



Preeclampsia and Risk of Atherosclerotic Coronary Artery Disease

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Preeclampsia-eclampsia

- Pregnancy-specific HTN disorder, characterized by proteinuria
- Affects 5% of all pregnancies worldwide
- One of the leading causes of maternal and fetal morbidity and mortality
- In USA, 12% of pregnancy-related mortality 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

Paradigm Shift

Disease of theories



Preeclamptic syndrome

Disease limited to pregnancy



Disease with long-term effects

Preeclampsia and Future CVD

- Studies in 1970's and 1980's does not herald future HTN
- In 1990's, associations between HPD and CVD are increasingly recognized
- 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

Meta-analysis

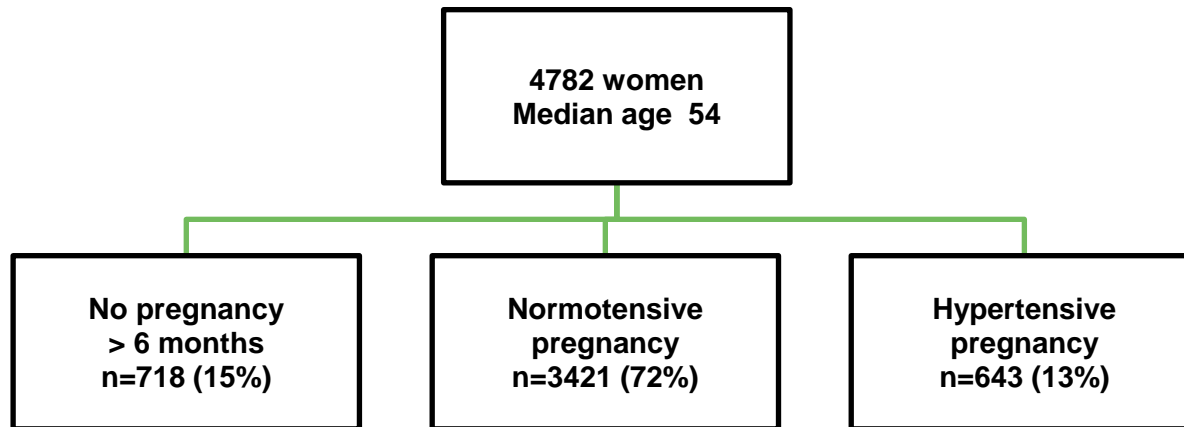
- The relative risks (95% CI)
 - HTN 3.70 (2.70 to 5.05) after 14.1 years
 - CHD 2.16 (1.86 to 2.52) after 11.7 years
 - Stroke 1.81 (1.45 to 2.27) after 10.4 years
 - Venous thromboembolism 1.79 (1.37 to 2.33) after 4.7 years.
 - Overall mortality after pre-eclampsia: 1.49 (1.05 to 2.14) after 14.5 years
- Bellamy et al. BMJ,2007*

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

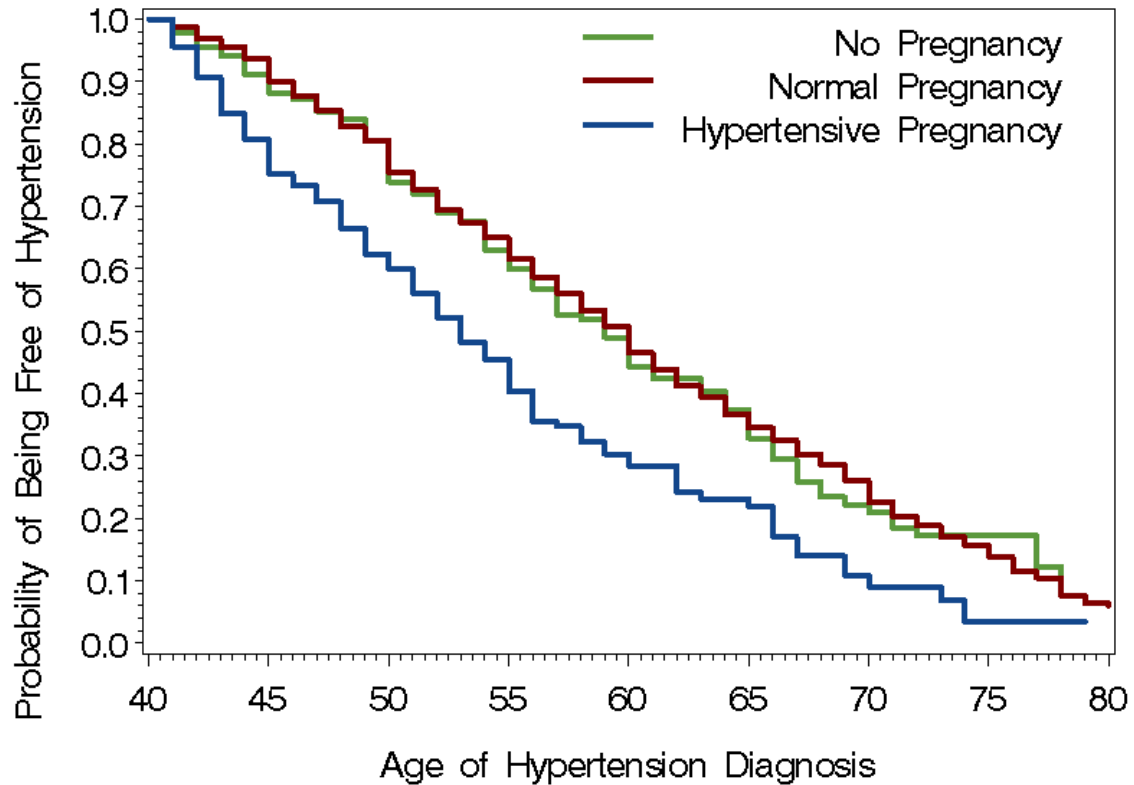
Garovic et al. J Hypertens. 2010

Sample Description FBPP participants



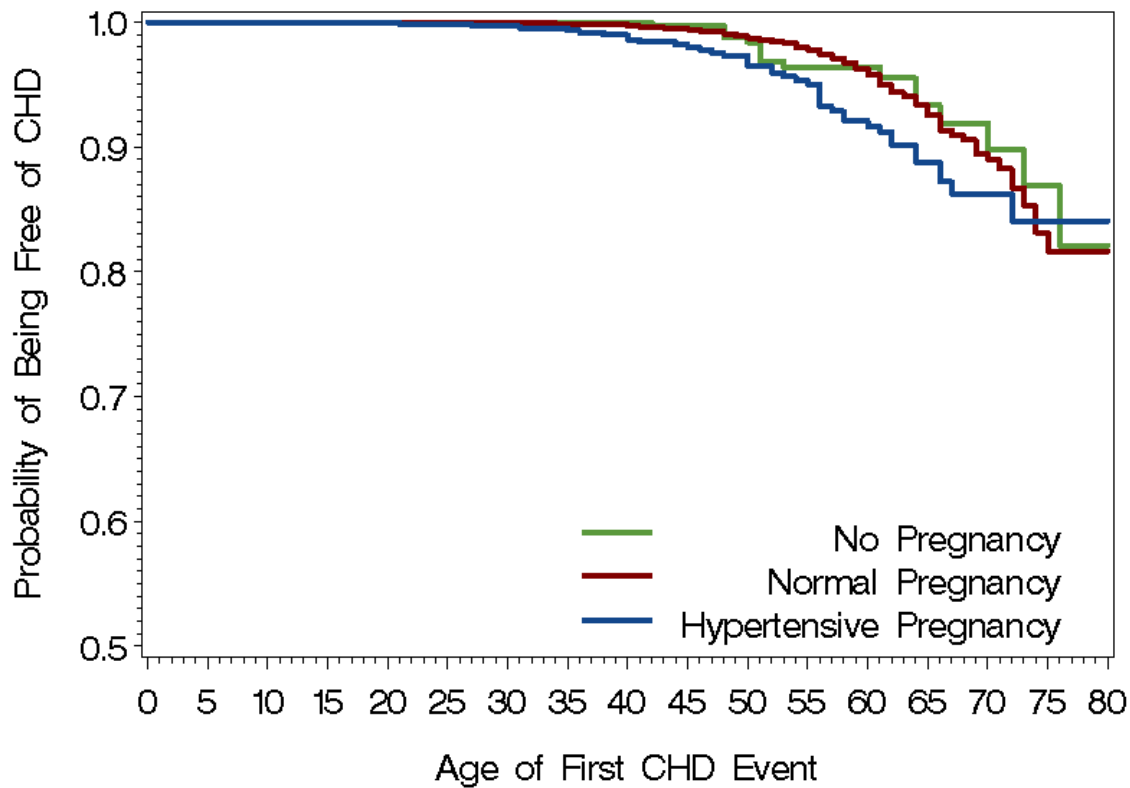
Garovic et al. J of Hypertens 2010

HTN Later in Life



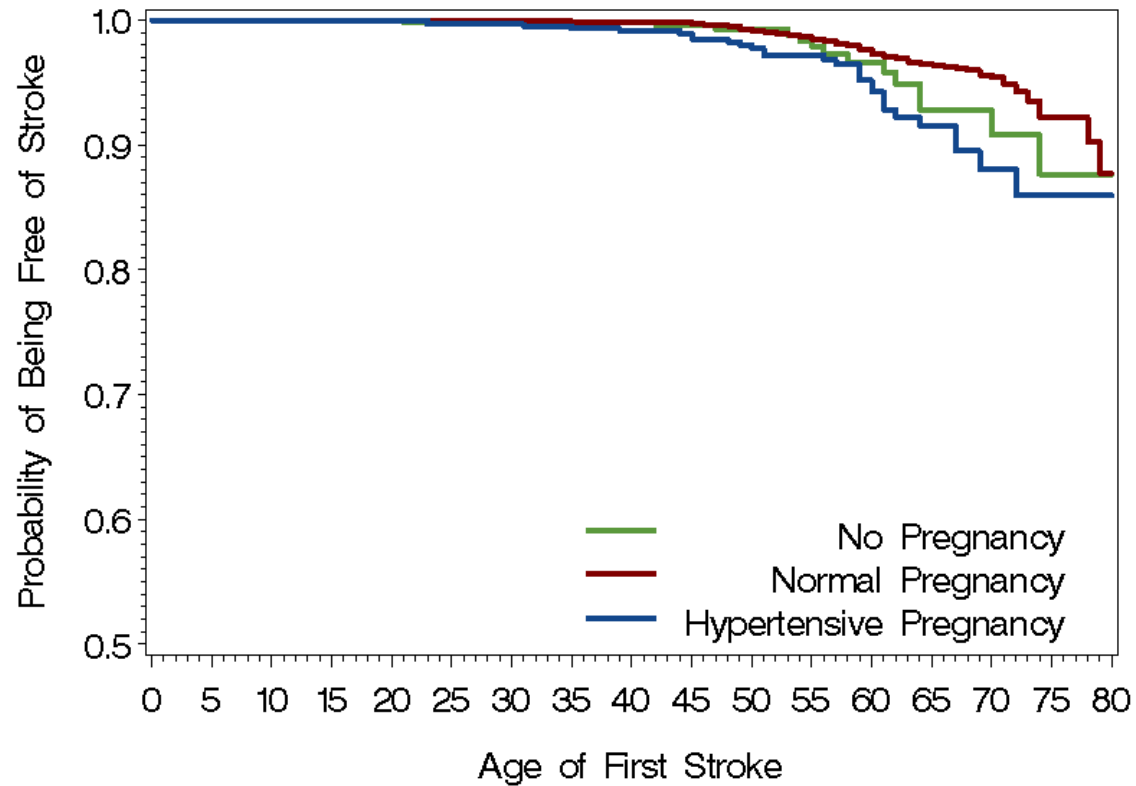
P<0.001

CHD Later in Life



P=0.009

Stroke Later in Life



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

n=1754, 37% FBPP

Group contrasts	HTN after age 40			CHD			Stroke		
	HR	95% CI	P	HR	95% CI	P	HR	95%CI	P
Normotensive vs. Nulliparous	0.78	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 a risk factor for future HTN and CVD

- ? The mechanisms underlying this association

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?

Association between preeclampsia and future CVD

- Flow-mediated dilation-FMD
 - Endothelial function
- Carotid intima medial thickness-CIMT
 - Subclinical atherosclerosis
- Coronary Artery Calcification- CAC
 - Cardiac events

FMD and Preeclampsia

- Whether women with PE had worse vascular function compared with women without PE
- Meta-analysis of 37 studies that examined endothelial dysfunction using flow-mediated dilation (FMD)
- Women with PE had lower FMD before the development of PE, at 20-29 weeks gestation, at the time of PE, and for 3 years postpartum
- Vascular dysfunction predates PE, may contribute to its pathogenesis; it may represent a mechanistic link with increased CVD risk

Weissgerber et al. *Hypertension* , 2016

CIMT and Preeclampsia

- Meta-analysis of CIMT studies conducted during pregnancy or during the first decade postpartum
- Fourteen studies: seven studies were carried out during pregnancy, 10 up to 10 years postpartum, and three at both time periods
- Women who had PE had significantly higher CIMT than did those who did not have PE, both at the time of diagnosis and in the first decade

Milic et al. *Ultrasound Ob. & Gyn*, 2017

Prospective studies

- Forty women (median age, 59 years) with histories of PE and 40 with histories of normotensive pregnancy (confirmed by medical record review) were selected from women who resided and gave birth 1976-1982. The participants were identified and recruited in 2014-2015.
- CT was performed to measure CAC
- CIMT was measured by B-mode ultrasonography

CIMT and Preeclampsia

- CIMT was greater in the preeclamptic than in the normotensive group
- The odds of having CIMT higher than threshold was significant after adjusting for confounding factors
- CIMT may identify those with subclinical atherosclerosis among women with PE histories

Garovic et al. *MCP*, 2017

CAC and Preeclampsia

- Prospective cohort of women with and without histories of preeclampsia
- The odds of having a higher CAC score was 3.54 (confidence interval [CI], 1.39-9.02) times greater in women with prior preeclampsia without adjustment
- and 2.61 (CI, 0.95-7.14) times greater after adjustment for current hypertension

White et al. *AJOG*, 2016

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

Postpartum Care

- Evaluation for hypertension and other CVD risk factors within 6 months to 1-year post-partum
- Treatment according to current guidelines
- GDM: testing postpartum and screening at least every three years thereafter
 - Life-style modifications to reduce the DM incidence

Future Directives

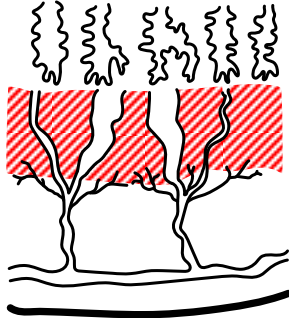
- Longitudinal studies of women with HTN in pregnancy
 - Pregnancy HTN as an independent CVD risk
 - Renal outcomes, A fib, CHF
- Improved screening and treatment of hypertensive pregnancy disorders may impact not only pregnancy outcomes, but future health of the affected women

Questions?



Maternal preeclampsia
Endothelial dysfunction that predates pregnancy (hypertension, diabetes, and obesity)

Placental preeclampsia



Impaired spiral arteries remodeling → damaged placenta → release of factors to maternal circulation that cause endothelial dysfunction



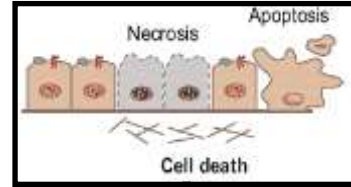
Altered Myocardial Wall

Damaged Cardiomyocytes



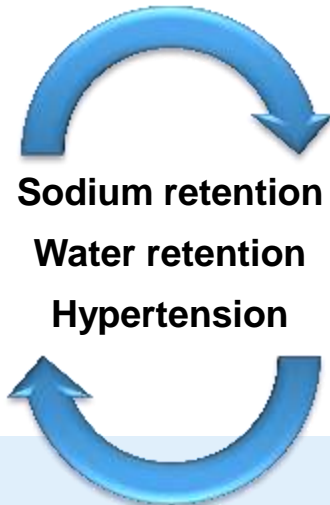
Podocyte Damage & Loss

Endotheliosis



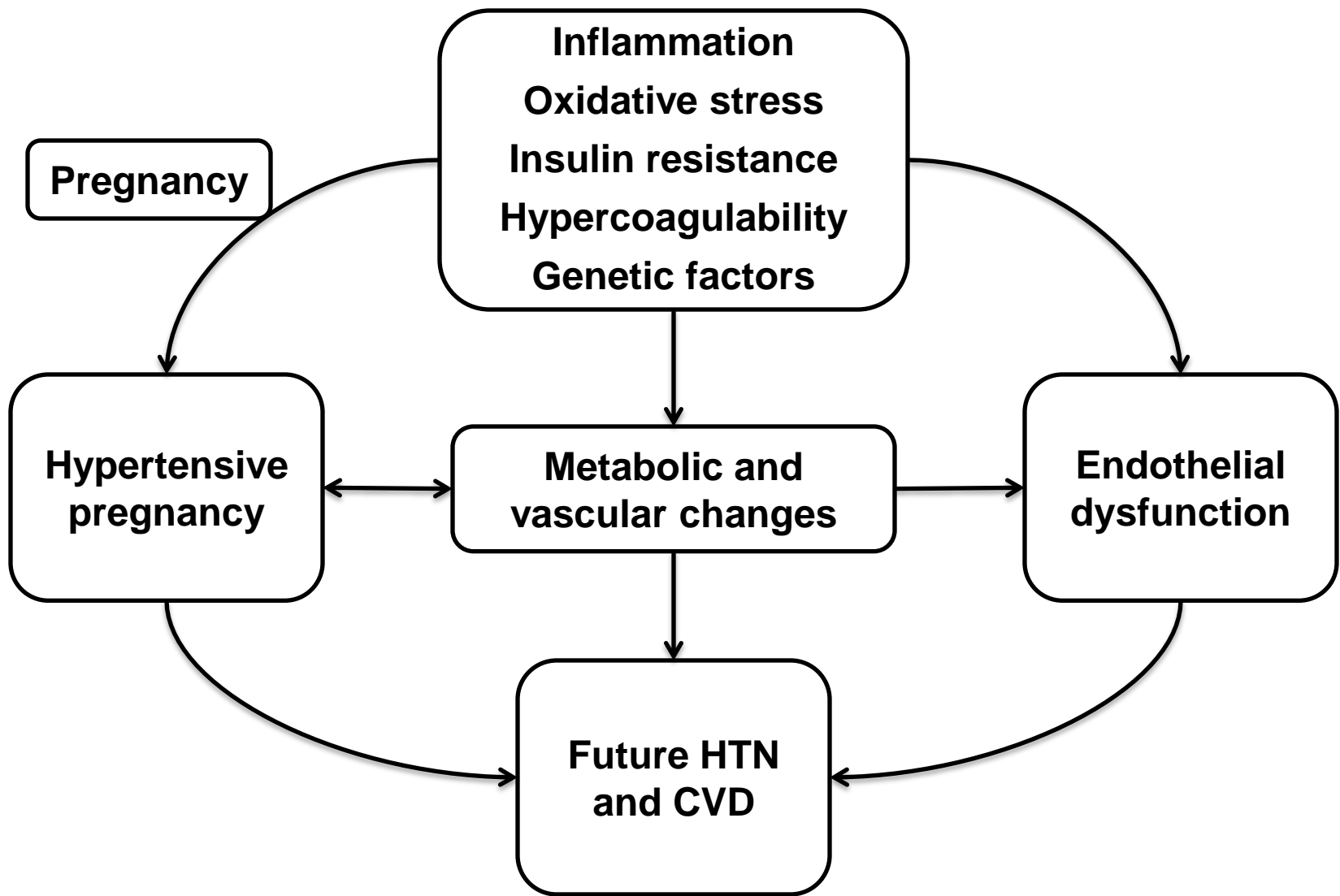
Cardiomyocyte reduction
Impaired contractility
Myocardial stiffness
Myocardial remodelling
Diastolic dysfunction

Glomerular & tubular damage
Renal mass reduction
↓ Renal plasma flow
↓ Glomerular filtration rate
Proteinuria



Heart Disease

Chronic Kidney Disease



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

Heart after Preeclampsia

- A retrospective cohort study of 1.1 M women with a delivery in Ontario between 1992 and 2009: women with MPS were at greater risk for HF and dysrhythmias

Ray et al. *Heart*, 2012

- Women with HPD are at greater risk for LVH

Scantlebury et al. *Heart*, 2015

Preeclampsia and BP treatment

- Inadequately BP control common in PE
- Limited number of pregnancy-safe meds
- Assumption that HTN of short duration does not translate in significant CVD risk
- Concern that treatment may compromise fetoplacental perfusion
- The absence of evidence that treatment improves outcomes
- ? Long-term effects

Treatment of Hypertension in Pregnancy

- Different approach than in non-pregnant patients
- **Assumption:** HTN of 5-6 months duration in a young premenopausal woman without other risk factors does not increase her overall risk for CVD
- **Concern:** Decrease BP in mother can compromise feto-placental unit

Treatment of Hypertension

Preeclampsia

- Established benefit for treating SBP \geq 160 mm Hg or DBP \geq 105 mmHg

Chronic HTN

- SBP 120-160 mm Hg
- DBP 80-105 mm Hg

The Control of Hypertension In Pregnancy Study CHIPS

- Trial comparing less-tight control of HTN (target DBP, 100 mm Hg) with tight control (85 mm Hg) among pregnant women
- Outcomes: pregnancy loss, high-level neonatal care, serious maternal complications (preeclampsia, severe maternal hypertension >160/110 mm Hg)

CHIPS-Conclusions

- Tight control of HTN in pregnancy confers no apparent benefit to the fetus, but also does not pose a risk to fetus or newborn
- Tight control shows moderate benefit in preventing progression to severe HTN for the mother