Hypertenze po porodu

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Hypertenze v těhotenství

- Nejčastější komplikace v těhotenství
- Výskyt ≈ 10 % těhotenství:

  1-5 % preexistující hypertenze
  5-6 % gestační hypertenze
  1-4 % preeklampsie

Hypertenze v těhotenství je hlavní příčinou:

- mateřské
- fetální
- novorozenecké *morbidity a mortality*

Klasifikace hypertenze v těhotenství

- preexistující hypertenze
- gestační hypertenze
- preexistující hypertenze a naroubovaná gestační hypertenze s proteinurií
- hypertenze neklasifikovatelná před narozením

Kardiovaskulární změny v těhotenství

Parametr	Změna	Časování
STK	↓4-6 mmHg	nejnižší hodnoty 20.-24. týden, pak postupný nárůst k hodnotám před těhotenstvím, kterých je dosaženo kolem porodu
DTK	↓8-15 mmHg	
střední TK	↓6-10 mmHg	
TF	↑12-18 tepů/min.	počátkem 2. trimestru, dále stabilní
SV	↑10-30%	počátkem 2. trimestru, dále stabilní
CO	↑33-45%	nejvyšší hodnoty počátkem 2. trimestru, dále stabilní do porodu

Main DM, Main EK: Obstetrics and Gynecology, 1984

Hypertenze po porodu

- TK narůstá v průběhu prvních 5 dnů po porodu, nejvyšší hodnoty TK 3. až 6. den po porodu.
- 10 % úmrtí matek v důsledku hypertenze v těhotenství nastává po porodu.
- Další komplikace závažné hypertenze po porodu
  - CMP
  - eklampsie

Trends in Pregnancy Hospitalizations That Included a Stroke in the United States From 1994 to 2007

Reasons for Concern?

Elena V. Kuklina, MD, PhD; Xin Tong, MPH; Pooja Bansil, MPH;
Mary G. George, MD, MSPH; William M. Callaghan, MD, MPH

Background and Purpose—Stroke is an important contributor to maternal morbidity and mortality, but there are no recent data on trends in pregnancy-related hospitalizations that have involved a stroke. This report describes stroke hospitalizations for women in the antenatal, delivery, and postpartum periods from 1994 to 1995 to 2006 to 2007 and analyzes the changes in these hospitalizations over time.

Methods—Hospital discharge data were obtained from the Nationwide Inpatient Sample, developed as part of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. Pregnancy-related hospitalizations with stroke were identified according to the International Classification of Diseases, Ninth Revision. All statistical analyses accounted for the complex sampling design of the data source.

Results—Between 1994 to 1995 and 2006 to 2007, the rate of any stroke (subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke, transient ischemic attack, cerebral venous thrombosis, or unspecified) among antenatal hospitalizations increased by 47% (from 0.15 to 0.22 per 1000 deliveries) and among postpartum hospitalizations by 83% (from 0.12 to 0.22 per 1000 deliveries) while remaining unchanged at 0.27 for delivery hospitalizations. In 2006 to 2007, ≈32% and 53% of antenatal and postpartum hospitalizations with stroke, respectively, had concurrent hypertensive disorders or heart disease. Changes in the prevalence of these 2 conditions from 1994 to 1995 to 2006 to 2007 explained almost all of the increase in postpartum hospitalizations with stroke during the same period.

Conclusions—Our results have demonstrated an increasing trend in the rate of pregnancy-related hospitalizations with stroke in the United States, especially during the postpartum period, from 1994 to 1995 to 2006 to 2007.

Stroke 2011;42:2564-2570

Hypertenze po porodu

1. pokračování hypertenze v těhotenství
   - preexistující hypertenze (obvykle přetrvává > 6 týdnů po porodu)
   - gestační hypertenze včetně preeklampsie (měla by vymizet do 6 až 12 týdnů po porodu)
2. *de novo* preeklampsie (bolesti hlavy, bolest v epigastriu, poruchy vizu, křeče)
3. iatrogenní příčiny
   - léky: NSAID pro tlumení bolesti, ergotové alkaloidy k zastavení krvácení po porodu, efedrin
   - hypervolémie (např. po svodné anestézii)
4. bolest (nedostatečná analgézie)
5. anxieta

Možné příčiny hypertenze po porodu

- Přesun tekutiny z extravaskulárního do intravaskulárního prostoru (6–8 l a 950 mEq sodíku v těle)
- Exkrece sodíku močí (natriuréza) – může být způsobena zvýšení ANP
- Iatrogenní příčiny (bromokriptin, NSAID)

Hypertension

Epidemiology and Mechanisms of De Novo and Persistent Hypertension in the Postpartum Period

Arvind Goel, MD; Manish R. Maski, MD; Surichhya Bajracharya, MD; Julia B. Wenger, MPH; Dongsheng Zhang, PhD; Saira Salahuddin, MD, PhD; Sajid S. Shahul, MD, MPH; Ravi Thadhani, MD, MPH; Ellen W. Seely, MD; S. Ananth Karumanchi, MD; Sarosh Rana, MD

Background—The pathophysiology of hypertension in the immediate postpartum period is unclear.

Methods and Results—We studied 988 consecutive women admitted to a tertiary medical center for cesarean section of a singleton pregnancy. The angiogenic factors soluble fms-like tyrosine kinase 1 and placental growth factor, both biomarkers associated with preeclampsia, were measured on antepartum blood samples. We then performed multivariable analyses to determine factors associated with the risk of developing postpartum hypertension. Of the 988 women, 184 women (18.6%) developed postpartum hypertension. Of the 184 women, 77 developed de novo hypertension in the postpartum period, and the remainder had a hypertensive disorder of pregnancy in the antepartum period. A higher body mass index and history of diabetes mellitus were associated with the development of postpartum hypertension. The antepartum ratio of soluble fms-like tyrosine kinase 1 to placental growth factor positively correlated with blood pressures in the postpartum period (highest postpartum systolic blood pressure [r=0.29, P<0.001] and diastolic blood pressure [r=0.28, P<0.001]). Moreover, the highest tertile of the antepartum ratio of soluble fms-like tyrosine kinase 1 to placental growth factor was independently associated with postpartum hypertension (de novo hypertensive group: odds ratio, 2.25; 95% confidence interval, 1.19–4.25; P=0.01; in the persistent hypertensive group: odds ratio, 2.61; 95% confidence interval, 1.12–6.05; P=0.02) in multivariable analysis. Women developing postpartum hypertension had longer hospitalizations than those who remained normotensive (6.5±3.5 versus 5.7±3.4 days; P<0.001).

Conclusions—Hypertension in the postpartum period is relatively common and is associated with prolonged hospitalization. Women with postpartum hypertension have clinical risk factors and an antepartum plasma angiogenic profile similar to those found in women with preeclampsia. These data suggest that women with postpartum hypertension may represent a group of women with subclinical or unresolved preeclampsia.

Circulation 2015;132:1726-1733

Epidemiology and mechanisms of *de novo* and persistent hypertension in the postpartum period

n = 988 po sobě následujících žen hospitalizovaných k porodu císařským řezem pro jednočetné těhotenství

n = 188 (18,6 %) hypertenze po porodu

n = 111 (59 %) hypertenze před porodem

n = 77 (41 %) ***de novo*** hypertenze

Circulation 2015;132:1726–1733

Záchyt hypertenze po porodu

NICE Clinical Guideline 107

- měření TK do 6 hodin po porodu u všech normotenzních žen bez komplikací
- měření TK 5. den po porodu (k záchytu žen s pozdní manifestací preeklampsie)
- měření TK ob den po propuštění z nemocnice

Prevention and treatment of postpartum hypertension (Review)

Magee L, von Dadelszen P

Závěry autorů

- U žen s preeklampsií může podání furosemidu po porodu snížit potřebu antihypertenziv v průběhu hospitalizace (je třeba získat více údajů).
- Neexistují spolehlivé údaje pro léčbu hypertenze po porodu.

Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD004351

PLOS ONE

RESEARCH ARTICLE

Clonidine versus Captopril for Severe Postpartum Hypertension: A Randomized Controlled Trial

Carlos Noronha Neto C, Sabina S. B. Maia, Leila Katz, Isabela C. Coutinho, Alex R. Souza, Melania M. Amorim*

Post Graduate Program on Maternal and Child Health, Instituto de Medicina Integral Prof. Fernando Figueira, Recife, Pernambuco, Brazil

- **randomizovaná, trojitě zaslepená klinická studie**
- **n = 90 žen po porodu**
- **STK ≥ 180 a/nebo DTK ≥ 110 mm Hg**

Závěry: Clonidin a captopril představují bezpečnou a účinnou léčbu pro závažnou hypertenzi po porodu.

PLoS ONE 12(1): e0168124. doi:10.1371/journal. pone.0168124

The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 692 • April 2017 *(Replaces Committee Opinion No. 623, February 2015)*

Committee on Obstetric Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice in collaboration with committee members Yasser Y. El-Sayed, MD, and Ann E. Borders, MD, MSc, MPH.

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period

ABSTRACT: Acute-onset, severe systolic hypertension; severe diastolic hypertension; or both can occur during the prenatal, intrapartum, or postpartum periods. Pregnant women or women in the postpartum period with acute-onset, severe systolic hypertension; severe diastolic hypertension; or both require urgent antihypertensive therapy. Introducing standardized, evidence-based clinical guidelines for the management of patients with preeclampsia and eclampsia has been demonstrated to reduce the incidence of adverse maternal outcomes. Individuals and institutions should have mechanisms in place to initiate the prompt administration of medication when a patient presents with a hypertensive emergency. Treatment with first-line agents should be expeditious and occur as soon as possible within 30–60 minutes of confirmed severe hypertension to reduce the risk of maternal stroke. Intravenous labetalol and hydralazine have long been considered first-line medications for the management of acute-onset, severe hypertension in pregnant women and women in the postpartum period. Although relatively less information currently exists for the use of calcium channel blockers for this clinical indication, the available evidence suggests that immediate release oral nifedipine also may be considered as a first-line therapy, particularly when intravenous access is not available. In the rare circumstance that intravenous bolus labetalol, hydralazine, or immediate release oral nifedipine fails to relieve acute-onset, severe hypertension and is given in successive appropriate doses, emergent consultation with an anesthesiologist, maternal–fetal medicine subspecialist, or critical care subspecialist to discuss second-line intervention is recommended.

Obstet Gynecol 2017;129:769-770

Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period

- **Labetalol i.v.** a **hydralazin i.v.** byly dlouho považovány za **léky první volby** pro léčbu závažné hypertenze s náhlým začátkem u těhotných žen a u žen po porodu.
- **Krátkodobě působící nifedipin p.o.** může být rovněž považován za lék první volby, zejména pokud i.v. přístup není dostupný.
- Podání labetalolu i.v., hydralazinu i.v., nebo krátkodobě působícího nifedipinu p.o. pro léčbu závažné hypertenze s náhlým začátkem u těhotných žen a žen po porodu **nevyžaduje monitoraci srdečních funkcí**.

Obstet Gynecol 2017;129:769-770

Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis

Laura A Magee, Chris Cham, Elizabeth J Waterman, Arne Ohlsson, Peter von Dadelszen

Abstract

Objective To review outcomes in randomised controlled trials comparing hydralazine against other antihypertensives for severe hypertension in pregnancy.

Study design Meta-analysis of randomised controlled trials (published between 1966 and September 2002) of short acting antihypertensives for severe hypertension in pregnancy. Independent data abstraction by two reviewers. Data were entered into RevMan software for analysis (fixed effects model, relative risk and 95% confidence interval); in a secondary analysis, risk difference was also calculated.

Results Of 21 trials (893 women), eight compared hydralazine with nifedipine and five with labetalol. Hydralazine was associated with a trend towards less persistent severe hypertension than labetalol (relative risk 0.29 (95% confidence interval 0.08 to 1.04); two trials), but more severe hypertension than nifedipine or isradipine (1.41 (0.95 to 2.09); four trials); there was significant heterogeneity in outcome between trials and differences in methodological quality. Hydralazine was associated with more maternal hypotension (3.29 (1.50 to 7.13); 13 trials); more caesarean sections (1.30 (1.08 to 1.59); 14 trials); more placental abruption (4.17 (1.19 to 14.28); five trials); more maternal oliguria (4.00 (1.22 to 12.50); three trials); more adverse effects on fetal heart rate (2.04

BMJ 2003;327:955-60

Hypertenze v těhotenství
emergentní stavy

- **STK ≥ 170 nebo DTK ≥ 110 mm Hg**

hydralazin, labetalol, metyldopa nebo nifedipin nicardipin, nitroprusid sodný (riziko otravy kyanidem při delším podávání), nitroglycerin

Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period

- **Labetalol i.v.** a **hydralazin i.v.** byly dlouho považovány za **léky první volby** pro léčbu závažné hypertenze s náhlým začátkem u těhotných žen a u žen po porodu.
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Obstet Gynecol 2017;129:769-770

DOI: 10.1111/1471-0528.13463
www.bjog.org

Systematic review

Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis

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Correspondence: S Shekhar, 401/4, Residential Complex, AIIMS, Jodhpur, Rajasthan 342005, India. Email longshanks28@gmail.com

- **7 studií (pooled analysis); 4 provedeny v rozvojových zemích**
- **363 žen**

Závěr: Nifedipin p.o. je stejně účinný a bezpečný jako labetalol i.v. a může být výhodnější v podmínkách omezených finančních zdrojů.

BJOG 2016;123:40-47

SEMINARS IN PERINATOLOGY 37 (2013) 280–287

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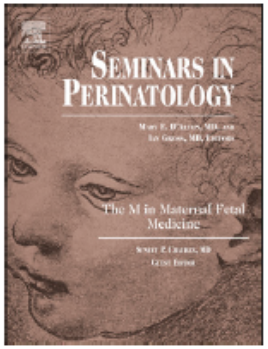


Hypertensive crisis during pregnancy and postpartum period

*Gloria T. Too, MD, and James B. Hill, MD**

Department of Obstetrics and Gynecology, Division of Maternal–Fetal Medicine, Eastern Virginia Medical School, 825 Fairfax Ave, Suite 310, Norfolk, VA 23507

- **10 % těhotenství je komplikováno hypertenzí**
- **Z toho 1–2 % se mohou projevit hypertenzní krizí kdykoli v těhotenství včetně období po porodu**
- **Incidence preeklampsie po porodu 5,7 % (*Matthys 2004*)**

Seminars in Perinatol 2013;37:280–287

Léčba hypertenze po porodu

- **Urgentní stavy: *per os***

  labetalol, nifedipin ER, diltiazem, verapamil, clonidin

- **Emergentní stavy:**

  ***i.v.* labetalol, hydralazin, esmolol, nicardipin, nitroprusid Na**

  nifedipin *p.o.*

Seminars in Perinatol 2013;37:280–287

Léčba hypertenze po porodu

- **všechny ženy s hypertenzí v těhotenství by měly mít kontrolní vyšetření lékařem 6 týdnů po porodu (TK, vyšetření moče); ABPM v případě přetrvávající hypertenze**

Report of the National High Blood Pressure Educational Program Working Group on High Blood Pressure in Pregnancy; Am J Obstet Gynecol 2000;183:S1–22

- **u všech žen s hypertenzí ve věku < 40 let by mělo být provedeno vyšetření k vyloučení sekundární hypertenze**

NICE Guideline 2010

Kojení

- TK nestoupá u kojících matek
- Všechna antihypertenziva užívaná kojícími matkami se vylučují do mateřského mléka; většina z nich je však přítomna v nízkých koncentracích vyjma propranololu a nifedipinu, jejichž koncentrace je podobná jako v mateřské plazmě

Antihypertenzní medikace matek obvykle kompatibilní s kojením

Captopril
Diltiazem
Enalapril
Hydralazin
Hydrochlorothiazid
Labetalol
Metyldopa
Minoxidil
Nadolol
Nifedipin
Oxprenolol
Propranolol
Spironolacton
Timolol
Verapamil

Pediatrics 2001;108:776-789

Antihypertenzní medikace matek obvykle kompatibilní s kojením

- Diuretika (furosemid, hydrochlorothiazid, a spironolacton) mohou snižovat tvorbu mléka.
- Metoprolol je považován za kompatibilní s kojením, i když se vyskytuje v mateřském mléku.
- Acebutolol a atenolol nemají být podávány kojícím matkám.

Pediatrics 2001;108:776-789

Léčba hypertenze po porodu

Řada doporučení stále považuje metyldopu za lék volby; podávat s opatrnos
u žen s rizikem rozvoje deprese.

Diuretika nejsou preferována u kojících žen

- **thiazidová diuretika snižují tvorbu mléka**
  mohou vyvolat trombocytopénii u novorozenc
- **kličková diuretika snižují tvorbu mléka**
- **kalium šetřící diuretika (spironolacton, amilorid, triamteren) moho**
  být kompatibilní s kojením

J Clin Hypertens 2009;11:726–733

Léčba hypertenze po porodu

Beta-blokátory (propranolol, atenolol, acebutolol) dosahují vysokých hladin v mateřském mléku; vyvolávají známky beta-blokády u novorozenců.

Labetalol je účinný a relativně bezpečný lék během laktace.

Nifedipin má údaje podporující jeho bezpečnost během laktace (nevýznamné množství přechází do mateřského mléka).

Pozor: nicardipin dosahuje vyšších koncentrací v mateřském mléku a neměl by se podávat kojícím ženám.

Inhibitory ACE : captopril, enalapril a quinapril mohou být podávány během laktace.

J Clin Hypertens 2009;11:726–733

Závěry

- **TK obvykle stoupá v prvních 5 dnech po porodu.**
- **Hypertenze po porodu se může objevit u cca 20 % žen; může se jednat o pokračování hypertenze v těhotenství nebo může jít o rozvoj hypertenze *de novo*.**
- **Neexistují spolehlivé údaje pro léčbu hypertenze po porodu (*Cochrane Database of Systematic Reviews 2013*).**
- **Řada doporučení stále považuje metyldopu za lék volby (opatrnost u žen s rizikem rozvoje deprese).**
- **Možné léky: beta-blokátory (s výjimkou propranololu, atenololu a acebutolol), labetalol, nifedipin, inhibitory ACE.**

Pre-eclampsia

Gestational hypertension associated with *significant proteinuria*

- **300 mg/l or**
- **500 mg/24 h or**
- **dipstick 2+ or more**

Poor organ perfusion

Original Article

Changes in circulating concentrations of soluble fms-like tyrosine kinase-1 and placental growth factor measured by automated electrochemiluminescence immunoassays methods are predictors of preeclampsia

Alfredo Leaños-Miranda[a], Inova Campos-Galicia[a], Irma Isordia-Salas[c], Roxana Rivera-Leaños[a], Juan Fernando Romero-Arauz[b], José Antonio Ayala-Méndez[b], and Alfredo Ulloa-Aguirre[a]

Conclusion: **Changes in circulating concentrations of PlGF, sFlt-1, and in the sFlt-1/PlGF ratio precede the onset of preeclampsia. The risk profile of circulating angiogenic factors for developing preeclampsia distinctly evolves depending on whether this condition is manifested at preterm or term.**

J Hypertens 2012; 30 2173 - 2181

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 7, 2016 VOL. 374 NO. 1

Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia

Harald Zeisler, M.D., Elisa Llurba, M.D., Ph.D., Frederic Chantraine, M.D., Ph.D., Manu Vatish, M.B., Ch.B., D.Phil., Anne Cathrine Staff, M.D., Ph.D., Maria Sennström, M.D., Ph.D., Matts Olovsson, M.D., Ph.D., Shaun P. Brennecke, M.B., B.S., D.Phil., Holger Stepan, M.D., Deirdre Allegranza, B.A., Peter Dilba, M.Sc., Maria Schoedl, Ph.D., Martin Hund, Ph.D., and Stefan Verlohren, M.D., Ph.D.

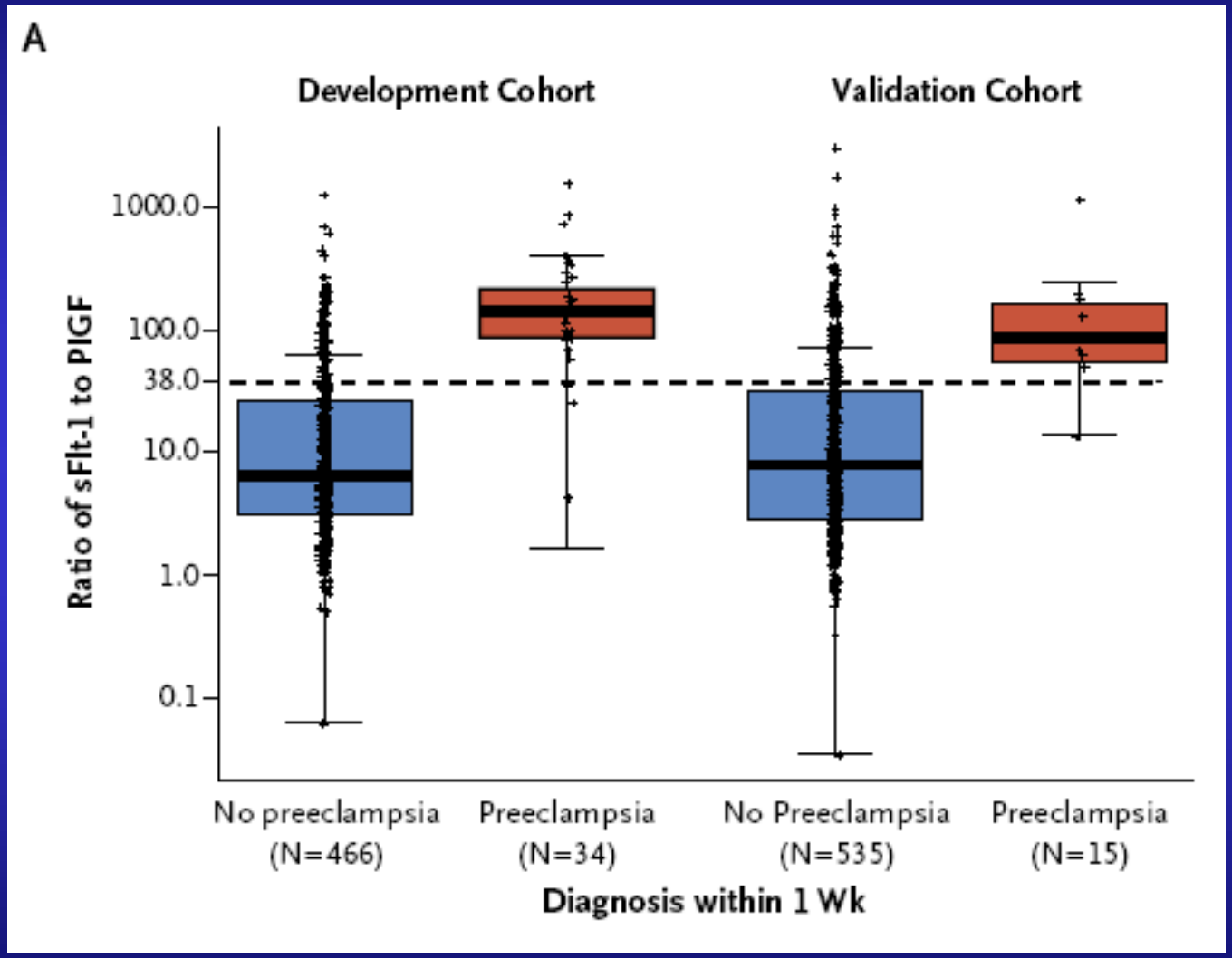
sFlt-1(soluble fms-like tyrosine-kinase-1):PlGF (placental growth factor)

Conclusions

An sFlt-1:PlGF **ratio of 38 or lower** can be used **to predict the short-term absence of preeclampsia** in women in whom the syndrome is suspected clinically. (funded by Roche Diagnostics)

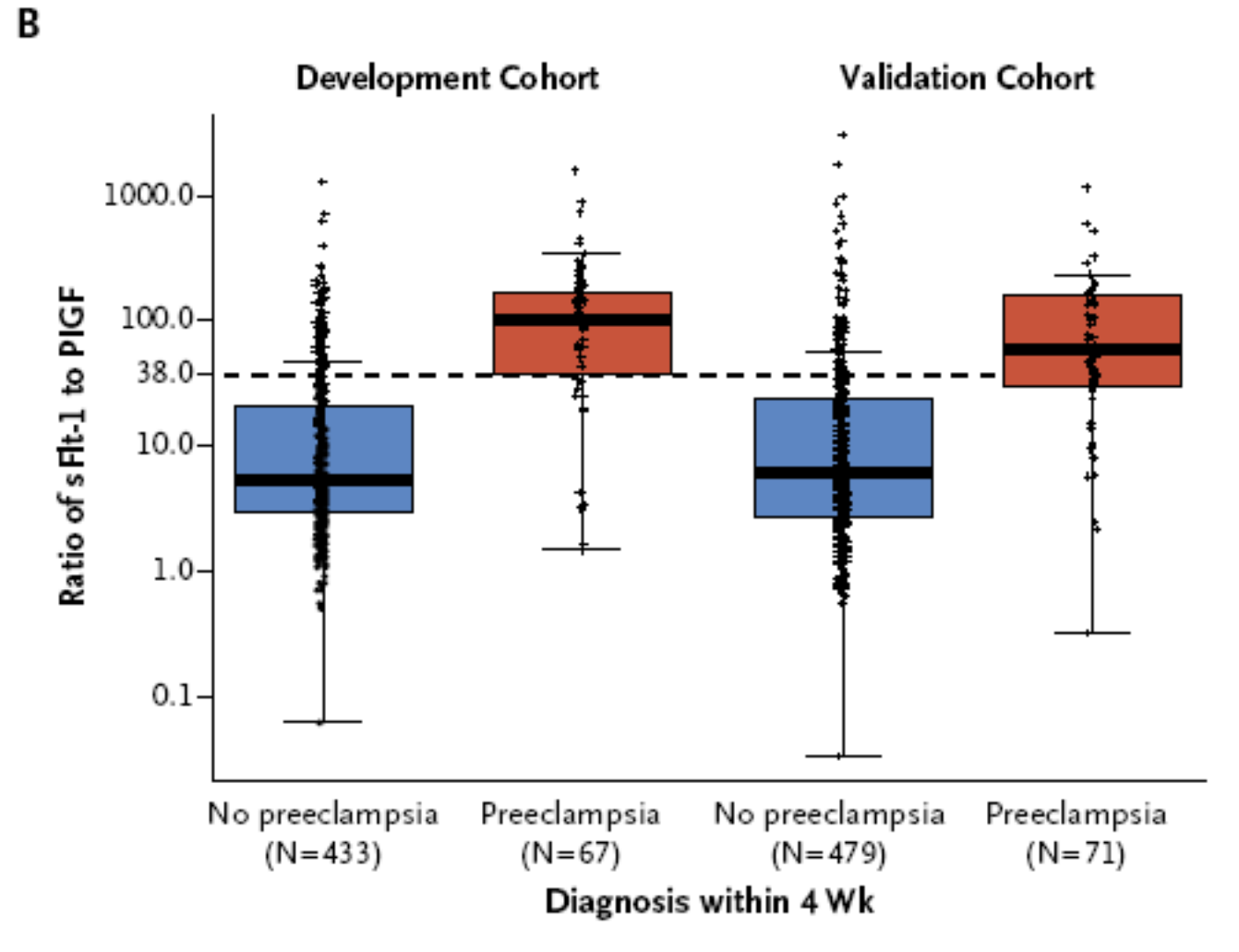
NEJM 2016;374:13-22

sFlt-1/PlGF



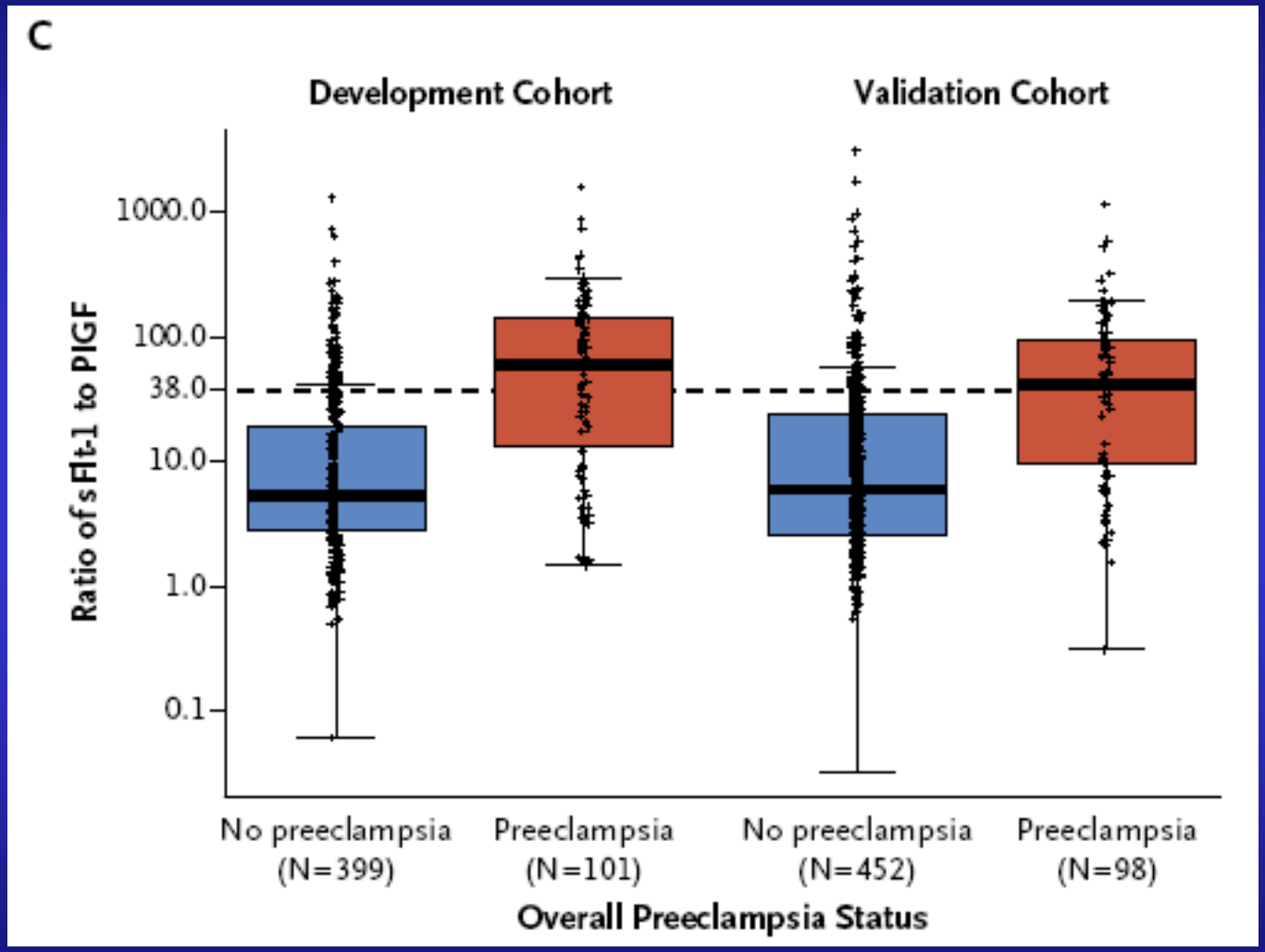
NEJM 2016;374:13-22

sFlt-1/PlGF



NEJM 2016;374:13-22

sFlt-1/PlGF



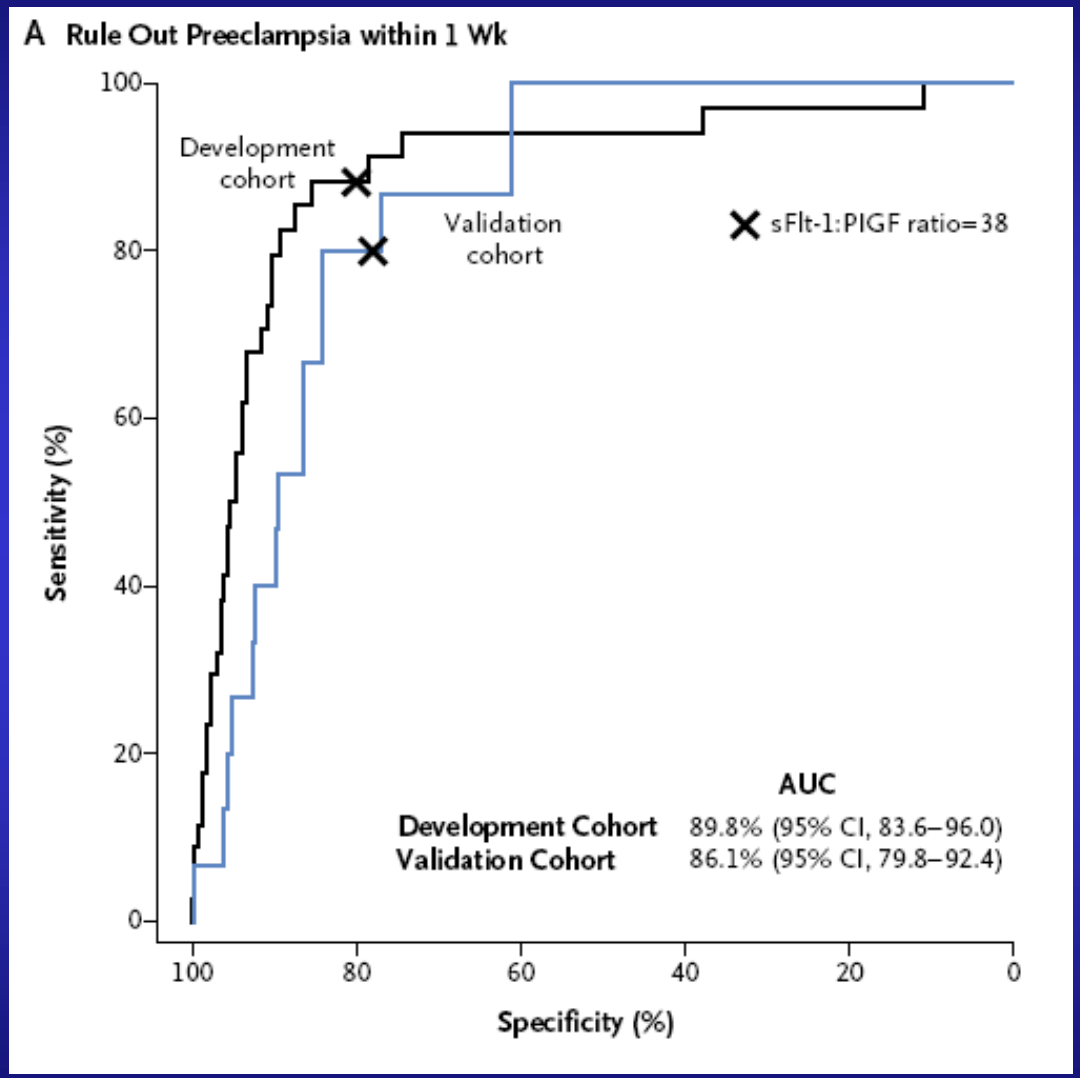
NEJM 2016;374:13-22

Cutoff point validation for sFlt-1/PlGF in predicting preeclampsia

Preeclampsia	Development Cohort	Validation Cohort
	percent (95% CI)	
Within 1 wk		
Negative predictive value: rule out	98.9 (97.3–99.7)	99.3 (97.9–99.9)
Sensitivity	88.2 (72.5–96.7)	80.0 (51.9–95.7)
Specificity	80.0 (76.1–83.6)	78.3 (74.6–81.7)
Within 4 wk		
Positive predictive value: rule in	40.7 (31.9–49.9)	36.7 (28.4–45.7)
Sensitivity	74.6 (62.5–84.5)	66.2 (54.0–77.0)
Specificity	83.1 (79.3–86.5)	83.1 (79.4–86.3)

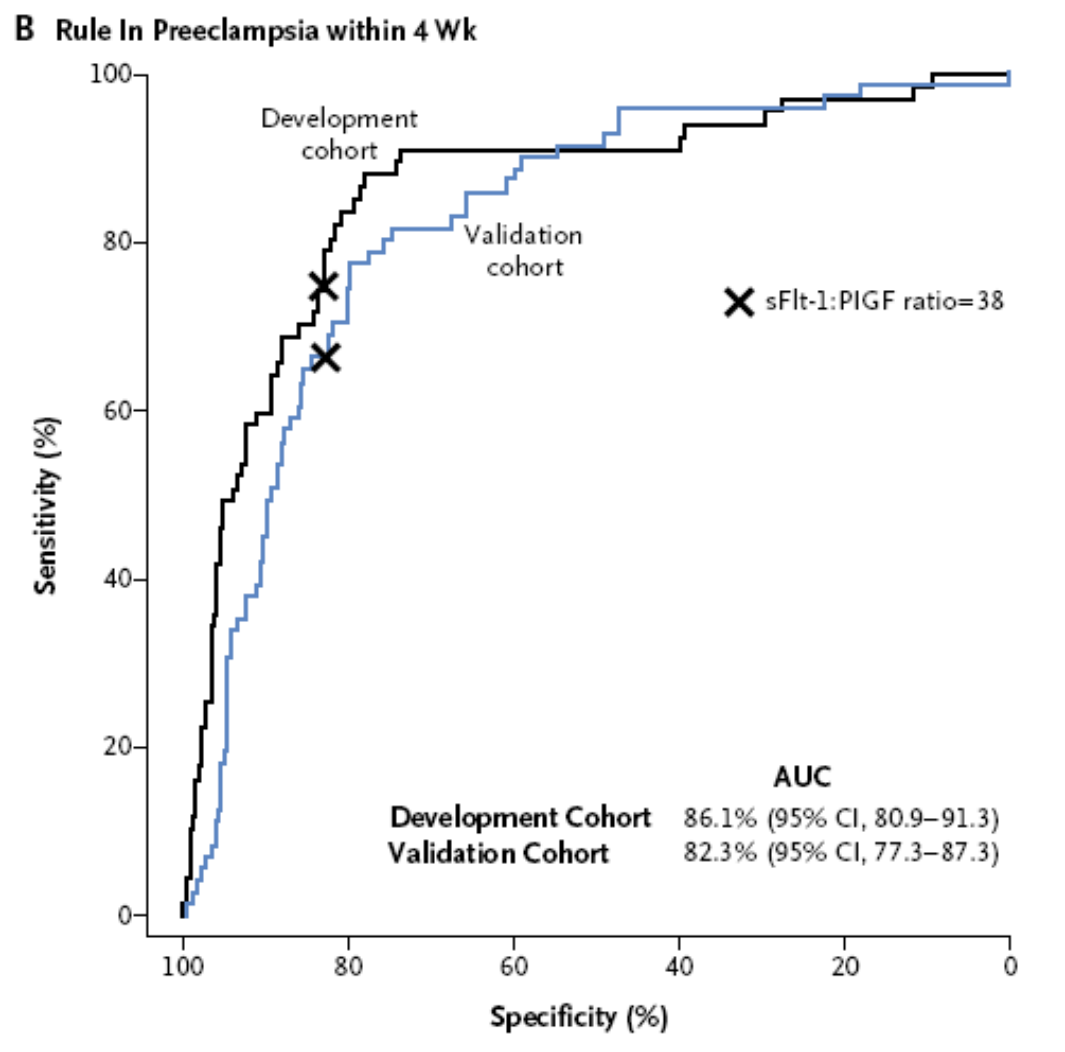
NEJM 2016;374:13-22

Predictive performance of sFlt-1/PlGF



NEJM 2016;374:13-22

Predictive performance of sFlt-1/PlGF



NEJM 2016;374:13-22

Classification of hypertension in pregnancy

- pre-existing hypertension
- gestational hypertension
- pre-existing hypertension plus superimposed gestational hypertension with proteinuria
- antenatally unclassifiable hypertension

Pre-existing hypertension

- 1-5% of pregnancies
- BP > 140/90 mmHg *predates pregnancy or develops before 20 weeks* of gestation
- In most cases, hypertension *persists more than 42 days post partum,* it may be associated with proteinuria

Gestational hypertension

Pregnancy-induced hypertension with or without proteinuria

Hypertension develops *after 20 weeks´ gestation,* in most cases, *it resolves within 42 days post partum*

Poor organ perfusion

Pre-existing hypertension plus superimposed gestational hypertension with proteinuria

Further worsening of BP and *protein excretion > 3 g/day* in 24-hour urine collection *after 20 weeks´ gestation*

Previous terminology "chronic hypertension with superimposed pre-eclampsia"

Antenatally unclassifiable hypertension

Hypertension with or without systemic manifestation

BP *first recorded after 20 weeks´ gestation,* re-assessment necessary at or after 42 days post partum

Management of hypertension in pregnancy

depends on

- BP levels
- gestational age
- associated maternal and fetal risk factors

Non-pharmacologic management

- SBP 140-149 mmHg or
  DBP 90-99 mmHg

- ↓activity, bed rest (left lateral position)

AVOID : weight reduction and salt restriction

Principles for treatment of mild-to-moderate hypertension in pregnancy

The benefits of antihypertensive therapy for mild-to-moderately elevated BP in pregnancy (≤ 160/110 mmHg), either chronic or pregnancy-induced, have not been demonstrated in clinical trials.

- **Less risk of developing severe hypertension**
- **No difference in outcome of preeclampsia, neonatal death, pre-term birth**
- **No difference in small-for-gestational-age babies**

Cochrane Database Syst Review 2007;CD002252

Thresholds for drug treatment initiation

BP > 140/90 mmHg in women

- **with gestational hypertension without proteinuria or**
- **pre-existing hypertension before 28 weeks' gestation or**
- **gestational hypertension and proteinuria or symptoms at any time or**
- **pre-existing hypertension and TOD or**
- **pre-existing hypertension and superimposed gestational hypertension**

BP > 150/95 mmHg

- **In all other circumstances**

  methyldopa, labetalol, calcium antagonists, and beta-blockers

AVOID: ACE inhibitors, AIIA, diuretics

magnesium sulfate: ***eclampsia, treatment and prevention of seizures***

Definitions of Pregnancy Drug Classifications

Category

A. Careful tests in humans have shown no harm.

B. Animal studies showed some harm, but well-designed studies in humans showed no harm, or animal studies did not show any harm and there are no good studies in humans.

C. Animal studies show some harm and there are no good studies in humans, or no human or animal studies have been done.

D. Human studies show some risk.

X. There is strong evidence that the drug causes birth defects, either in humans or in animals.

Antihypertensive drugs used in pregnancy

Women with pre-existing hypertension are advised to continue their current medication except for ACE inhibitors, AIIA and direct renin inhibitors

Why is RAS important in pregnancy?

- Regulation of renal hemodynamics (by maintaining GFR and urine production under conditions of low renal perfusion pressure, which are characteristic of the fetal and neonatal periods)
- Regulation of umbilical and placental circulation
- Regulation of fetal BP
- Kidney development (growth factors)
- Angiogenesis (angiotensin II)
- Regulation of fetal renal growth, function and development (ACE gene)

Administration of AT_1-blockers in pregnancy

- Fetal arterial hypotension
- Decreased glomerular perfusion pressure
- Impaired renal tubular development
- Reduced fetal urine output, oligohydramnios

  Sequelae: limb contractures

  pulmonary hypoplasia

  cranio-facial deformation and neonatal anuria
- Decreased placental and umbilical perfusion:

  intrauterine growth restriction
- Action on skull bones angiogenesis:

  impaired ossification processes

Critical period: second trimester !!

Maternal exposure to AT_1-blockers

Critical period: second trimester

5 cases of fetal death and 1 case of neonatal death on Day 4 postpartum, with persisting anuria; exposure in early pregnancy, oligohydramnion.

- Saji H, Yamanaka M, Hagiwara A, Ijiri R. Losartan and fetal toxic effects. *Lancet 2001;357:363.*
- Martinovic J, Benachi A, Laurent N, Daika-Dahmane F, Gubler MC. Fetal toxic effects and angiotensin-II receptor antagonists. *Lancet 2001;358:241-8.*
- Briggs GG, Nageotte MP. Fatal fetal outcome with the combined use of valsartan and atenolol. *Ann Pharmacoth 2001;35:859-61.*

Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

William O. Cooper, M.D., M.P.H., Sonia Hernandez-Diaz, M.D., Dr.P.H., Patrick G. Arbogast, Ph.D., Judith A. Dudley, B.S., Shannon Dyer, B.S., Patricia S. Gideon, R.N., Kathi Hall, B.S., and Wayne A. Ray, Ph.D.

RESULTS

Infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations (risk ratio, 2.71; 95 percent confidence interval, 1.72 to 4.27) as compared with infants who had no exposure to antihypertensive medications. In contrast, fetal exposure to other antihypertensive medications during only the first trimester did not confer an increased risk (risk ratio, 0.66; 95 percent confidence interval, 0.25 to 1.75). Infants exposed to ACE inhibitors were at increased risk for malformations of the cardiovascular system (risk ratio, 3.72; 95 percent confidence interval, 1.89 to 7.30) and the central nervous system (risk ratio, 4.39; 95 percent confidence interval, 1.37 to 14.02).

N Engl J Med 2006;354:2443-2451

Antihypertensive drugs used in pregnancy

Central alfa agonists	**Methyldopa is the drug of choice.**
Beta-blockers	**Atenolol and metoprolol appear to be safe and effective in late pregnancy.**
Alfa-/beta-blockers	**Labetalol has comparable efficacy with methyldopa, in case of severe hypertension, it could be given intravenously.**

Atenolol in essential hypertension during pregnancy

Lucy Butters, Susan Kennedy, Peter C Rubin

Abstract

Objective—To determine the effect of atenolol on the outcome of pregnancy in women with essential hypertension.

Design—Prospective, randomised, double blind, placebo controlled study.

Setting—Hospital clinic.

Patients—33 Women with mild essential hypertension (systolic blood pressure 140-170 mm Hg or diastolic pressure 90-110 mm Hg on two occasions at least 24 hours apart) consecutively referred to two obstetric medical clinics. Four patients in the placebo group were withdrawn from the study: control of blood pressure was inadequate in two, one developed breathlessness, and one changed her mind about participating. The mean gestation in the 29 remaining women on entry to the study was 15·9 weeks.

Main outcome measures—Blood pressure and birth weight.

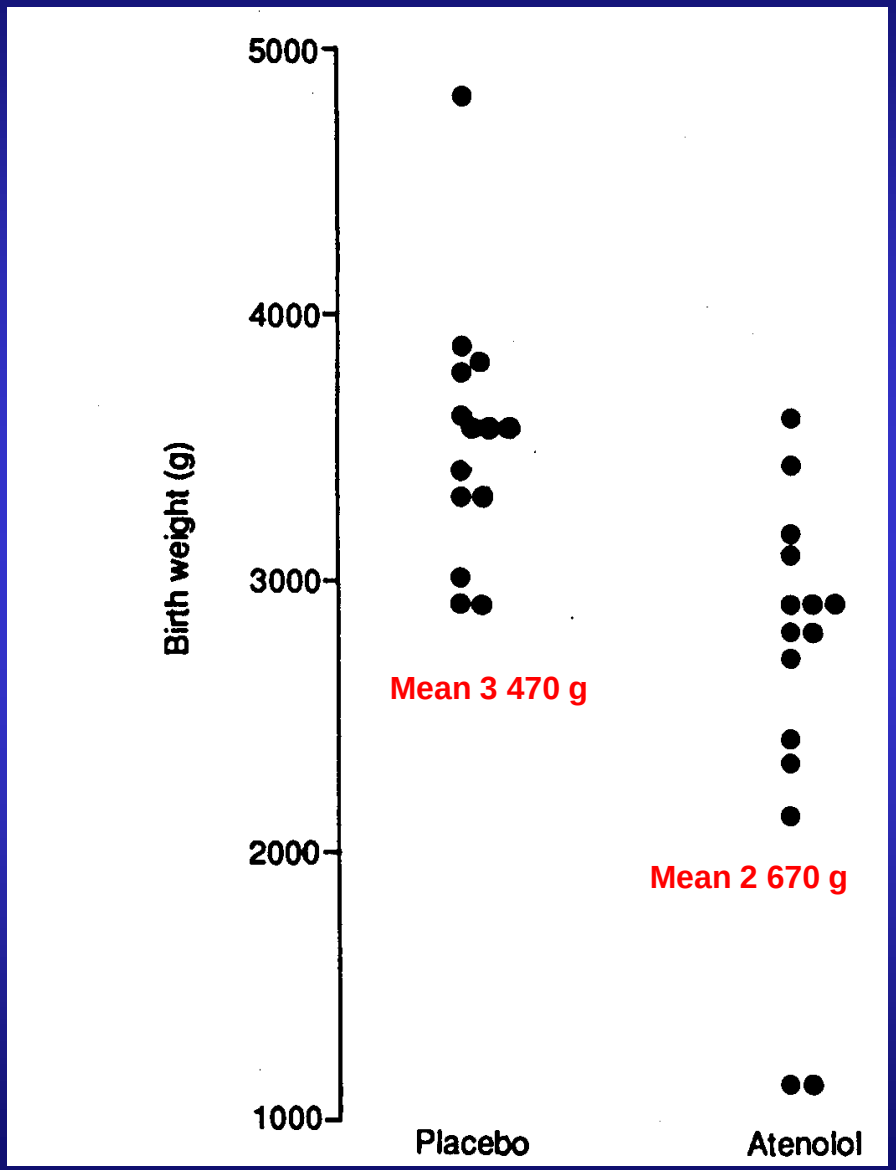
Intervention—14 Women received placebo. 15 Women received atenolol 50 mg daily initially, increasing until either the blood pressure was <140/90 mm Hg or a dose of 200 μg daily was reached.

Results—The mean blood pressure on entry was 148/86 mm Hg in the group given atenolol and 144/86 mm Hg in the group given placebo. During treatment the mean diastolic pressure was significantly reduced by atenolol compared with placebo (to 74 *v* 81 mm Hg; difference in means (95% confidence interval) 7·0 (2·9 to 10·0) mm Hg) but the effect on systolic pressure was marginal (132 *v* 136 mm Hg; 4·0 (−1·4 to 8·6) mm Hg). Babies in the atenolol group had a significantly lower birth weight than those in the placebo group (2620 g *v* 3530 g; 910 (440 to 1380) g).

Conclusion—Atenolol given from the end of the first trimester in patients with mild hypertension is associated with intrauterine growth retardation. When taken in conjunction with the results of a previous study in which methyldopa was given these findings indicate that benefit is unlikely to result from treating mild essential hypertension in pregnancy.

BMJ 1990;301:587-9

Birth weights of babies in atenolol and placebo groups



BMJ 1990;301:587-9

Effect of *Atenolol* on Birth Weight

Gregory Y.H. Lip, MD, Michèle Beevers, SRN, David Churchill, MD, Lara M. Shaffer, MB, and D. Gareth Beevers, MD

A previous small, prospective study from Glasgow reported that babies born to women treated with atenolol in early pregnancy had significantly lower birth weights than those in the placebo group.[1] Beta blockers, while safe in the third trimester of pregnancy, are also considered to cause significant growth restriction when used for longer periods.[2] An antenatal hypertension clinic has been in operation at City Hospital, Birmingham since 1980, where pregnant women with hypertension undergo careful follow-up jointly by an obstetrician and a physician with a special interest in hypertension. Patients were referred to the clinic by obstetricians and general practitioners on the basis of previous hypertension, or raised blood pressures detected for the first time in pregnancy. In many, the blood pressure decreased with no therapy, and where possible antihypertensive drugs were discontinued. After the Glasgow study,[1] the use of atenolol in early pregnancy was discontinued and an audit was conducted of birth weights in relation to drug therapy.

• • •

We conducted an analysis of our own prospectively gathered and computerized database of all women attending our clinic between 1980 and 1995. Information on demographic data, presenting blood pressures, drug therapies, pregnancy complications, and pregnancy outcome were recorded. The mean termine significant predictors for birth weights. A p value <0.05 was considered statistically significant.

We reviewed data from the antenatal records of 398 consecutive pregnancies (137 white, 103 black, 158 Asian women; mean age 30 ± 6 years) attending our antenatal hypertension clinic between 1980 and 1995. Two hundred thirty-five women were not taking any therapy during the first 20 weeks of pregnancy, whereas atenolol was taken by 76 women, labetolol by 7, other β blockers by 12, calcium antagonists by 22, diuretics by 26, methyldopa by 17, and angiotensin-converting enzyme inhibitors by 7 women; 18 women were taking multiple drug combinations.

Blood pressures during antihypertensive therapy are summarized in Table I. When compared with untreated cases, there was a trend toward higher mean systolic (1-way ANOVA, $p = 0.064$) and diastolic blood pressures ($p < 0.001$) in the first 20 weeks of pregnancy among women who were taking antihypertensive drugs (Table I). There were no significant differences in mean gestation period for each patient subgroup of treated and untreated women (1-way ANOVA, p = NS).

Mean birth weights, median placental weights, and ponderal index are also summarized in Table I. Babies born to women taking atenolol were significantly lighter (1-way ANOVA, $F = 5.3$, $p < 0.001$)

AmJ Cardiol 1997;79:1436-1438

Effect of *Atenolol* on Birth Weight

Gregory Y.H. Lip, MD, Michèle Beevers, SRN, David Churchill, MD, Lara M. Shaffer, MB, and D. Gareth Beevers, MD

In conclusion, this survey suggests that atenolol use may be detrimental in early pregnancy and provides confirmatory data with previous small prospective randomized trials. Our findings suggest that atenolol should be avoided in women who are trying to conceive or who are in the early stages of pregnancy.

Am J Cardiol 1997;79:1436-1438

Antihypertensive drugs used in pregnancy

Diuretics	**Diuretics are recommended for chronic hypertension if prescribed before gestation or if patients appear to be salt-sensitive. They are not recommended in pre-eclampsia.**
Direct vasodilators	**Hydralazine is no longer the parenteral drug of choice; perinatal adverse effects.**

Antihypertensive drugs used in pregnancy

Calcium-channel blockers	**Oral nifedipine or i.v. isradipine could be given in hypertensive emergencies. Potential synergism with magnesium sulfate may induce hypotension.**
ACE inhibitors, AIIA, direct renin inhibitors	**Fetal abnormalities including death can be caused and these drugs should not be used in pregnancy.**

Breast-feeding

- Does not increase BP in nursing mothers
- All antihypertensive agents taken by the nursing mother are excreted into breast milk; however, most of them are present at very low concentrations, except for propranolol and nifedipine concentrations, which are similar to maternal plasma

Maternal antihypertensive medications usually compatible with breastfeeding

Captopril
Diltiazem
Enalapril
Hydralazine
Hydrochlorothiazide
Labetalol
Methyldopa
Minoxidil
Nadolol
Nifedipine
Oxprenolol
Propranolol
Spironolactone
Timolol
Verapamil

Pediatrics 2001;108:776-789

Maternal antihypertensive medications usually compatible with breastfeeding

- Diuretics (furosemide, hydrochlorothiazide, and spironolactone) may reduce milk production.
- Metoprolol is classified as compatible with breastfeeding, although it is concentrated in human milk.
- Acebutolol and atenolol should not be used in nursing mothers.

Pediatrics 2001;108:776-789

Management of postpartum hypertension

Many guidelines still consider methyldopa the drug of choice; however, it should be used with caution in women at risk for developing depression.

Diuretics are not preferred in breastfeeding women

- **thiazide diuretics decrease milk production**
  may induce neonate thrombocytopenia
- **loop diuretics decrease milk production**
- **potassium-sparing diuretics (spironolactone, amiloride, triamterene) may be compatible with breastfeeding**

J Clin Hypertens 2009;11:726–733

Management of postpartum hypertension

Beta-blockers (propranolol, atenolol, acebutolol) attain high levels in breast milk to induce signs of neonatal beta-blockade.

Labetalol is efficacious and relatively safe during lactation.

Nifedipine has data supporting its safety during lactation (insignificant amounts transferred into breast milk).

Caution: nicardipine attains higher levels in breast milk and should be avoided in breastfeeding hypertensive mothers.

ACE inhibitors: captopril, enalapril, and quinapril could be used during lactation.

J Clin Hypertens 2009;11:726–733

COMMENTARY

Hypertension in Pregnancy: A Potential Window into Long-Term Cardiovascular Risk in Women

ELLEN W. SEELY*

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Hypertensive disorders of pregnancy affect approximately 6–8% of pregnancies and are the second leading cause of maternal mortality in the United States. They are also a leading cause of maternal and neonatal morbidity (1). Despite the frequency of these disorders, their cause is unknown and their treatment is inadequate. Hypertension in pregnancy is a gender specific condition by definition. As with many other disorders that affect women, hypertension in pregnancy involves the overlap of the fields of internal medicine and obstetrics. Whereas most essential hypertension is managed by internists, when a pregnant woman is hypertensive, the care of the hypertension is managed primarily by obstetricians. This leads to an interesting potential duality in the focus and approach of each specialty. In general, hypertension in pregnancy has been viewed as an obstetrical disorder and has not been an area of investigation for most internists. For the obstetrician, the disorder is one of pregnancy itself, and the focus is on the outcome of the individual pregnancy. On the other hand, for the internist an emerging focus is on the potential implications of hyperten-

and resolving postpartum. Preeclampsia differs from g
tional hypertension due to its multisystem involvement
as proteinuria as described below. When a women
preexisting hypertension develops an exacerbation o
hypertension during pregnancy accompanied by protei
or other systemic signs, this is termed hypertension
superimposed preeclampsia.

Diagnosis and clinical course

When a woman presents with hypertension in pregn
the first step is to establish whether it is of new onset
preexisting. With more women delaying child bearing
later ages, pregnancies are occurring more frequently
age when women have already developed essential h
tension. Essential hypertension carries with it an exc
prognosis in pregnancy unless superimposed preeclar
develops. Two major areas of difference in manage
between hypertension during pregnancy *vs.* hyperte
outside of pregnancy are in the choice of antihyperte
and the goal of treatment.

J Clin Endocrinology Metabol 1999;84:1858-1861

Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis

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doi:10.1136/bmj.39335.385301.BE

ABSTRACT

Objective To quantify the risk of future cardiovascular diseases, cancer, and mortality after pre-eclampsia.

Design Systematic review and meta-analysis.

Data sources Embase and Medline without language restrictions, including papers published between 1960 and December 2006, and hand searching of reference lists of relevant articles and reviews for additional reports.

Review methods Prospective and retrospective cohort studies were included, providing a dataset of 3 488 160 women, with 198 252 affected by pre-eclampsia (exposure group) and 29 495 episodes of cardiovascular disease and cancer (study outcomes).

Results After pre-eclampsia women have an increased risk of vascular disease. The relative risks (95% confidence intervals) for hypertension were 3.70 (2.70 to 5.05) after 14.1 years weighted mean follow-up, for ischaemic heart disease 2.16 (1.86 to 2.52) after 11.7 years, for stroke 1.81 (1.45 to 2.27) after 10.4 years, and for venous thromboembolism 1.79 (1.37 to 2.33) after 4.7 years. No increase in risk of any cancer was found (0.96, 0.73 to 1.27), including breast cancer (1.04, 0.78 to 1.39) 17 years after pre-eclampsia. Overall mortality after pre-eclampsia was increased: 1.49 (1.05 to 2.14) after 14.5 years.

Conclusions A history of pre-eclampsia should be considered when evaluating risk of cardiovascular

and some are also features of the "metabolic syndrome" a "risk factor" for cardiovascular disease.[10] It is possible that pre-eclampsia increases risk of later cardiovascular disease,[11] either because of a shared cause or because subclinical vascular damage occurs during pre-eclampsia.

If a history of pre-eclampsia exerts an independent risk for future cardiovascular disease it may increase the risk of cardiovascular disease in mid-life in affected women, which would render them eligible for preventive therapies at an earlier age than usual. To investigate the association between pre-eclampsia and atherosclerosis in later life we carried out a systematic review and meta-analysis of studies that had estimated the risk of arterial and venous diseases after pre-eclampsia. We also evaluated the risk of future cancer after pre-eclampsia, in particular breast cancer, one of the commonest causes of death in middle aged women.[13,14] Finally we investigated mortality from any cause after a pregnancy affected by pre-eclampsia.

METHODS

We searched Medline and Embase with no language restrictions up to December 2006. Additional eligible studies were sought by a hand search of reference lists from primary articles and relevant reviews. (See bmj.com for search terms and combinations).

BMJ 2007;355:974-986

AHA Guideline

Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update

A Guideline From the American Heart Association

EXECUTIVE WRITING COMMITTEE

Lori Mosca, MD, MPH, PhD, FAHA, Chair; Emelia J. Benjamin, MD, ScM, FAHA; Kathy Berra, MSN, NP; Judy L. Bezanson, DSN, CNS, RN; Rowena J. Dolor, MD, MHS; Donald M. Lloyd-Jones, MD, ScM; L. Kristin Newby, MD, MHS; Ileana L. Piña, MD, MPH, FAHA; Véronique L. Roger, MD, MPH; Leslee J. Shaw, PhD; Dong Zhao, MD, PhD

- **Pregnancy provides a unique opportunity to estimate a woman´s lifetime risk**
- **Preeclampsia may be an early indicator of CVD risk**

Circulation 2011;123:DOI:10.1161/CIR.0b013e31820faaf8

Recommendations for female-specific conditions

Recommendations	Class[a]	Level[b]	Ref[c]
In women with a history of pre-eclampsia and/or pregnancy-induced hypertension, periodic screening for hypertension and DM should be considered.	IIa	B	194–197
In women with a history of polycystic ovary syndrome or gestational DM, periodic screening for DM should be considered.	IIa	B	198–201
In women with a history of giving premature birth, periodic screening for hypertension and DM may be considered.	IIb	B	202, 203

Eur J Heart 2016

Recommendations for female-specific conditions

Recommendations	Class[a]	Level[b]	Ref[c]
In women with a history of pre-eclampsia and/or pregnancy-induced hypertension, periodic screening for hypertension and DM should be considered.	IIa	B	194–197

Eur J Heart 2016

Conclusions

- In *non-severe hypertension,* **oral methyldopa, labetalol, calcium antagonists,** and (less frequently) beta-blockers are drugs of choice
- In pre-eclampsia with pulmonary edema, nitroglycerin is the drug of choice, diuretic therapy is inappropriate because plasma volume is reduced
- As *emergency,* **intravenous labetalol, oral methyldopa, and oral nifedipine** are indicated. *Intravenous hydralazine is no longer the drug of choice* because of an excess of perinatal adverse effects

ASA in the prevention of pre-eclampsia

- **ASA (75 mg daily) is recommended in the prevention of pre-eclampsia in women at high or moderate risk of pre-eclampsia from 12 weeks of gestation until delivery**

Conclusions

- ***I.v. infusion of sodium nitroprusside*** **is useful** ***in hypertensive crisis,*** **but prolonged administration should be avoided**

- **Calcium supplementation, fish oil, and low-dose aspirin are not recommended. However,** ***low-dose aspirin may be used prophylactically in women with a history of an early onset of pre-eclampsia***

Hypertensive encephalopathy

1-2% of untreated essential hypertension
SBP > 250 or DBP > 150 mmHg

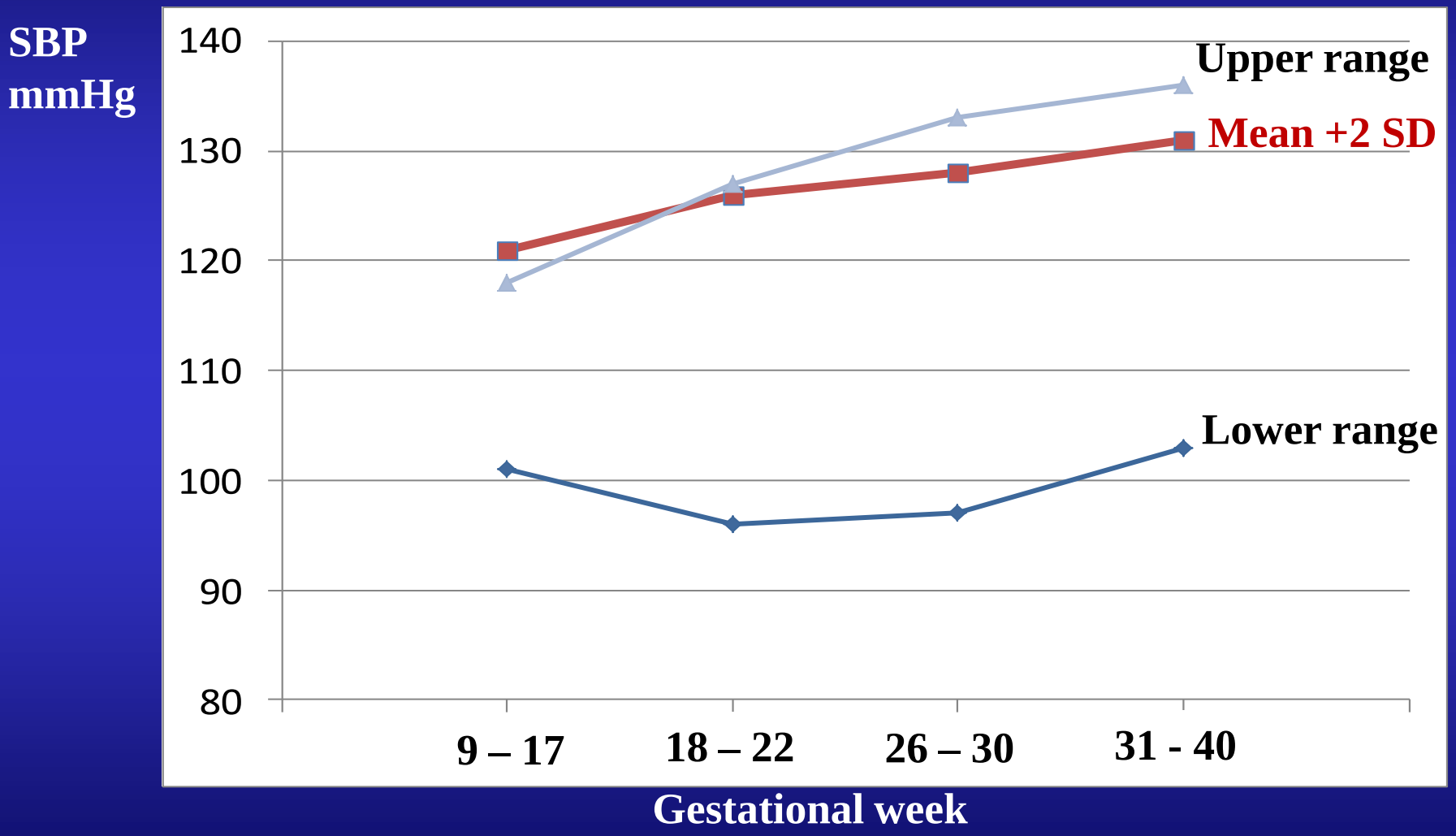
Treatment

- **↓Mean BP by no more than 15-25% towards DBP 100-110 mmHg**
- **Drug of choice: *sodium nitroprusside***
- **Other drugs: *nitroglycerin, nifedipine, labetalol***

Conclusions

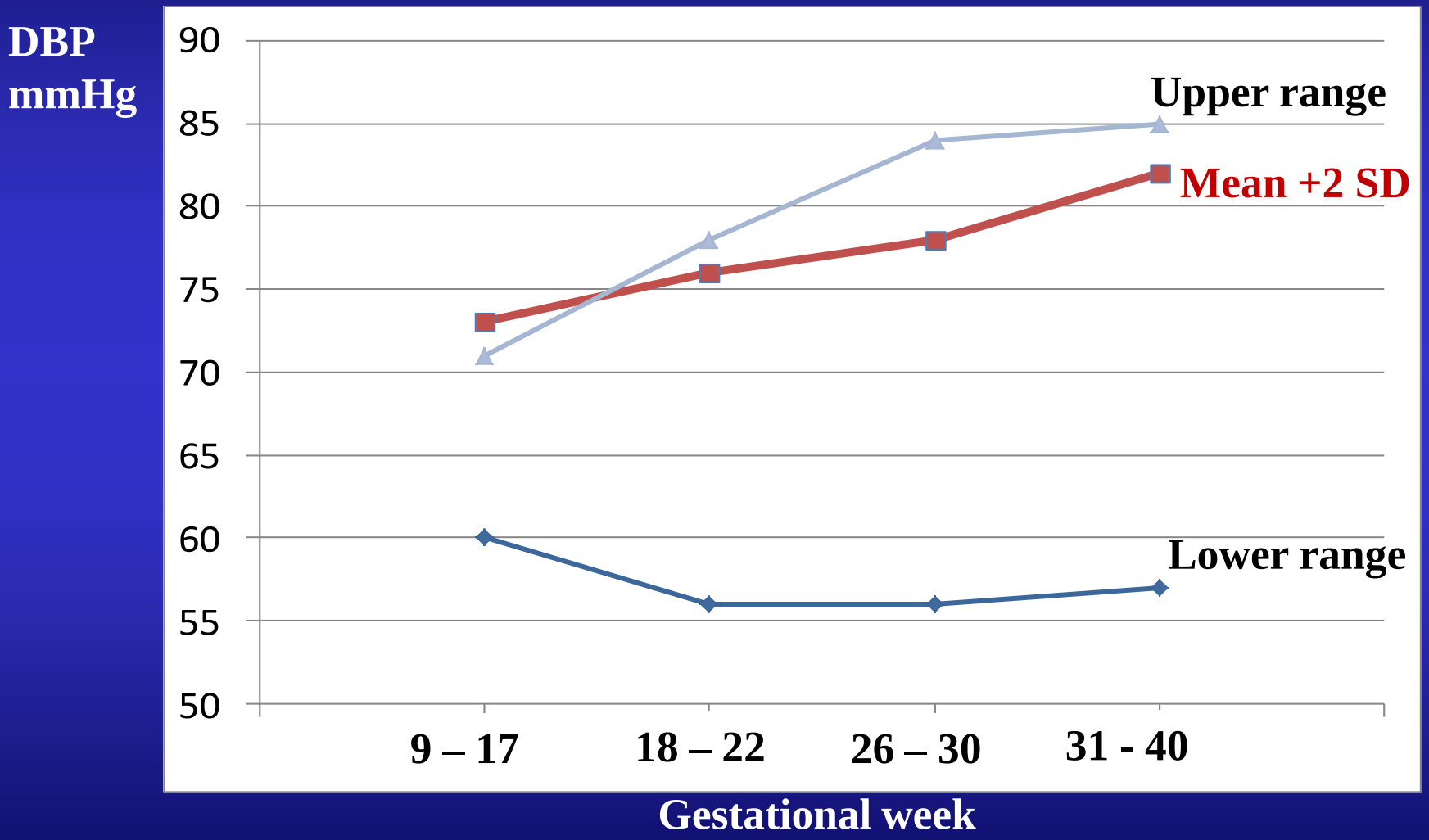
- ***Korotkoff Phase V is now recommended for the measurement of DBP in pregnancy*** **with Phase IV being indicated only if Korotkoff sounds persist at cuff pressures approaching 0 mmHg**
- ***Non-pharmacological management*** **should be considered for pregnant women with SBP 140-149 mmHg or DBP 90-95 mmHg**
- **In *gestational hypertension* with or without proteinuria, *drug treatment* is indicated at BP levels ≥ 140/90 mmHg**

24h ABPM values by gestational age



Am J Obstet Gynecol 1998;178:836-42

24h ABPM values by gestational age



Am J Obstet Gynecol 1998;178:836-42

Guideline

European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring

Eoin O'Brien*, Gianfranco Parati*, George Stergiou*, Roland Asmar, Laurie Beilin, Grzegorz Bilo, Denis Clement, Alejandro de la Sierra, Peter de Leeuw, Eamon Dolan, Robert Fagard, John Graves, Geoffrey A. Head, Yutaka Imai, Kazuomi Kario, Empar Lurbe, Jean-Michel Mallion, Giuseppe Mancia, Thomas Mengden, Martin Myers, Gbenga Ogedegbe, Takayoshi Ohkubo, Stefano Omboni, Paolo Palatini, Josep Redon, Luis M. Ruilope, Andrew Shennan, Jan A. Staessen, Gert vanMontfrans, Paolo Verdecchia, Bernard Waeber, Jiguang Wang, Alberto Zanchetti, Yuqing Zhang, on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring**

Ambulatory blood pressure monitoring (ABPM) is being used increasingly in both clinical practice and hypertension research. Although there are many guidelines that emphasize the indications for ABPM, there is no comprehensive guideline dealing with all aspects of the technique. It was agreed at a consensus meeting on ABPM

Keywords: ambulatory blood pressure monitoring, clinic blood pressure measurement, clinical indications, guidelines, home blood pressure measurement, recommendations, research application

J Hypertens 2013; 31: 1731-1738

Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial

*Corine M Koopmans, Denise Bijlenga, Henk Groen, Sylvia M C Vijgen, Jan G Aarnoudse, Dick J Bekedam, Paul P van den Berg, Karin de Boer, Jan M Burggraaff, Kitty W M Bloemenkamp, Addy P Drogtrop, Arie Franx, Christianne J M de Groot, Anjoke J M Huisjes, Anneke Kwee, Aren J van Loon, Annemiek Lub, Dimitri N M Papatsonis, Joris A M van der Post, Frans J M E Roumen, Hubertina C J Scheepers, Christine Willekes, Ben W J Mol, Maria G van Pampus, for the HYPITAT study group**

- **Multicentre, parallel, open-label randomised controlled trial in six academic and 32 non-academic hospitals in the Netherlands, 2005–8**
- **756 patients**
- **Induction of labour is associated with improved maternal outcome and should be advised for women with mild hypertensive disease beyond 37 weeks' gestation.**

Lancet 2009; 374 (9694): 979–988

Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial

Kim Broekhuijsen, Gert-Jan van Baaren, Maria G van Pampus, Wessel Ganzevoort, J Marko Sikkema, Mallory D Woiski, Martijn A Oudijk, Kitty W M Bloemenkamp, Hubertina C J Scheepers, Henk A Bremer, Robbert J P Rijnders, Aren J van Loon, Denise A M Perquin, Jan M J Sporken, Dimitri N M Papatsonis, Marloes E van Huizen, Corla B Vredevoogd, Jozien T J Brons, Mesrure Kaplan, Anton H van Kaam, Henk Groen, Martina M Porath, Paul P van den Berg, Ben W J Mol, Maureen T M Franssen, Josje Langenveld; for the HYPITAT-II study group

- **open-label, randomised controlled trial, in seven academic hospitals and 44 non-academic hospitals in the Netherlands.**
- **703 were enrolled and randomly assigned to immediate delivery or expectant monitoring**

Lancet 2015; 385 (9986): 2492 – 2501

Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial

Kim Broekhuijsen, Gert-Jan van Baaren, Maria G van Pampus, Wessel Ganzevoort, J Marko Sikkema, Mallory D Woiski, Martijn A Oudijk, Kitty W M Bloemenkamp, Hubertina C J Scheepers, Henk A Bremer, Robbert J P Rijnders, Aren J van Loon, Denise A M Perquin, Jan M J Sporken, Dimitri N M Papatsonis, Marloes E van Huizen, Corla B Vredevoogd, Jozien T J Brons, Mesrure Kaplan, Anton H van Kaam, Henk Groen, Martina M Porath, Paul P van den Berg, Ben W J Mol, Maureen T M Franssen, Josje Langenveld; for the HYPITAT-II study group

- **For women with non-severe hypertensive disorders at 34–37 weeks of gestation, immediate delivery might reduce the already small risk of adverse maternal outcomes. However, it significantly increases the risk of neonatal respiratory distress syndrome. Therefore, routine immediate delivery does not seem justified and a strategy of expectant monitoring until the clinical situation deteriorates can be considered.**

Lancet 2015; 385 (9986): 2492–2501

Cochrane Library

Cochrane Database of Systematic Reviews

Prevention and treatment of postpartum hypertension (Review)

Magee L, von Dadelszen P

Author´s conclusions

- **For women with preeclampsia, postnatal furosemide may decrease the need for postnatal antihypertensive therapy in hospital (more data are needed).**
- **There are no reliable data to guide management of postpartum hypertension.**

Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD004351

Postpartum hypertension

- BP rises progressively over the first 5 postnatal days, peaking on days 3–6 after delivery.
- 10% of maternal deaths due to hypertensive disorders in pregnancy occur in the postpartum period.
- Other complications of severe postpartum hypertension
    - stroke
    - eclampsia

Possible causes of postpartum hypertension

- Mobilization from the extravascular to the intravascular space (6–8 liters of total body water and 950 mEq of total body sodium)
- Urinary sodium excretion (natriuresis) – may result from increase in ANP
- Iatrogenic causes (bromocriptine, NSAIDs)

PLOS ONE

RESEARCH ARTICLE

Clonidine versus Captopril for Severe Postpartum Hypertension: A Randomized Controlled Trial

Carlos Noronha Neto C, Sabina S. B. Maia, Leila Katz, Isabela C. Coutinho, Alex R. Souza, Melania M. Amorim*

Post Graduate Program on Maternal and Child Health, Instituto de Medicina Integral Prof. Fernando Figueira, Recife, Pernambuco, Brazil

- **randomized, drug-controlled, triple-blind clinical trial**
- **n = 90 postpartum women**
- **SBP ≥ 180 and/or DBP ≥ 110 mmHg**

Conclusions: Clonidine and captopril represent safe, effective treatments for severe postpartum hypertension.

PLoS ONE 12(1): e0168124. doi:10.1371/journal. pone.0168124

Hypertension

Epidemiology and Mechanisms of De Novo and Persistent Hypertension in the Postpartum Period

Arvind Goel, MD; Manish R. Maski, MD; Surichhya Bajracharya, MD; Julia B. Wenger, MPH; Dongsheng Zhang, PhD; Saira Salahuddin, MD, PhD; Sajid S. Shahul, MD, MPH; Ravi Thadhani, MD, MPH; Ellen W. Seely, MD; S. Ananth Karumanchi, MD; Sarosh Rana, MD

Background—The pathophysiology of hypertension in the immediate postpartum period is unclear.

Methods and Results—We studied 988 consecutive women admitted to a tertiary medical center for cesarean section of a singleton pregnancy. The angiogenic factors soluble fms-like tyrosine kinase 1 and placental growth factor, both biomarkers associated with preeclampsia, were measured on antepartum blood samples. We then performed multivariable analyses to determine factors associated with the risk of developing postpartum hypertension. Of the 988 women, 184 women (18.6%) developed postpartum hypertension. Of the 184 women, 77 developed de novo hypertension in the postpartum period, and the remainder had a hypertensive disorder of pregnancy in the antepartum period. A higher body mass index and history of diabetes mellitus were associated with the development of postpartum hypertension. The antepartum ratio of soluble fms-like tyrosine kinase 1 to placental growth factor positively correlated with blood pressures in the postpartum period (highest postpartum systolic blood pressure [r=0.29, P<0.001] and diastolic blood pressure [r=0.28, P<0.001]). Moreover, the highest tertile of the antepartum ratio of soluble fms-like tyrosine kinase 1 to placental growth factor was independently associated with postpartum hypertension (de novo hypertensive group: odds ratio, 2.25; 95% confidence interval, 1.19–4.25; P=0.01; in the persistent hypertensive group: odds ratio, 2.61; 95% confidence interval, 1.12–6.05; P=0.02) in multivariable analysis. Women developing postpartum hypertension had longer hospitalizations than those who remained normotensive (6.5±3.5 versus 5.7±3.4 days; P<0.001).

Conclusions—Hypertension in the postpartum period is relatively common and is associated with prolonged hospitalization. Women with postpartum hypertension have clinical risk factors and an antepartum plasma angiogenic profile similar to those found in women with preeclampsia. These data suggest that women with postpartum hypertension may represent a group of women with subclinical or unresolved preeclampsia.

Circulation 2015;132:1726-1733

Epidemiology and mechanisms of *de novo* and persistent hypertension in the postpartum period

n = 988 consecutive women admitted for Caesarian section of a singleton pregnancy

n = 188 (18.6%) postpartum hypertension

n = 111 (59%) hypertension in the antepartum period

n = 77 (41%) ***de novo*** **hypertension**

Circulation 2015;132:1726–1733

Clinical perspective

- **Women with postpartum hypertension**
  - **use more healthcare resources (prolonged hospitalization, more antihypertensive drugs)**
  - **have the same risk factors and antepartum circulating plasma angiogenic profile as women with preeclampsia**
- **Conclusion: Women with postpartum hypertension may represent a group of women with subclinical preeclampsia or unresolved preeclampsia.**

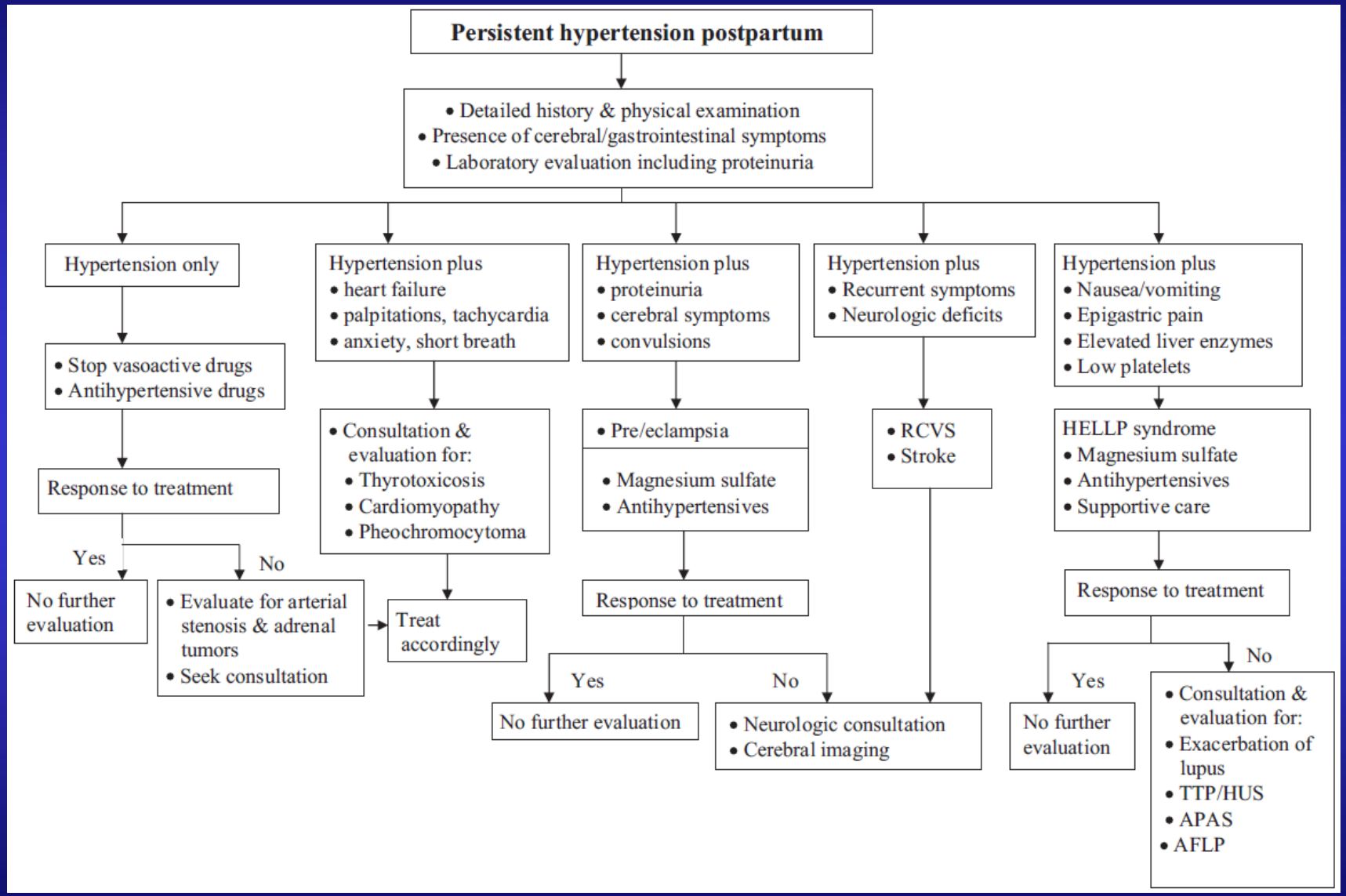
Circulation 2015;132:1726–1733

Potential causes of postpartum hypertension

- Chronic hypertension (primary or secondary)
- Gestational hypertension
- Preeclampsia, unresolved with delivery
- Volume excess associated with fluid or drug administration (e.g., nonsteroidal anti-inflammatory drugs for postoperative pain)
- Postpartum hyperthyroidism (thyroiditis)

J Clin Hypertens 2009;11:726–733

Recommended evaluation and management



Am J Obstet Gynecol 2012:206:470-5

The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 692 • April 2017 *(Replaces Committee Opinion No. 623, February 2015)*

Committee on Obstetric Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice in collaboration with committee members Yasser Y. El-Sayed, MD, and Ann E. Borders, MD, MSc, MPH.

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period

ABSTRACT: Acute-onset, severe systolic hypertension; severe diastolic hypertension; or both can occur during the prenatal, intrapartum, or postpartum periods. Pregnant women or women in the postpartum period with acute-onset, severe systolic hypertension; severe diastolic hypertension; or both require urgent antihypertensive therapy. Introducing standardized, evidence-based clinical guidelines for the management of patients with preeclampsia and eclampsia has been demonstrated to reduce the incidence of adverse maternal outcomes. Individuals and institutions should have mechanisms in place to initiate the prompt administration of medication when a patient presents with a hypertensive emergency. Treatment with first-line agents should be expeditious and occur as soon as possible within 30–60 minutes of confirmed severe hypertension to reduce the risk of maternal stroke. Intravenous labetalol and hydralazine have long been considered first-line medications for the management of acute-onset, severe hypertension in pregnant women and women in the postpartum period. Although relatively less information currently exists for the use of calcium channel blockers for this clinical indication, the available evidence suggests that immediate release oral nifedipine also may be considered as a first-line therapy, particularly when intravenous access is not available. In the rare circumstance that intravenous bolus labetalol, hydralazine, or immediate release oral nifedipine fails to relieve acute-onset, severe hypertension and is given in successive appropriate doses, emergent consultation with an anesthesiologist, maternal–fetal medicine subspecialist, or critical care subspecialist to discuss second-line intervention is recommended.

Obstet Gynecol 2017;129:769-770

Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period

- **Intravenous (IV) labetalol and hydralazine have long been considered first-line medications for the management of acute-onset, severe hypertension in pregnant women and women in the postpartum period.**
- **Immediate release oral nifedipine also may be considered as a first-line therapy, particularly when IV access is not available.**
- **The use of IV labetalol, IV hydralazine, or immediate release oral nifedipine for the treatment of acute-onset, severe hypertension for pregnant or postpartum patients does not require cardiac monitoring.**

Obstet Gynecol 2017;129:769-770

DOI: 10.1111/1471-0528.13463
www.bjog.org

Systematic review

Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis

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- **7 trials (pooled analysis); 4 from developing countries**
- **363 women**

Conclusion: Oral nifedipine is as efficacious and safe as intravenous labetalol and may have an edge in low resource settings.

BJOG 2016;123:40-47

CLINICAL REVIEW

Postpartum management of hypertension

Kate Bramham *clinical research fellow*[1], Catherine Nelson-Piercy *professor of obstetric medicine*[2], Morris J Brown *professor of clinical pharmacology*[3], Lucy C Chappell *clinical senior lecturer in maternal and fetal medicine*[4]

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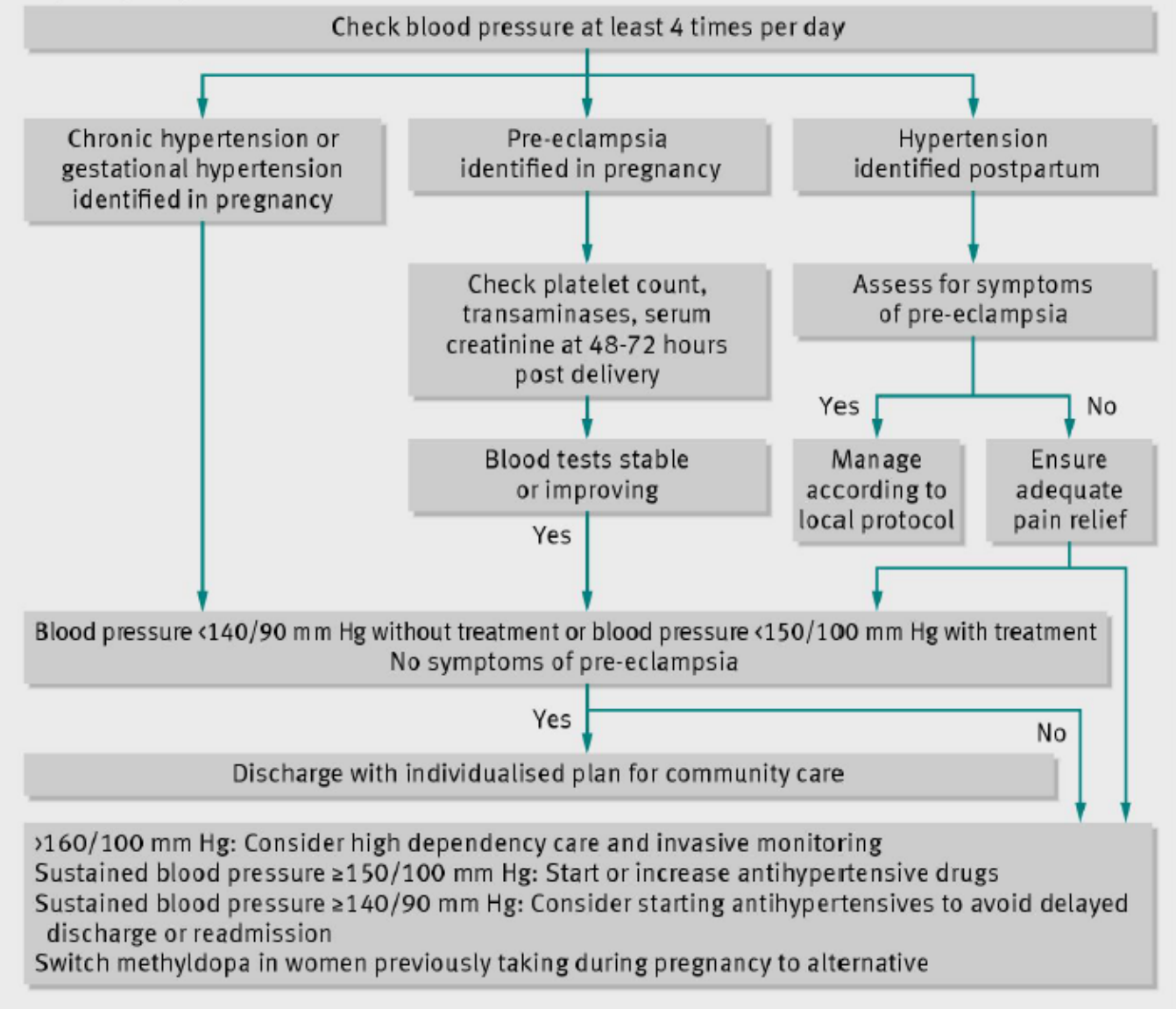
BMJ 2013 Feb 25;346:f894. doi: 10.1136/bmj.f894

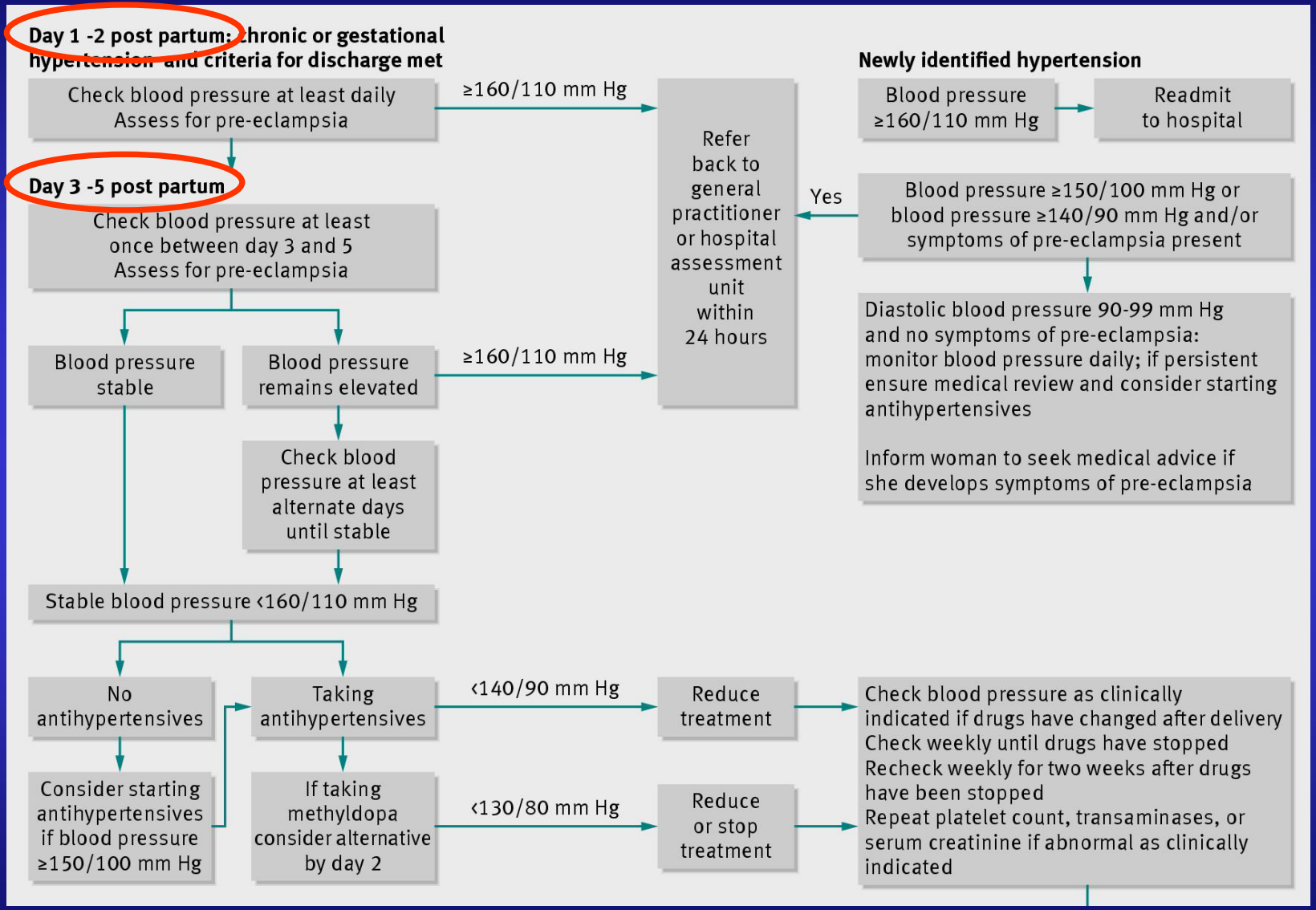
Inpatient management of postpartum HT

Day 1–3



BMJ 2013 Feb 25;346:f894. doi: 10.1136/bmj.f894

Outpatient management of postpartum HT



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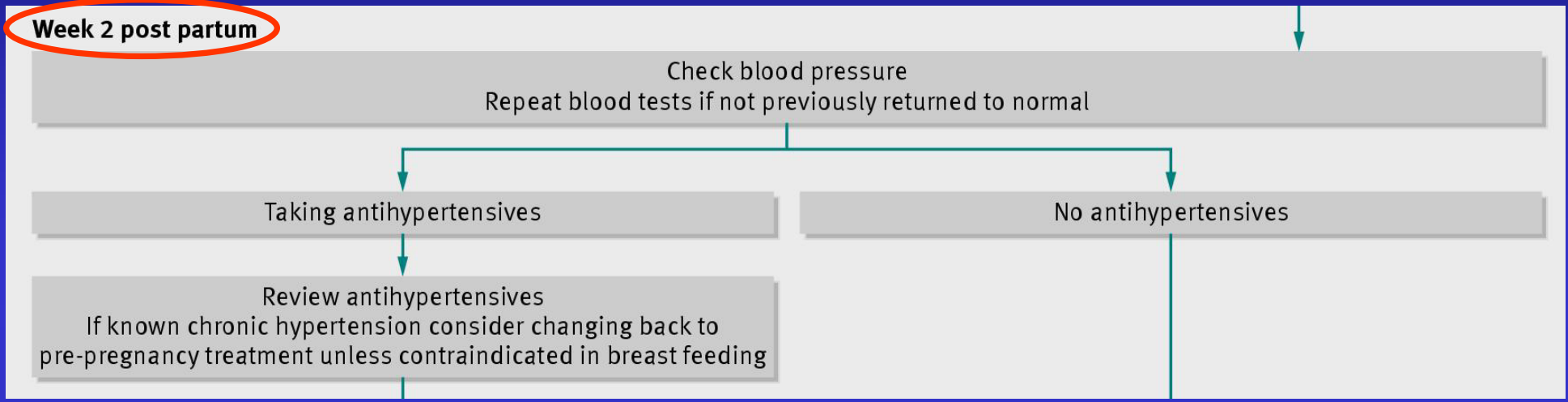
Outpatient management of postpartum HT



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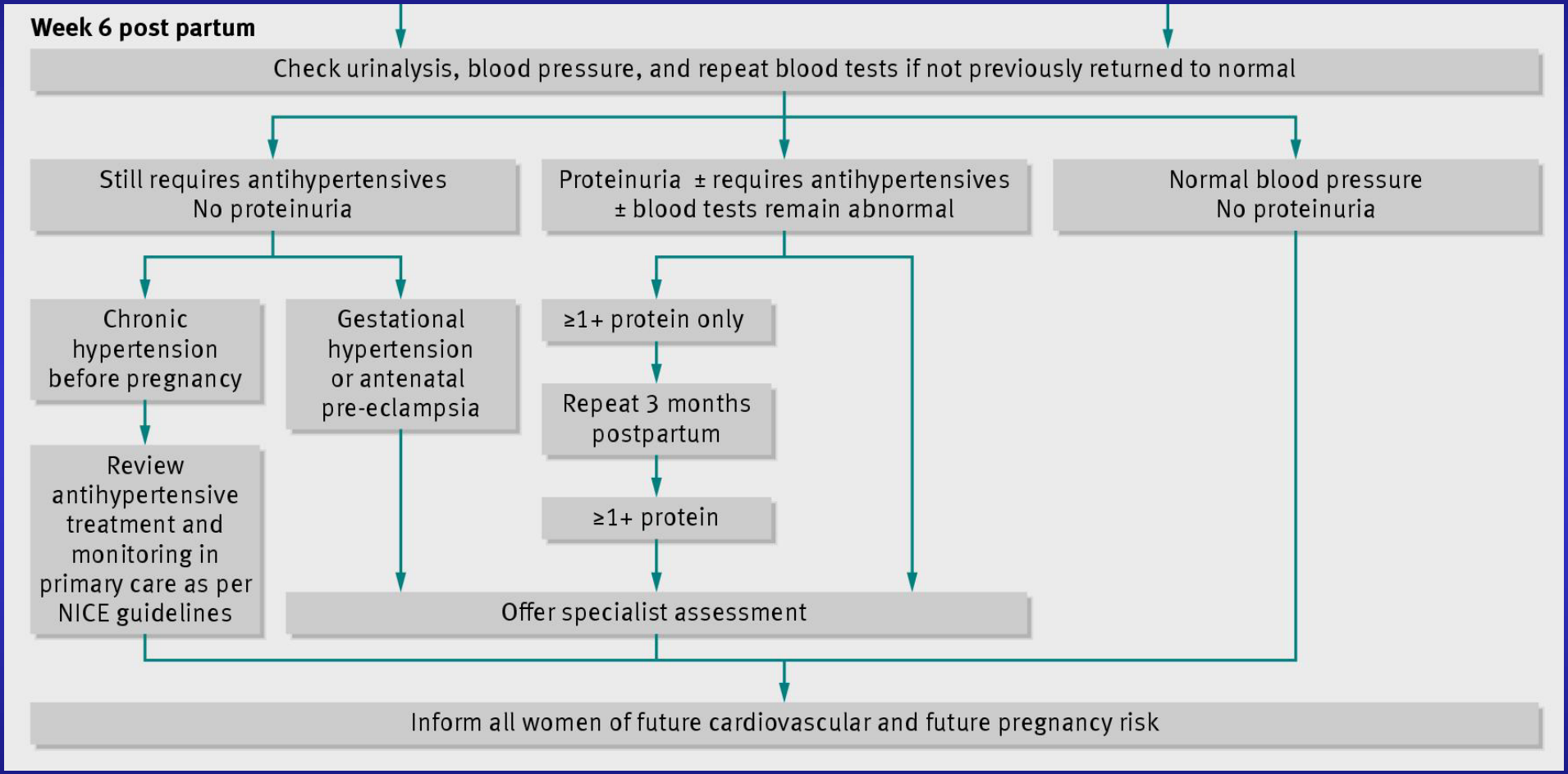
Outpatient management of postpartum HT



BMJ 2013 Feb 25;346:f894. doi: 10.1136/bmj.f894

Clinical factors associated with re-admission for postpartum hypertension in women with pregnancy-related hypertension

- Nested-case control study in women with previously diagnosed pregnancy-related hypertension re-admitted within 4 weeks postpartum (25 cases; 74 controls)

Conclusions: Postpartum re-admission for hypertension in women with known pregnancy-related hypertension was not associated with mode of delivery, appeared to be increased with longer duration of labor and decreased in those initially started on antihypertensive medications.

J Perinatal 2016;36:405–409

Hypertension in the postpartum period

1. continuation of hypertensive disorders in pregnancy
   - pre-existing hypertension (usually persists > 6 weeks postpartum)
   - gestational hypertension including pre-eclampsia (should resolve within 6 to 12 weeks postpartum)
2. *de novo* pre-eclampsia (headaches, epigastric pain, visual changes, seizures)
3. iatrogenic causes
   - drugs: NSAIDs for analgesia, ergot derivatives for postpartum hemorrhage, or ephedrine
   - hypervolemia (e.g., after regional anesthesia)
4. pain (inadequate analgesia)
5. anxiety

Identification of postpartum hypertension

NICE Clinical Guideline 107

- checking BP within 6 hours of delivery in all normotensive women without complications
- checking BP on day 5 postpartum (to identify women with a late presentation of pre-eclampsia)
- checking BP after discharge from hospital every other day

Management of postpartum hypertension

- all women with hypertension in pregnancy should have BP and urine checked by a doctor at 6 weeks and persistent hypertension confirmed by ABPM (Report of the National High Blood Pressure Educational Program Working Group on High Blood Pressure in Pregnancy; Am J Obstet Gynecol 2000;183:S1–22)
- all women under the age of 40 with hypertension should be assessed for a secondary cause (NICE Guideline 2010)

SEMINARS IN PERINATOLOGY 37 (2013) 280–287

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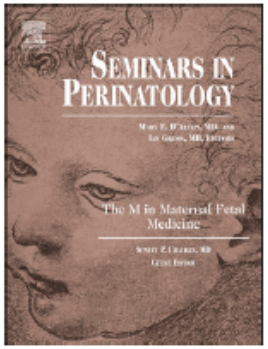

Hypertensive crisis during pregnancy and postpartum period

*Gloria T. Too, MD, and James B. Hill, MD**

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- **10% of pregnancies are complicated by hypertension**
- **1–2% of those may undergo a hypertensive crisis at some point including the postpartum period**
- **Incidence of postpartum pre-eclampsia 5.7% (Matthys 2004)**

Seminars in Perinatol 2013;37:280–287

Management of postpartum hypertension

Many guidelines still consider methyldopa the drug of choice; however, it should be used with caution in women at risk for developing depression.

Diuretics are not preferred in breastfeeding women

- **thiazide diuretics decrease milk production**
  may induce neonate thrombocytopenia
- **loop diuretics decrease milk production**
- **potassium-sparing diuretics (spironolactone, amiloride, triamterene) may be compatible with breastfeeding**

J Clin Hypertens 2009;11:726–733

Management of postpartum hypertension

Beta-blockers (propranolol, atenolol, acebutolol) attain high levels in breast milk to induce signs of neonatal beta-blockade.

Labetalol is efficacious and relatively safe during lactation.

Nifedipine has data supporting its safety during lactation (insignificant amounts transferred into breast milk).

Caution: nicardipine attains higher levels in breast milk and should be avoided in breastfeeding hypertensive mothers.

ACE inhibitors: captopril, enalapril, and quinapril could be used during lactation.

J Clin Hypertens 2009;11:726–733

Management of postpartum hypertension

- **Hypertensive urgencies:**

  oral labetalol, nifedipine ER, diltiazem, verapamil, clonidine

- **Hypertensive emergencies:**

  IV labetalol, hydralazine, esmolol, nicardipine, sodium nitroprusside

  oral nifedipine

Seminars in Perinatol 2013;37:280–287