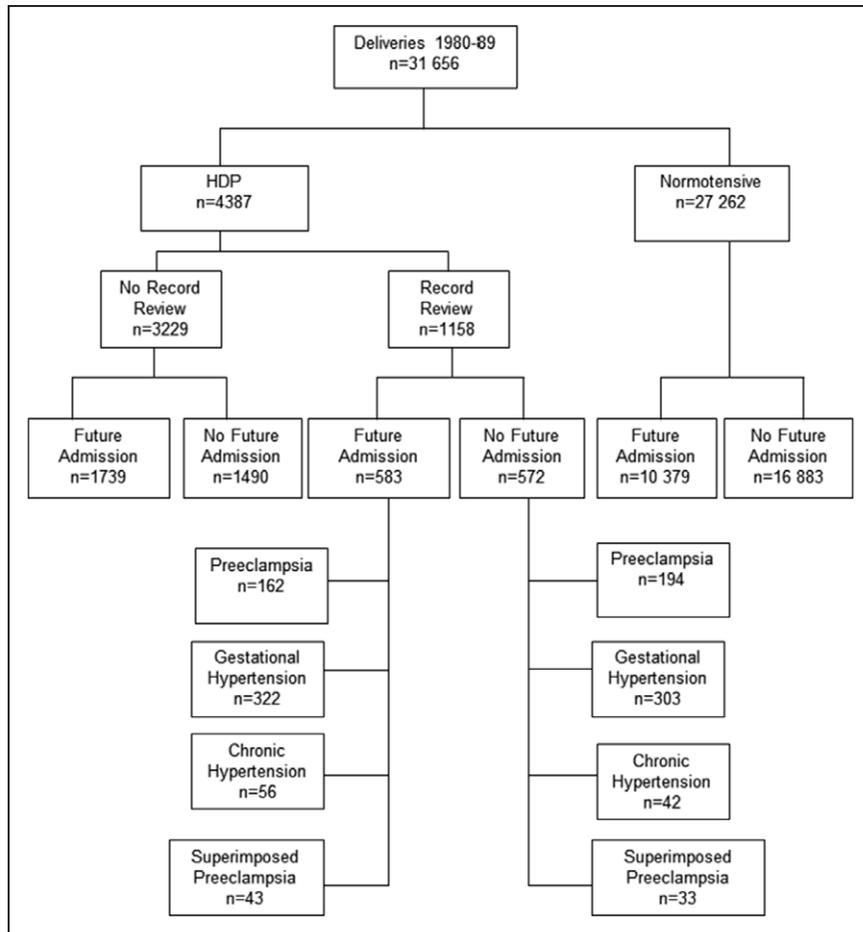
Figure 1. Flowchart of future hospital admission per diagnostic group. Please note: Of the women with hypertensive disorders of pregnancy (HDP; n=4387) and the women who remained normotensive (n=27 262), 7 were not able to be linked (total =31 656). Of the individual notes examined, n=583 (admitted) and n=572 (not admitted), 3 records were missing, and the HDP diagnosis was unable to be determined (n=1158).

difference between these 2 groups and future admission for IHD (OR, 0.95; 95% CI, 0.54–1.67), stroke (OR, 0.65; 95% CI, 0.22–1.94), or renal disease (OR, 0.98; 95% CI, 0.41–2.35). The women with preeclampsia were more likely to have severe blood pressure compared with the women with gestational hypertension with an OR of 4.34 (95% CI, 3.25–5.78). However, the women with severe blood pressure with gestational hypertension were more likely to have an admission for future hypertension compared with the women with severe blood pressure and preeclampsia (OR, 1.92; 95% CI, 1.02–3.64).

When examining the whole cohort, the CVD composite outcome was significantly different between the women who had HDP than in those who remained normotensive in their pregnancy (Figure 2). The median time from the index pregnancy to onset of CVD (comprised IHD, stroke, and heart disease) was 20 years with a range of 3 to 29 years. When examining the validated cohort, there was no significant difference between the women who developed severe hypertension and those who without severe hypertension in regards to years to onset of CVD. However, there was a significant difference between the women who delivered at ≤34 weeks gestation versus those women who delivered >34 weeks gestation and years to onset of CVD (Figure 3).

Of the women whose medical records were examined, antihypertensive medications were given to 696 (51%) women with HDP. Of all women developing severe

hypertension (n=394), 311 (79%) were given antihypertensive medication. There was no significant difference between the women who received antihypertensive medication in their pregnancy and those who did not receive antihypertensive medication and future admission for hypertension, IHD, stroke, or renal disease. Future risk of admission was not affected by the type of antihypertensive agent used during the pregnancy.

Table 1. The Adjusted OR of Admissions for Future Disease for Women With Preeclampsia, Gestational Hypertension, and All Women With HDP Compared With Women Who Remained Normotensive

Future Disease	Preeclampsia, OR (95% CI)*	Gestational Hypertension, OR (95% CI)*	All HDP, OR (95% CI)†
Future hypertension	3.06(2.18–4.29)	4.08 (3.23–5.10)	2.78 (2.47–3.13)
Ischemic heart disease	2.67 (1.49–4.81)	3.19 (2.11–4.83)	2.16 (1.98–3.84)
Stroke	2.03 (0.75–5.49)	0.57 (0.14–2.31)	1.94 (1.39–2.69)
Renal disease	4.74 (2.19–10.20)	3.45 (1.74–6.85)	2.76 (1.98–3.84)

CI indicates confidence interval; HDP, hypertensive disorders of pregnancy; and OR, odds ratio.

*Adjusted for age, gestation, and parity.

†Adjusted for current age.

Table 2. The Birth Outcomes Between Hypertensive Disorders of Pregnancy Women With Severe Blood Pressure and the Women Without Severe Blood Pressure

Outcome	Severe Blood Pressure	Nonsevere Blood Pressure	P Value
Age at delivery, y*	28 (6.3)†	27 (5.8)†	0.025
Gestational age, wk*	35 (3.9)†	38 (2.3)†	<0.001
Neonatal weight, g*	2473 (956.1)†	3245 (682.3)†	<0.001
Weight centile*	26 (9–55)†	47 (20–77)†	<0.001

*Mean.
†SD.

The women who had been diagnosed with HDP and delivered >1 week after diagnosis were at an increased risk of severe blood pressure (OR, 1.37; 95% CI, 1.07–1.75), being prescribed antihypertensive medication (OR, 3.44; 95% CI, 2.70–4.35) and developing neurological symptoms (OR, 1.77; 95% CI, 1.08–2.91) compared with the women who had been diagnosed with HDP and delivered in <1 week of diagnosis. However, there was no difference in future hospital admissions for CVD between the women who delivered in <2 days of diagnosis compared with those women who delivered at >1 week after diagnosis (P=0.141, after adjustment for smoking, primiparity, age, diagnosis, and disease severity).

Overall, there was a difference of future admissions between the women who had HDP (n=4387) and those who remained normotensive (n=27 262) in their pregnancy (OR, 1.07; 95% CI, 1.01–1.14). The women who had HDP were at greater risk of an admission for future CVD (IHD, angina, myocardial infarction, and stroke combined) compared with the women who remained normotensive in their pregnancy (OR, 2.06; 95% CI, 1.65–2.58). The women with HDP were also at greater risk of future hypertension (OR, 2.78; 95% CI, 2.47–3.13) compared with the women who remained normotensive in their pregnancy.

Discussion

This study has shown that women with gestational hypertension have a greater risk for future hypertension compared to women with preeclampsia, results similar to Kestenbaum et al[5] (2003) who found that women with gestational hypertension

Table 3. Comparison of Severity of Blood Pressure and Women Who Remained Normotensive in Their Pregnancy and Future Cardiovascular Admissions

Future Disease	Odds Ratio	Adjusted Odds Ratio*	95% Confidence Interval	P Value
Risk factor				
Future hypertension	5.78	5.82	4.47–7.58	<0.001
CVD				
Ischemic heart disease	4.05	3.91	2.46–6.23	<0.001
Stroke	2.73	2.65	1.16–6.04	0.020
Renal disease	4.83	4.66	2.25–9.62	<0.001

CVD indicates cardiovascular disease.
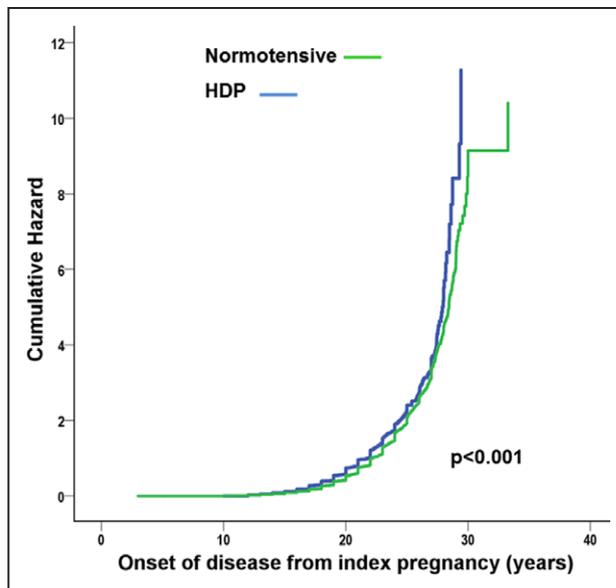*Adjusted for current age.

Figure 2. Comparison of time from index pregnancy to time of onset of cardiovascular disease (CVD) comparing the women with hypertensive disorders of pregnancy (HDP) and those who remained normotensive in their pregnancy.

had RR of 2.8 compared with RR of 2.2 for preeclampsia and future CVD. Most of the literature refers to the risk following preeclampsia alone, and women with gestational hypertension are not informed of their increased risk of CVD.[6] A study by Wikström et al[6] (2005) showed that gestational hypertension was associated with future CVD risk of 1.6 (95% CI, 1.30–2.00) but suggested that notwithstanding this result, informing women of this would cause undue anxiety. However, recent studies have identified gestational hypertension as having a higher CVD risk profile compared with women who had preeclampsia in their pregnancy.[7,8]

Veerbeek et al[7] (2015) demonstrated that women with gestational hypertension presented with higher modifiable risk factors and had significantly higher blood pressure compared
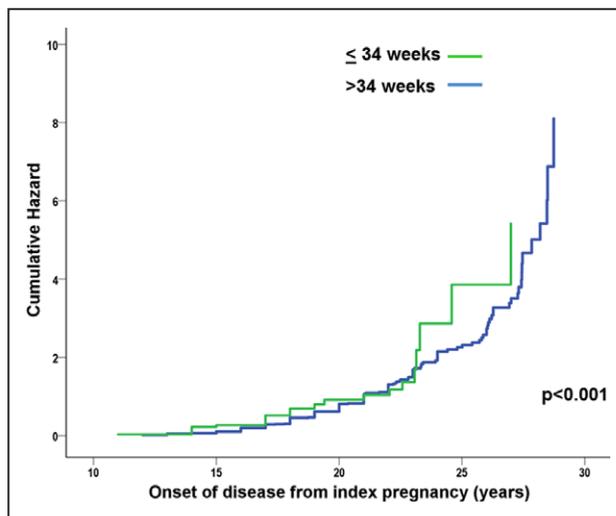

Figure 3. Comparison of years from index pregnancy to time of onset of cardiovascular disease (CVD) between the women who delivered ≤34 wk gestation and those who delivered >34 wk gestation.

with the preeclamptic group 2 to 5 years after their pregnancy. A study by Andersgaard et al[8] (2012) demonstrated that there was a greater risk of future hypertension for women with gestational hypertension compared with the women with preeclampsia. This study relied on patient recall many years after the index pregnancy and a clinical diagnosis was not validated. Even though the numbers are small in this study, we were able to correctly diagnosed the subtype hypertension that these women experienced in their pregnancy. This study demonstrates that women with HDP may benefit from regular monitoring after delivery and that the modification and intervention programs may need to be developed according to the subtype of disease experienced.

Although the use of antihypertensive medication was found to be beneficial during pregnancy in terms of neonatal and maternal outcomes (consistent with the results of Magee et al[9] 2015), these results demonstrated that there was no significant difference for future admission for any of the diseases between the women who received antihypertensive medication in their pregnancy and those who did not receive any antihypertensive medication. This adds to the research that the presence of HDP, whether it is of a long or short duration or whether the hypertension was treated or not during the pregnancy, increases the risk of future CVD for all women. It is worth noting that the higher the level of hypertension in the pregnancy, the greater the risk of future hypertension in all groups.

This study has shown that after a pregnancy complicated by HDP, women were at an increased risk of future hypertension and had a higher CVD risk profile compared with those pregnancies not complicated by HDP. The results are supported by large epidemiological studies which have shown that both gestational hypertension and preeclampsia impose a greater risk of future CVD than women who remained normotensive in their pregnancy.[10–12] Wilson et al[12] showed an increased risk for future hypertension after preeclampsia (RR, 2.6 95%; 95% CI, 1.77–3.86), whereas Magnussen et al[10] found a similar result with an increased risk of hypertension after preeclampsia with an RR of 3.1 (95% CI, 2.20–4.30). Wilson et al[12] also showed that women who had gestational hypertension (RR, 1.89; 95% CI, 1.23–2.88) and preeclampsia (RR, 1.90; 95% CI, 1.27–2.86) were at greater risk of being on antihypertensive medication in later life compared with women who remained normotensive in their pregnancy.

The majority of studies involve a large number of women using linked data and thereby relying on the accuracy of the data entered.[11,12] Inaccuracy may lead to misclassifying the type of hypertension in pregnancy.[13] Many of the current studies look at retrospective data on pregnancy outcomes >10 years from the index pregnancy which leaves room for recall bias with regards to the pregnancy event. Even though this study is limited by the number of participants, the strength of this study is the accuracy of diagnoses confirmed for the pregnancies using individual review of the medical records. A weakness of this study is the inability to account for all women with chronic hypertension as women within this younger age group are not routinely screened for hypertension and that the linked data for current health status is unlikely to capture all women with hypertension as it is dealt with at the community

level and usually does not require hospitalization and therefore underreported.[10–12,14] It is also acknowledged that women may have been admitted to hospitals outside the Admitted Patient Data Collection area, and, therefore, the number of women diagnosed with future hypertension and CVD has been underestimated.

The medical records of these women were examined to provide accurate and detailed clinical information providing data on the different classifications of HDP in terms of proportional risk. The study demonstrated that women with any classification of HDP are at greater risk of developing hypertension in later life. The risk of IHD, renal disease, and links to hypertension indicate widespread endothelial injury after any classification of HDP of any duration, irrelevant of any antihypertensives administered during the pregnancy. These women need lifelong close monitoring of blood pressure and CVD modifiable risk factors post-pregnancy.

Perspectives

These results indicate that a woman who experiences HDP should be monitored closely to identify early recognition of any CVD risk factors. It is also important that both women and clinicians are well informed of the increased risk of future CVD after a history of HDP. Further research is required to determine whether early identification and prevention strategies actually decrease the risk of future CVD.

Acknowledgments

Disclosures
None.

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Novelty and Significance

What Is New?

- The medical records of these women were examined to provide accurate and detailed clinical information.
- The study provides data on the different classifications of hypertensive disorders of pregnancy.
- The study examines the association between the use of antihypertensive agents and future cardiovascular disease.

What Is Relevant?

- Women who have hypertensive disorders of pregnancy are at greater risk of developing hypertension in later life.
- These women need close monitoring of blood pressure post-pregnancy.
- Cardiovascular risk assessment should include a woman's obstetric history.

Summary

Hypertension during pregnancy infers a lifelong risk of cardiovascular disease.

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