MAYO CLINIC

# Preeclampsia and Future Cardiovascular, Chronic and End-stage Renal Disease


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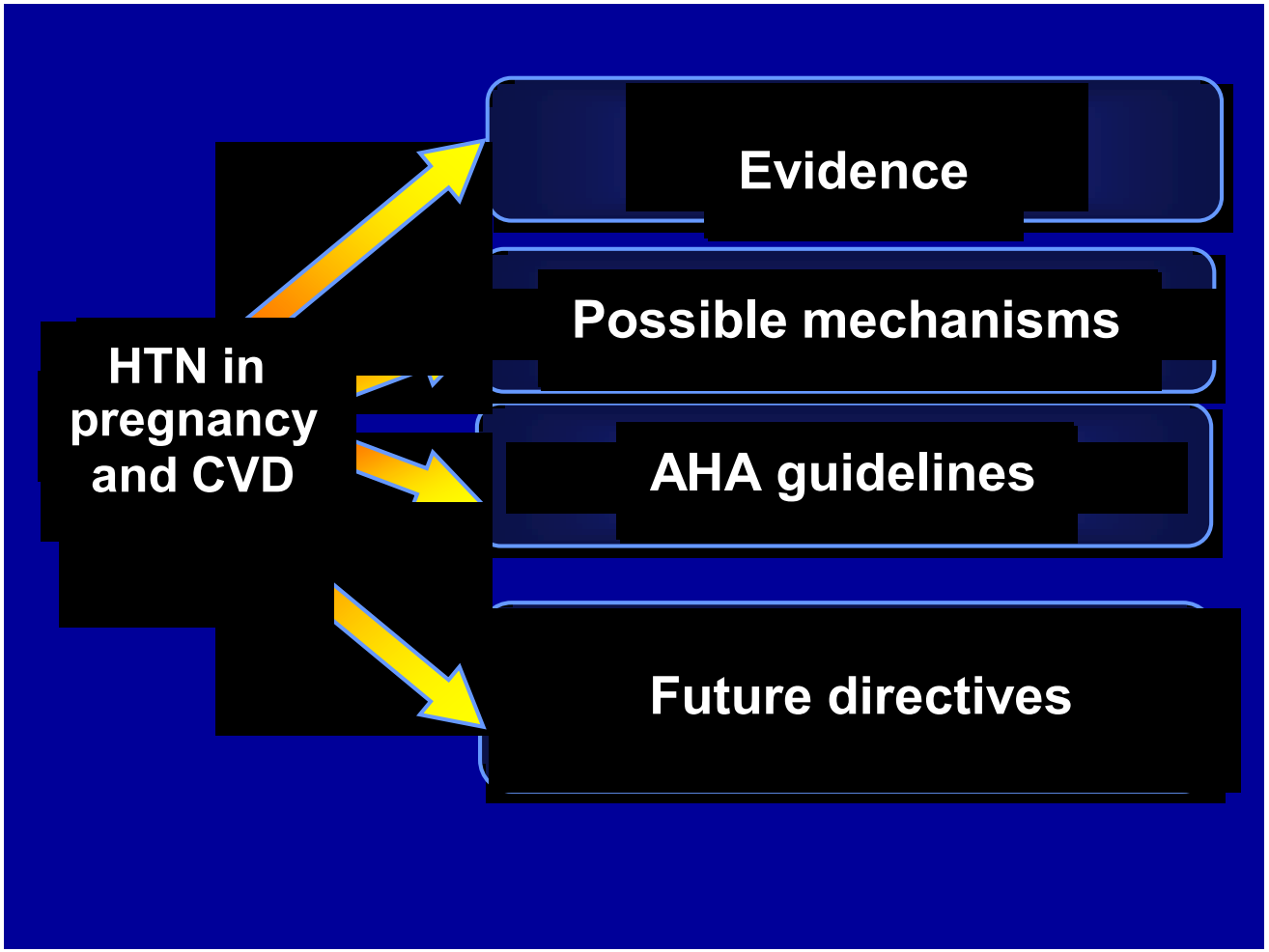
# Conflict of interest and Funding

No conflict of interest

Funding P-50 AG44170

# Pregnancy hypertension and future CVD



# Preeclampsia-eclampsia

- Affects 5% of all pregnancies worldwide
- Remains a leading cause of maternal and fetal morbidity and mortality
- In USA, pregnancy-related mortality 14.5/100,000 livebirths (1998-2005); 12% due to pregnancy HTN

*Berg et al. Obstet Gynecol 2010*

- Increasing trend in USA in pregnancy related-hospitalizations with stroke, ↑54% ('94→'07)
  - with hypertensive disorders as a leading cause

*Kuklina et al. Stroke 2011*

# Preeclampsia and Future CVD?

- Studies in 1970's and 1980's: Preeclampsia does not herald future HTN
- No difference in in the prevalence of HTN and CVD mortality and morbidity between eclamptic women and age-matched controls after 33 years
  - Small sample sizes
  - Suboptimal control groups

# Subsequent Studies

Associations between HTN pregnancy disorders and CVD are increasingly recognized

# Subsequent Studies

- A population-based retrospective cohort study in Ontario, Canada, of 1.03 million women free from CVD before their first documented delivery
- Maternal placental syndromes: preeclampsia, gestational hypertension, placental abruption, and placental infarction
- HR 2.0 for CVD for women who had had a MPS compared with women who had not
- This risk was higher in MPS plus poor fetal growth (3.1) or MPS plus intrauterine fetal death (4.4)

*Ray et al. Lancet, 2005*

# Subsequent Studies

14 403 women in the Child Health and Development Studies pregnancy cohort - the Kaiser Permanente Health Plan in California

- The risk of subsequent cardiovascular disease death was notably higher among women with onset of preeclampsia by 34 weeks of gestation

*Mongraw-Chaffin, Hypertension, 2010*

# Meta-analysis

- The relative risks (95% CI)
- HTN 3.70 (2.70 to 5.05) after 14.1 years
- CHD 2.16 (1.86 to 2.52) after 11.7 years
- Stroke 1.81 (1.45 to 2.27) after 10.4 years
- Venous thromboembolism 1.79 (1.37 to 2.33) after 4.7 years.
- Overall mortality after pre-eclampsia: 1.49 (1.05 to 2.14) after 14.5 years

*Bellamy et al. BMJ,2007*

# Subsequent Studies

Limitations

- Small sample sizes
- Short follow-up
- Lack of racial and ethnic diversity
- Registry-based designs
- Limited number of outcomes

*Garovic and Hayman NCPN, 2007*

# Specific Aims

In a large multiracial cohort, test association of HTN pregnancy disorders with

- Subsequent hypertension
- CHD
- Stroke

*Garovic et al. J Hypertens, 2010*

# Study Design

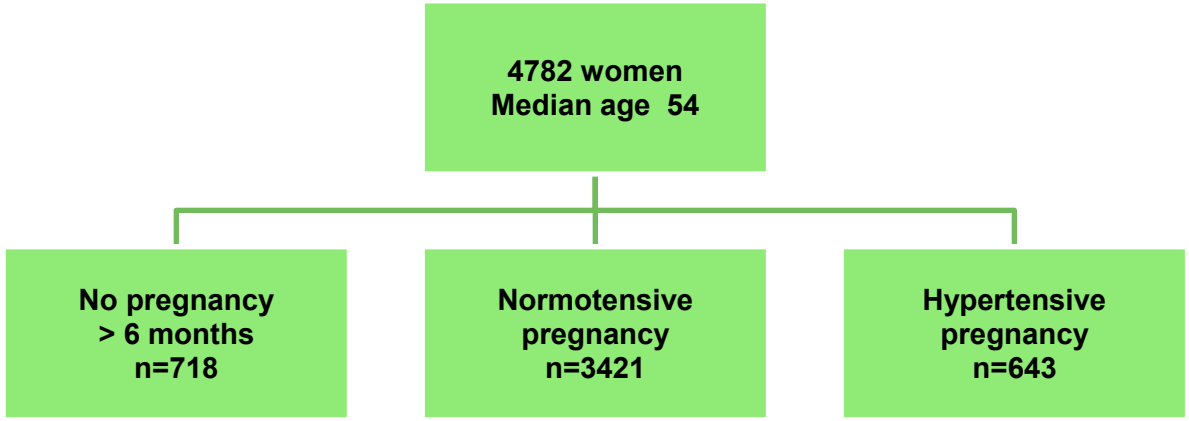
- 4782 women from FBPP sibships with ≥ 2 members diagnosed with HTN age < 60 years
- Medical history: DM, Stroke, CHD, HTN
- Smoking
- Family history
- Physical examination
- Blood biochemistries

# Pregnancy Questionnaire

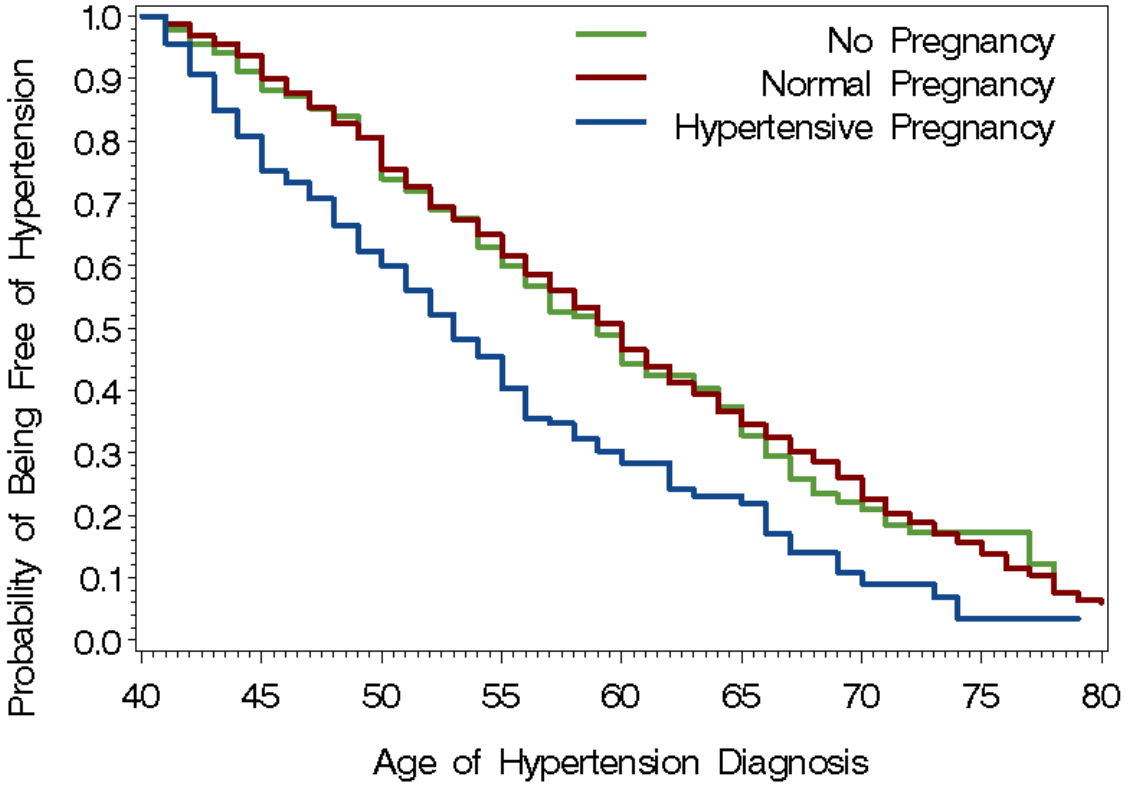
- At least one pregnancy > 6 months?
- How many?
- During any of these pregnancies, did a physician ever tell you that you had high blood pressure or hypertension?

*Garovic et al. AJOG, 2008*

# Sample Description

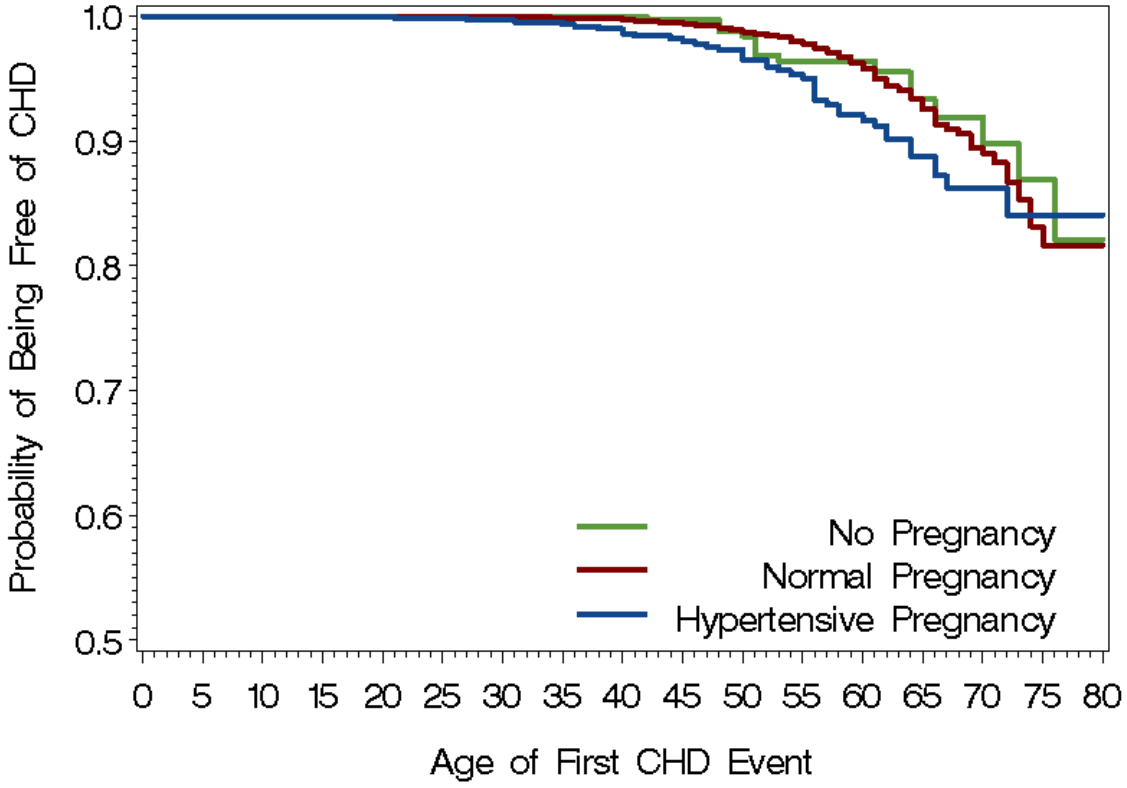


# HTN Later in Life



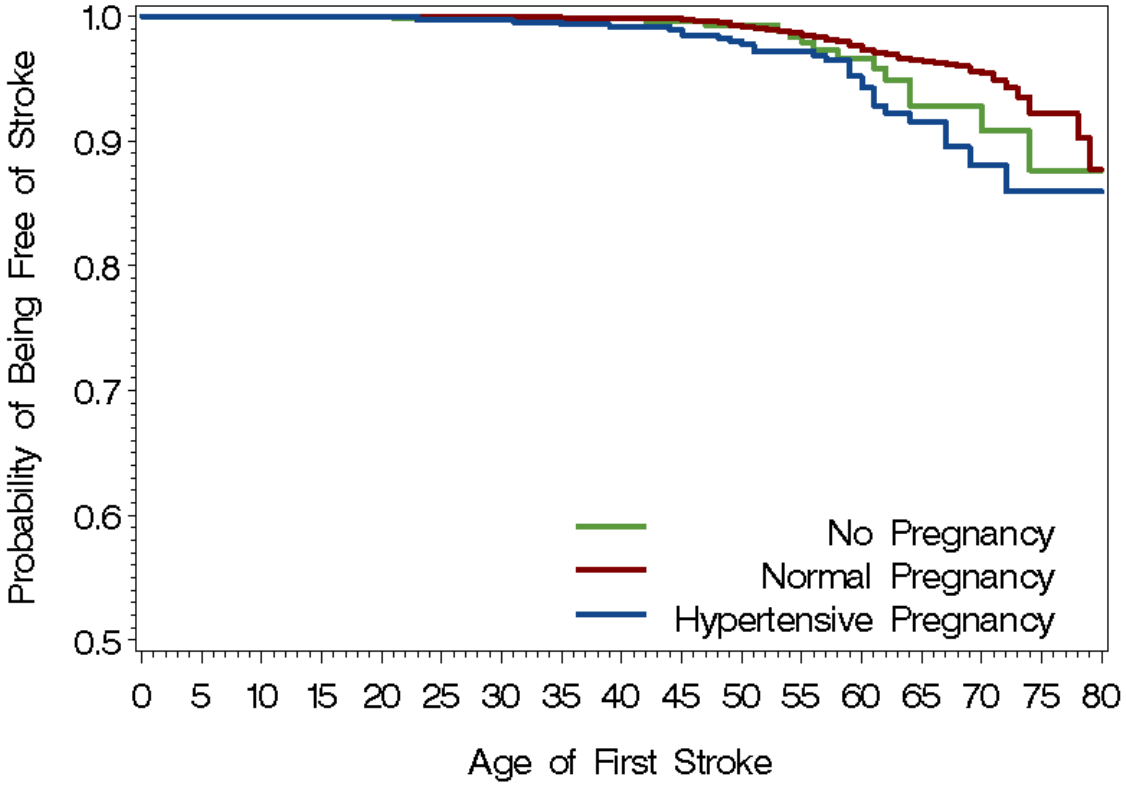

P<0.001

# CHD Later in Life




P=0.009

# Stroke Later in Life




P<0.001

# Adjusted HR for HTN after Age 40, CHD, and Stroke-FBPP

| Group contrasts | HTN after age 40 | | | CHD | | | Stroke | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P | HR | 95% CI | P |
| Normotensive vs. Nulliparous | 0.88 | 0.73-1.08 | 0.22 | 1.02 | 0.60-1.75 | 0.94 | 0.55 | 0.31-1.00 | ***0.050*** |
| Hypertensive vs. Normotensive | 1.55 | 1.26-1.89 | ***<.001*** | 1.14 | 0.78-1.68 | 0.50 | 1.86 | 1.16-2.98 | ***0.010*** |

# Adjusted HR for HTN after Age 40, CHD, and Stroke-GENOA

| Group contrasts | HTN after age 40 | | | CHD | | | Stroke | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P | HR | 95%CI | P |
| Normotensive vs. Nulliparous | 0.78 | 0.59-1.04 | 0.09 | 0.84 | 0.39-1.82 | 0.67 | 0.61 | 0.27-1.40 | 0.24 |
| Hypertensive vs. Normotensive | 1.88 | 1.49-2.39 | ***<.001*** | 0.65 | 0.32-1.30 | 0.22 | 2.10 | 1.19-3.71 | ***0.010*** |

# Conclusions

May represent an independent risk factor for future HTN and CVD

- The association with CHD might have been underestimated given the age of the FBPP cohort
- ? The mechanisms underlying this association

# Risk for Atrial fibrillation and CHF

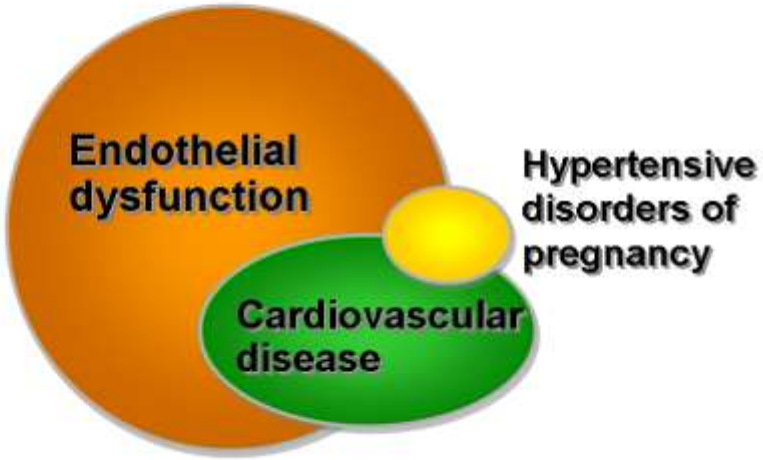
- Retrospective large cohort study (Ontario, Canada)
- Women with placental abruption, placental infarction, preeclampsia, and gestational HTN
- 61% relative increase in the risk for HF and dysrhythmia

*Ray et al. Heart, 2012*

# Association between preeclampsia and future CVD

## Due to shared risk factors

### Endothelial dysfunction



# Association between preeclampsia and future CVD

## Due to shared risk factors

### Endothelial dysfunction

# Association between preeclampsia and future CVD

- May cause metabolic and vascular changes that modify future risks
  - Brachial artery endothelium-dependent dilatation impaired 3 years post PE pregnancies

    *Chambers et al. JAMA 2001*
  - Possible independent risk factor?

# Eclampsia and Posterior Reversible Encephalopathy Syndrome (PRES)

- PRES first described in 1996, in 15 patients, 3 with eclampsia
  - Clinical signs and symptoms: headaches, visual changes, lethargy, seizures and
  - Radiological findings: vasogenic edema involving posterior circulation
- In pregnancy at considerably lower BP elevations (SBP 150-170 mm Hg) compared to hypertensive encephalopathy (SBP 180-200 mm Hg)

*Hinchey et al. NEJM 1996*

# Eclampsia and Posterior Reversible Encephalopathy Syndrome (PRES)

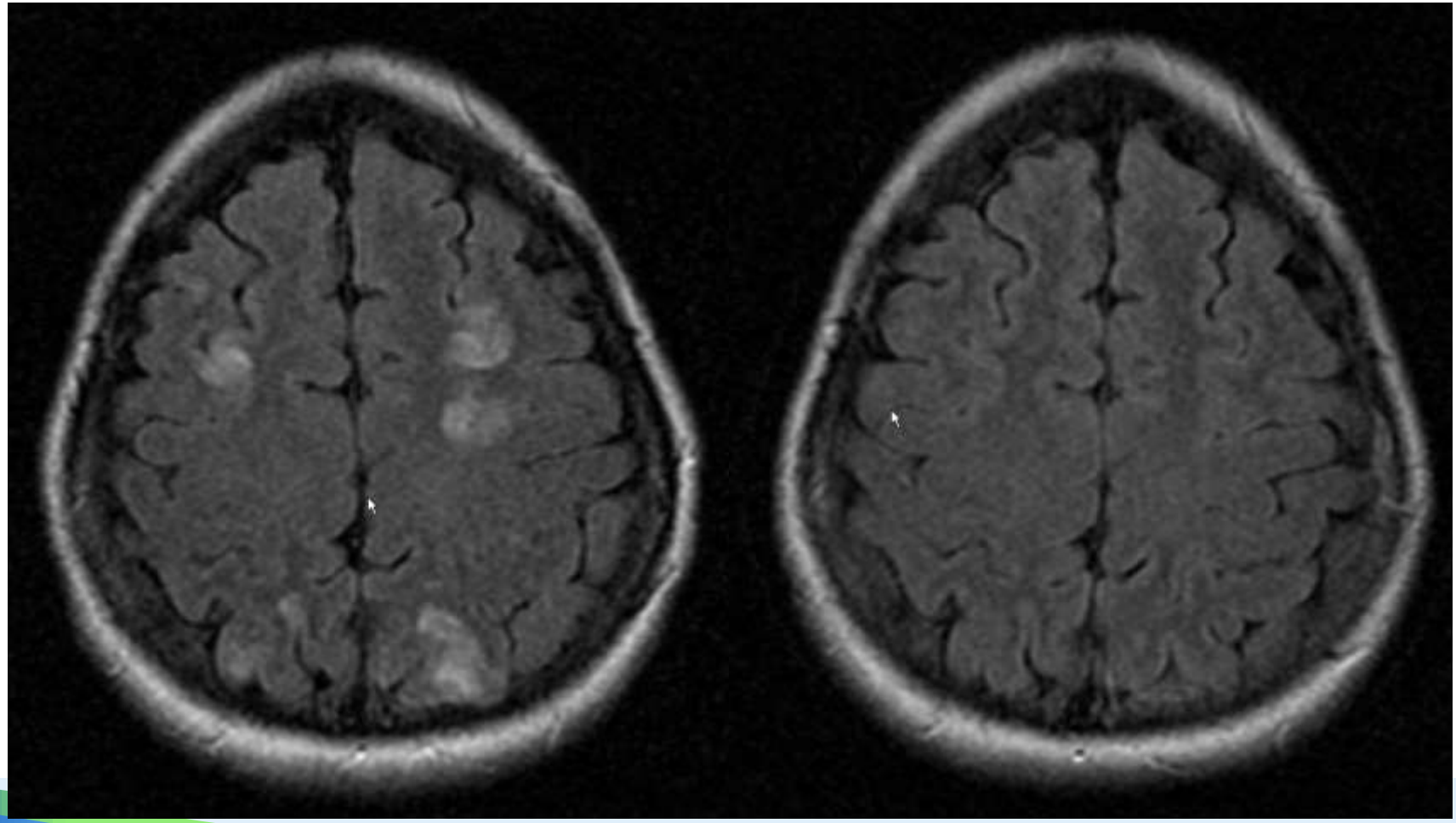
- In a prospective study of 27 women with eclampsia, 25 had PRES, and 5 demonstrated persistent neuro-imaging abnormalities (gliosis)

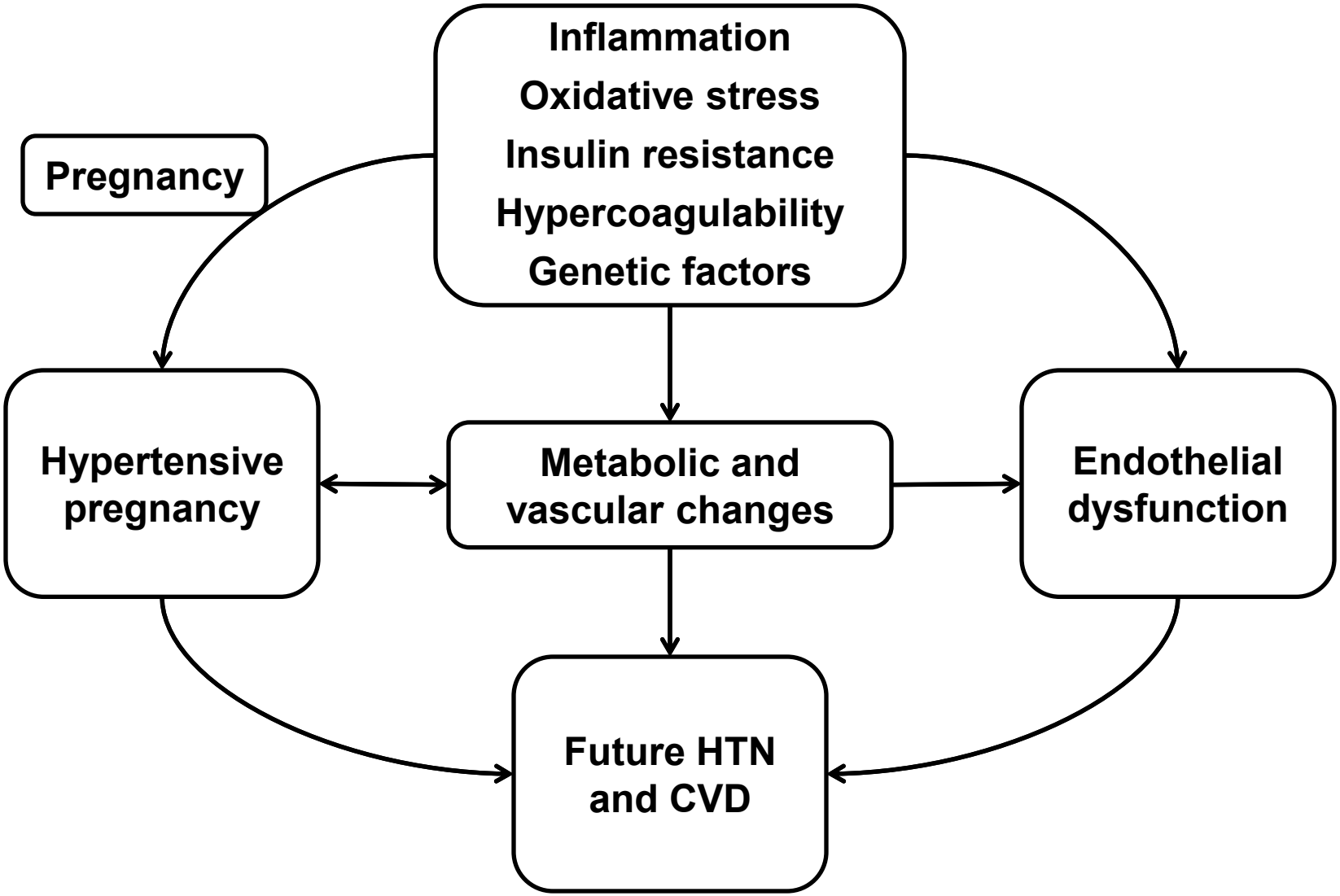
  *Zeeman et al. AJOG, 2004*

- Mayo study
  - 7 of 22 patients with eclampsia underwent neuro-imaging
  - All 7 demonstrated signs of PRES
  - Maximum SBP > 180 mm Hg in 2/7
  - Persistent neuroimaging abnormalities (1/7)

    *Wagner et al. MCP 2011*

23 year old, G3 /P1 presenting with headache, blurred vision, and seizure, peak SBP 151mm Hg; f/u MRI 2 weeks postpartum : punctuate T2 abnormality in the right superior frontal lobe






**Possible mechanisms of the association of pregnancy hypertension, endothelial dysfunction, and future HTN and CVD**

# Hypertension in pregnancy and future cardiovascular damage

ORIGINAL ARTICLE

## Left ventricular hypertrophy after hypertensive pregnancy disorders

*Scantlebury DC, et al. Heart 2015*
*doi:10.1136/heartjnl-2015-308098*

# Hypertension in pregnancy and future cardiovascular vascular damage

Atherosclerosis 229 (2013) 212–216

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

## Hypertension in pregnancy is a risk factor for peripheral arterial disease decades after pregnancy

Tracey L. Weissgerber[a], Stephen T. Turner[a], Kent R. Bailey[b], Thomas H. Mosley Jr.[c], Sharon L.R. Kardia[d], Heather J. Wiste[b], Virginia M. Miller[e], Iftikhar J. Kullo[f], Vesna D. Garovic[a,*]

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# Hypertension in pregnancy and future cardiovascular damage-mediators

Original Article

## Hypertension in pregnancy is associated with elevated C-reactive protein levels later in life

Catherine M. Brown[a], Stephen T. Turner[a], Kent R. Bailey[b], Thomas H. Mosley Jr[c], Sharon L.R. Kardia[d], Heather J. Wiste[b], Iftikhar J. Kullo[e], and Vesna D. Garovic[a]

*J of Hypertens 2013*
*31:2213–2219*

# Hypertension in pregnancy and future cardiovascular damage- mediators

## Hypertension in pregnancy is associated with elevated homocysteine levels later in life

Wendy M. White, MD; Stephen T. Turner, MD; Kent R. Bailey, PhD; Thomas H. Mosley Jr, PhD; Sharon L. R. Kardia, PhD; Heather J. Wiste, BA; Iftikhar J. Kullo, MD; Vesna D. Garovic, MD

*Am J Obstet Gynecol 2013;209:454.e1-7.*

# Hypertension in pregnancy and future cardiovascular damage- mediators

MAYO CLINIC

ORIGINAL ARTICLE

## Uric Acid: A Missing Link Between Hypertensive Pregnancy Disorders and Future Cardiovascular Disease?

Tracey L. Weissgerber, PhD; Natasa M. Milic, MD, PhD; Stephen T. Turner, MD; Reem A. Asad, MD; Thomas H. Mosley Jr, PhD; Sharon L.R. Kardia, PhD; Craig L. Hanis, PhD; and Vesna D. Garovic, MD

*Mayo Clin Proc. 2015*

# 2011 AHA Guidelines for the Prevention of CVD in women

- Postpartum: monitored and treated for modifiable risk factors
- Questions re: HTN in pregnancy should become a routine part of medical history
- Future studies of exposures and events across a woman's lifespan-need for population based studies

*Mosca et al. Circulation, 2011*

# 2014 AHA Guidelines for the Prevention of Stroke in women

- Increased risk during pregnancy, post-partum, and years after
- Prospective studies on the pathophysiology underlying the association, especially in diverse populations
- These studies will provide evidence to inform screening, prevention, and treatment strategies in women with a history of HTN in pregnancy

*Bushnell et al. Stroke, 2014*

# Preeclampsia and ESRD

- Recent studies have shown association of preeclampsia and ESRD

  Large registry study in Norway 1976-2004 of 570,433 women

  - Increased risk of ESRD after preeclamptic pregnancy
    - RR 3.2 after single preeclamptic pregnancy
    - RR 15.5 after multiple preeclamptic pregnancies

*Vikse et al, NEJM, 2008*

- Insurance claims data from 1998-2009 in Taiwan
  - Increased risk of CKD (HR 9.3) and ESRD (HR 12.4) after hypertensive pregnancy

*Wang et al, CMAJ,2013*

# Hypertension in pregnancy and future CVD and CKD/ESRD

THE JCH The Journal of Clinical Hypertension

OFFICIAL JOURNAL OF THE WORLD HYPERTENSION LEAGUE

ORIGINAL PAPER

## Hypertension in Pregnancy Is a Risk Factor for Microalbuminuria Later in Life

Andrea G. Kattah, MD;[1] Reem Asad, MD;[1] Dawn C. Scantlebury, MBBS;[2] Kent R. Bailey, PhD;[3] Heather J. Wiste, BA;[3] Steven C. Hunt, MD;[4] Thomas H. Mosley, PhD;[5] Sharon L. R. Kardia, PhD;[6] Stephen T. Turner, MD;[1] Vesna D. Garovic, MD[1]

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# Hypertension in pregnancy and future ESRD

AJKD

Original Investigation

## Preeclampsia and ESRD: The Role of Shared Risk Factors

*Andrea G. Kattah, MD,[1] Dawn C. Scantlebury, MBBS,[2] Sanket Agarwal, MBBS,[1] Michelle M. Mielke, PhD,[3,4] Walter A. Rocca, MD, MPH,[3,4] Amy L. Weaver, MS,[5] Lisa E. Vaughan, MS,[5] Virginia M. Miller, PhD,[6] Tracey L. Weissgerber, PhD,[1] Wendy White, MD,[7] and Vesna D. Garovic, MD[1]*

*From the Division of Nephrology and Hypertension, Mayo Clinic;[1] Division of Cardiovascular Diseases, Mayo Clinic;[2] Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN;[3] Department of Internal Medicine, University of Utah, Salt Lake City, UT;[4] Department of Neurology, University of Mississippi, Jackson, MS;[5] and Department of Epidemiology, University of Michigan, Ann Arbor, MI[6]*

# Hypertension in pregnancy and future ESRD

- 8 of 44 (18%) cases versus 4 of 88 (5%) controls had preeclamptic pregnancies (unadjusted OR, 4.0; 95% CI, 1.21-13.28)
- Evidence of kidney disease prior to the first pregnancy in 9 of 44 (21%) cases and 1 of 88 (<1%) controls

# Hypertension in pregnancy and future ESRD

- Results were similar after independent adjustment for race, education, diabetes, and hypertension prior to pregnancy
- However, the association was attenuated and no longer significant after adjustment for obesity (OR, 3.25; 95% CI, 0.93-11.37)
- .

# Hypertension in pregnancy and future ESRD

- Our findings confirm that there is a sizable association between preeclampsia and ESRD
- However, obesity is a previously unexplored confounder
- Pre-existing kidney disease was common, but not consistently coded or diagnosed

# CVD in Offspring

- Barker’s hypothesis: The famine of !944 or the "Hunger Winter" during WWII
- previously well-nourished population
- the liberation of the Netherlands in 1945 restored the food supply
- maternal under-nutrition led to IUGR and higher risks of chronic conditions in adult life

# CVD in Offspring

- Barker's hypothesis: fetal origins of adult disease, AKA Fetal Programming
  - Inadequate maternal diet → the baby changes its metabolism to prepare for food shortages
  - Metabolic processes result in IUGR
  - When the living environment switches from malnutrition to abundant supply of nutrients
- Preeclampsia: abnormal placental development
  - Mother: preeclampsia phenotype
  - Fetus: IUGR

# IUGR and Cardiovascular Disease

- Obesity
- Insulin resistance
- Metabolic syndrome
- Hyperlipidemia
- Reduced nephron number

# IUGR and Cardiovascular Disease

- Increased risk for DM2
- Obesity
- Increased risk for CVD (HTN, MI, CHF)
- CVD mortality

# HTN in Pregnancy and Future CVD Risk in Siblings

- A sibling history of HTN in pregnancy was associated with
  - An increased risk of hypertension in brothers and unaffected sisters
  - An increased risk of cardiovascular events was seen in brothers only

HTN in pregnancy is a novel familial risk factor for CVD

*Weissgerber et al. JASN, 2015*

# Future Directives

- Longitudinal studies of women with HTN in pregnancy
  - Pregnancy HTN as an independent CVD risk
  - Renal outcomes, A fib, CHF
- Improved screening and treatment of hypertensive pregnancy disorders may impact not only pregnancy outcomes, but future health of the affected women

# Questions?

# Treatment of Hypertension in Pregnancy

- Poorly controlled, retrospective observations of different types of HTN
- Great divergence of opinion
- “Shamefully few” well-designed studies

# US Department of Health and Human Services 2001-2004

- Women 45-54: 35.2 %
- Women 55-64: 54.4%
- **Our Data**
- HTN in pregnancy: 50% HTN by age 53
- Normotensive pregnancy: 50% HTN by age 60