Hypertension in Pregnancy

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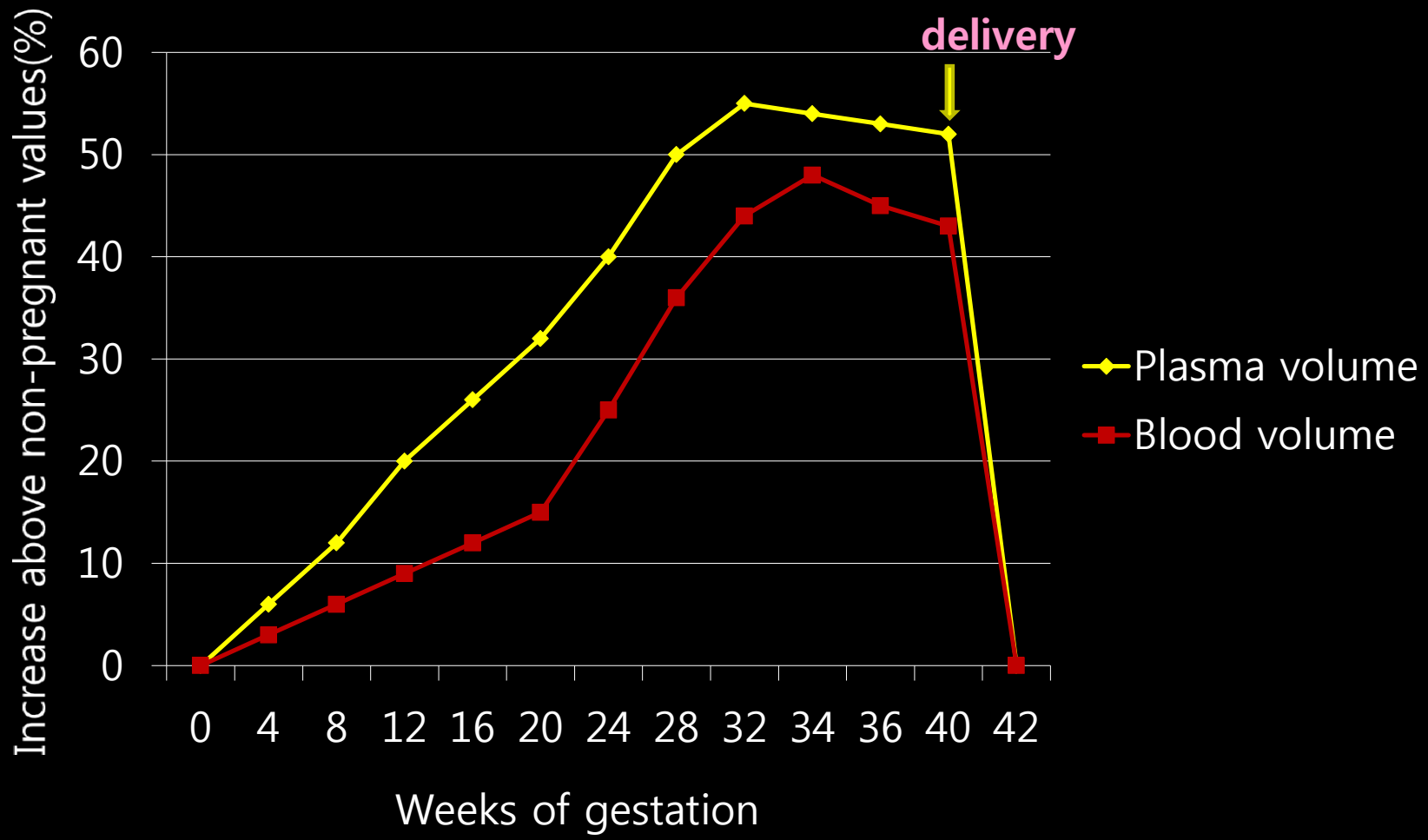
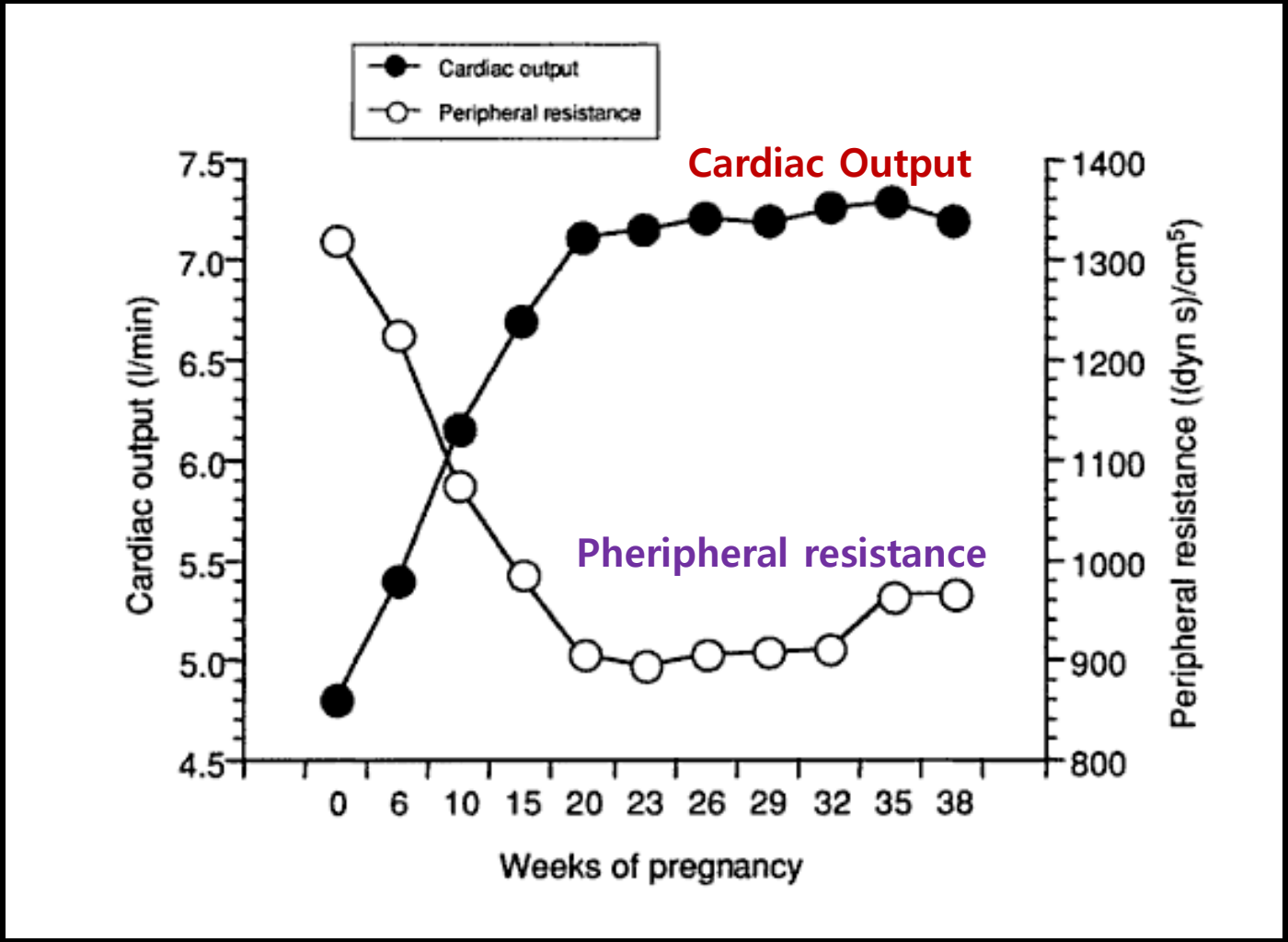
Adaptations in Normal Pregnancy

1) Plasma and blood volume



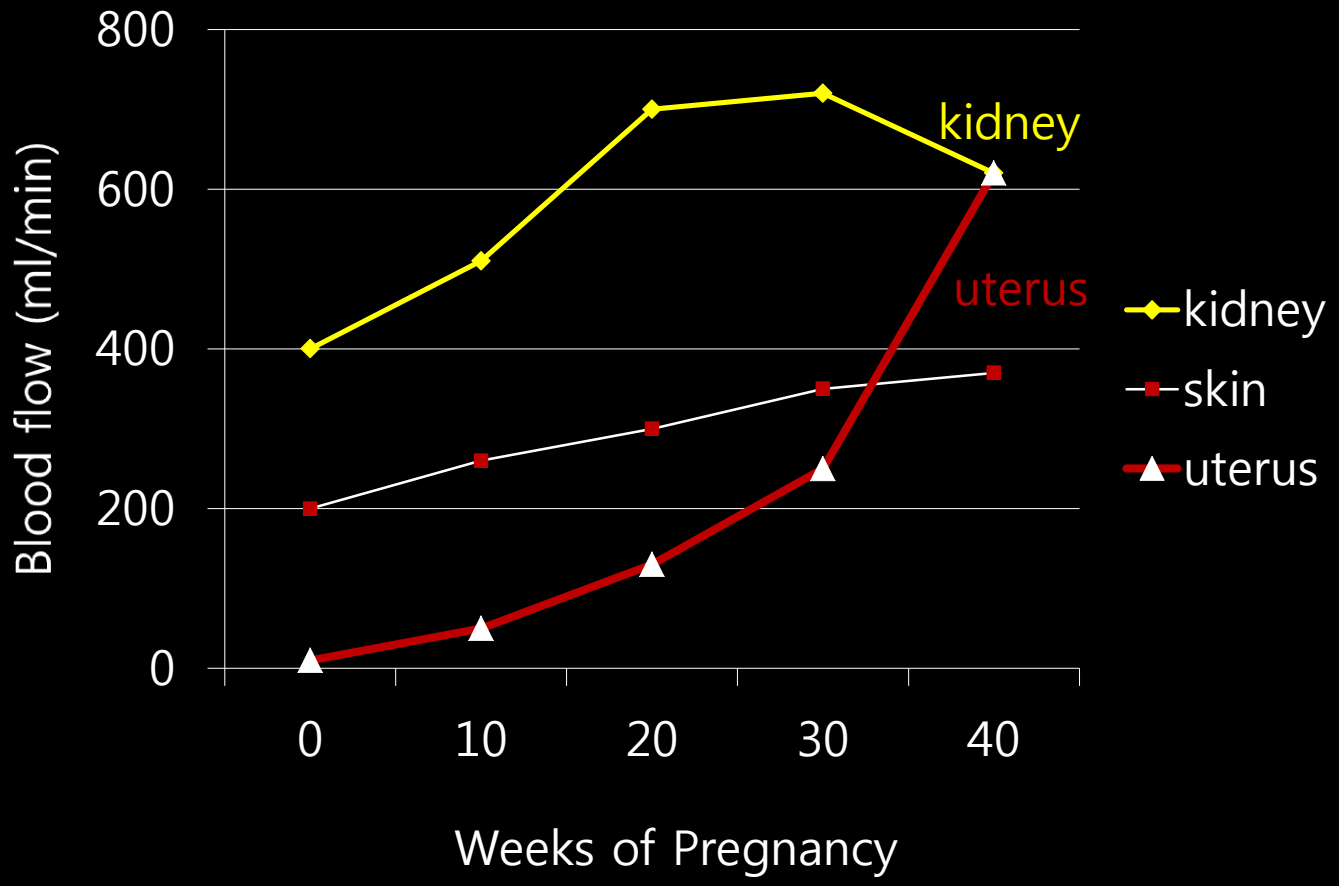
Alexander H. et.al Hypertension in pregnancy, Cambridge clinical guide,2010

2)Cardiac output & Peripheral resistance during pregnancy



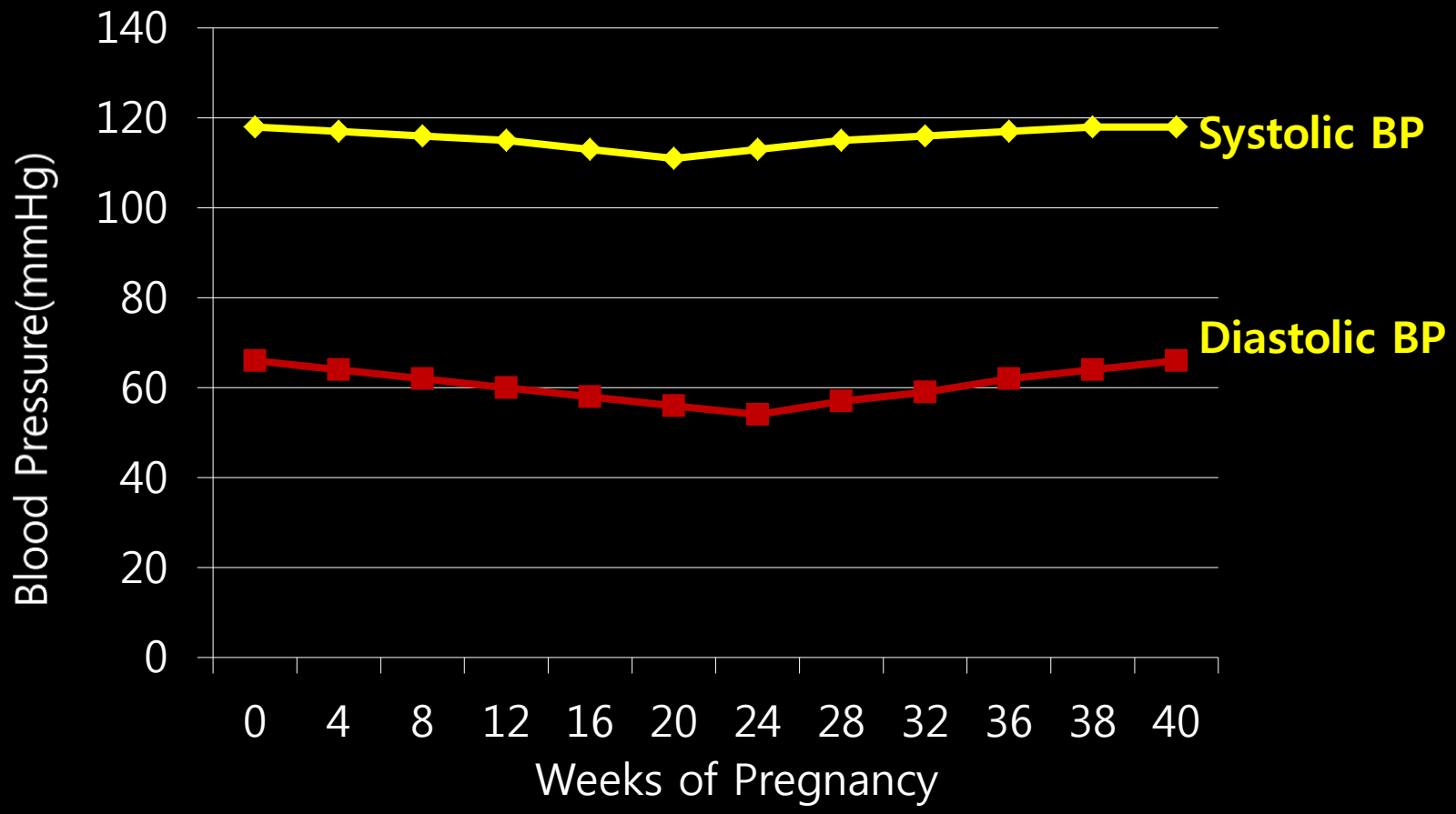
Philip JS, , Heart disease and pregnancy, 2006

3) blood flow to peripheral organs before and during pregnancy



Philip JS, Heart disease and pregnancy, 2006

4) Systolic and Diastolic BP during pregnancy



BP:blood pressure

Philip JS, Heart disease and pregnancy, 2006

Diagnosis of hypertension in pregnancy(HP)

Blood pressure ≧ 140/90mmHg during pregnancy

Edward JR, et al. Am J Obstet Gynecol 163:1689, 1990

Classification in HP

- **Preeclampsia**
  -Hypertension developing after 20 weeks` gestation with proteinuria(≧300mg/day) and/or edema

- **Gestational hypertension**
  -Hypertension developing after 20 weeks` gestation without other signs of preeclampsia
  (transient hypertension or chronic hypertension)

- **Chronic hypertension**
  -Hypertension before 20 weeks` gestation in the absence of neoplastic trophoblastic disease

- **Preeclampsia superimposed on chronic hypertension**
  -Preeclampsia developing in a woman with preexisting hypertension

Edward JR, et al. Am J Obstet Gynecol 163:1689, 1990

Subclass by symptoms in HP

- **Severity**
- **Mild**

-systolic BP >140mmHg but not exceeding 160mmHg &/or
-diastolic BP >90mmHg but not exceeding 110mmHg &/or
-Proteinuria >300mg/day but not exceeding 2g/day

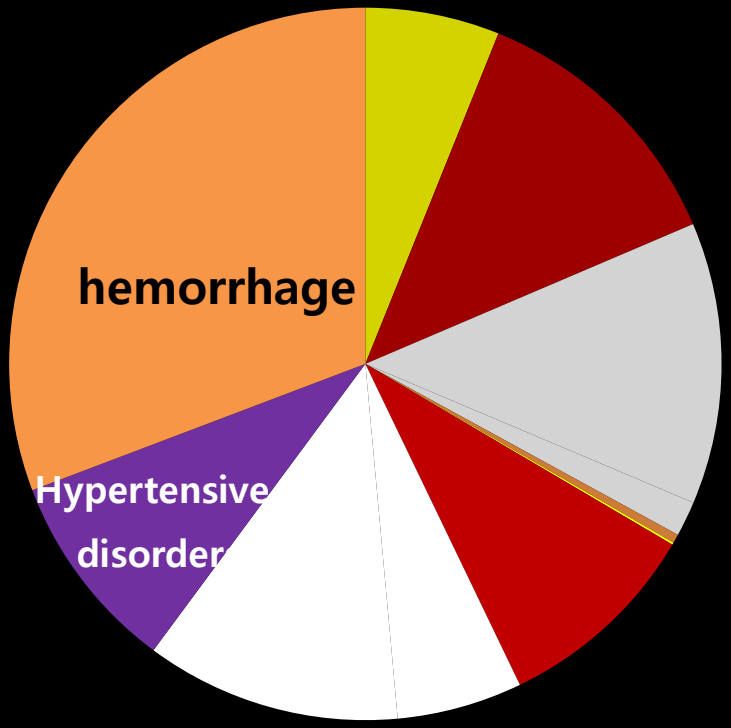
- **Severe**

-systolic BP >160mmHg and/or diastolic BP ≧ 110mmHg
-proteinuria >2g/day
(24hour urine sample should be used
random urine sample; repeated test results of 3+ are considered to be severe)

JSH 2009

Incidence

- incidence; 5-10% of pregnancies
- second most common cause(15-25%) of maternal death

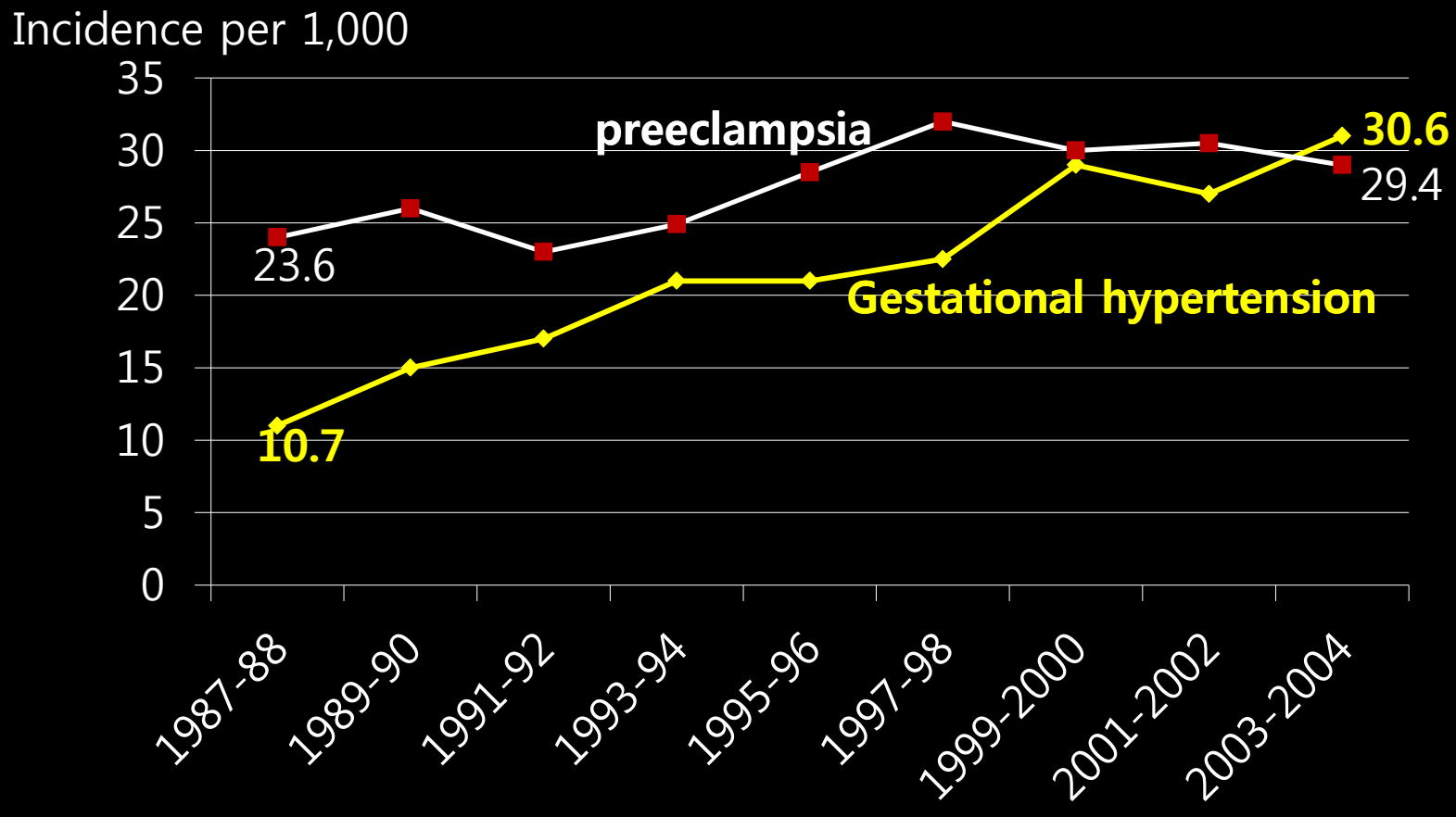


Asia

- unclassified death
- other indirect cause of death
- anemia
- HIV/AIDS
- other direct cause of death
- embolism
- ectopic pregnancy
- obstructed labor
- abortion
- sepsis/infection
- hypertenvise disorders
- hemorrhage

Khalid SK, et al Lancet 2006;367:1066

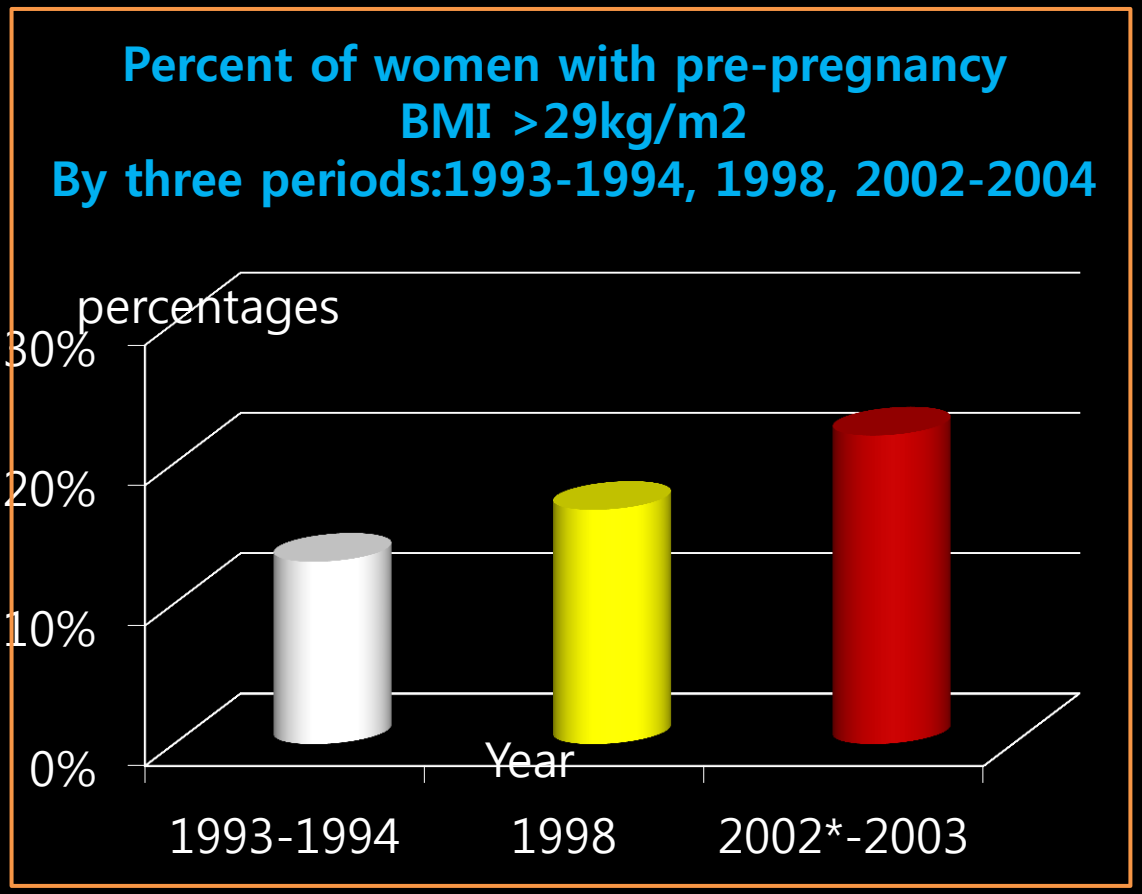
Age-adjusted incidence per 1,000 deliveries for women with GH and preeclampsia for 2 year periods, 1987-2004 in United Stated (National Hospital Discharge Survey)



Anne BW, et al. Am J hyper 2008 21(5):521

Risk factors for HP

- pre-pregnancy obesity and metabolic syndrome
- diabetes
- multiple births
- maternal age



Patrick MC. Reproduction 2010;140:365

Complication of HP

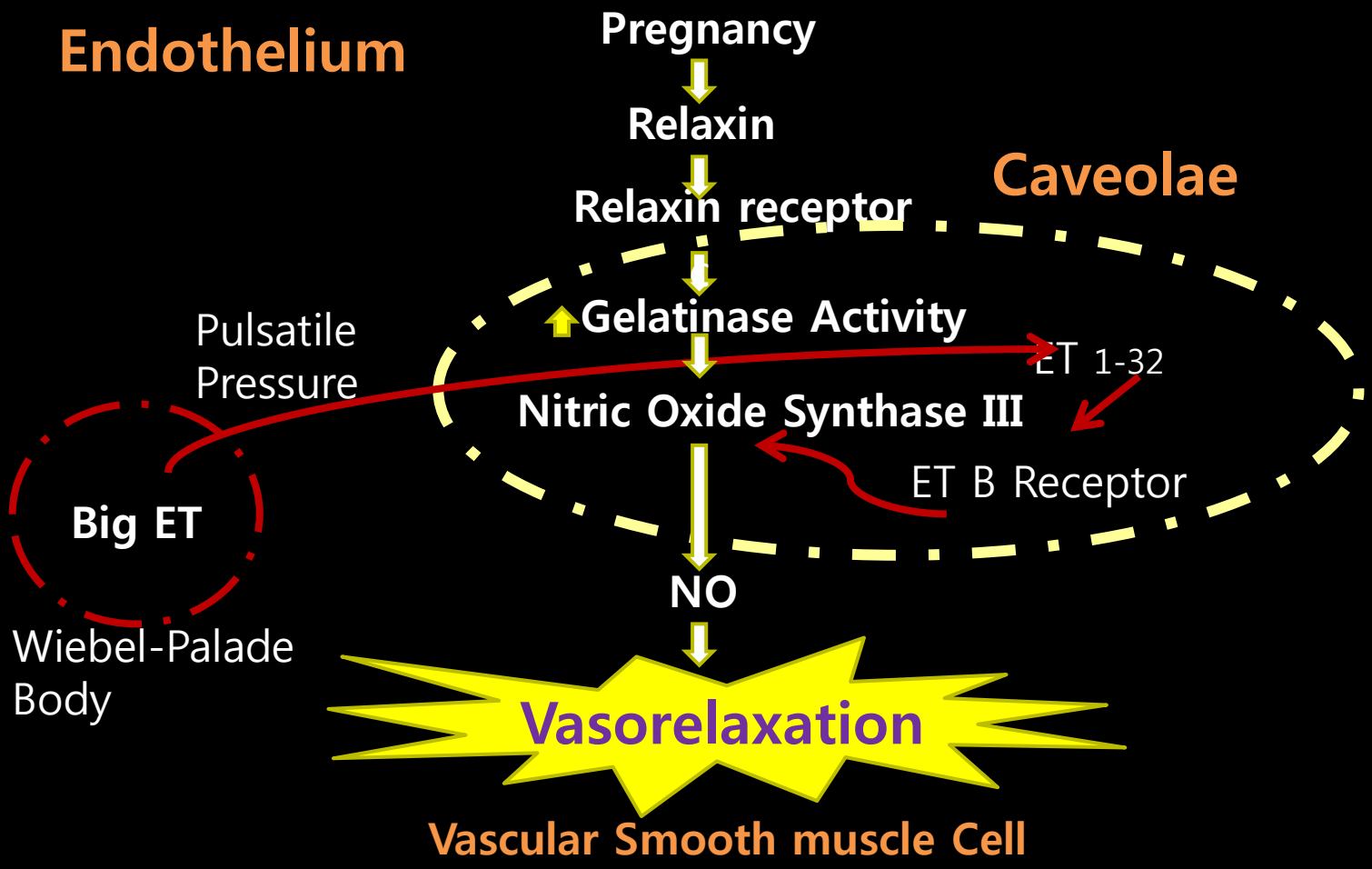
Maternal Complications

- Placenta abruption
- Disseminated intravascular coagulations
- Cerebral Hemorrhage
- Hepatic failure
- Acute Renal Failure

Fetal and Neonatal Complications

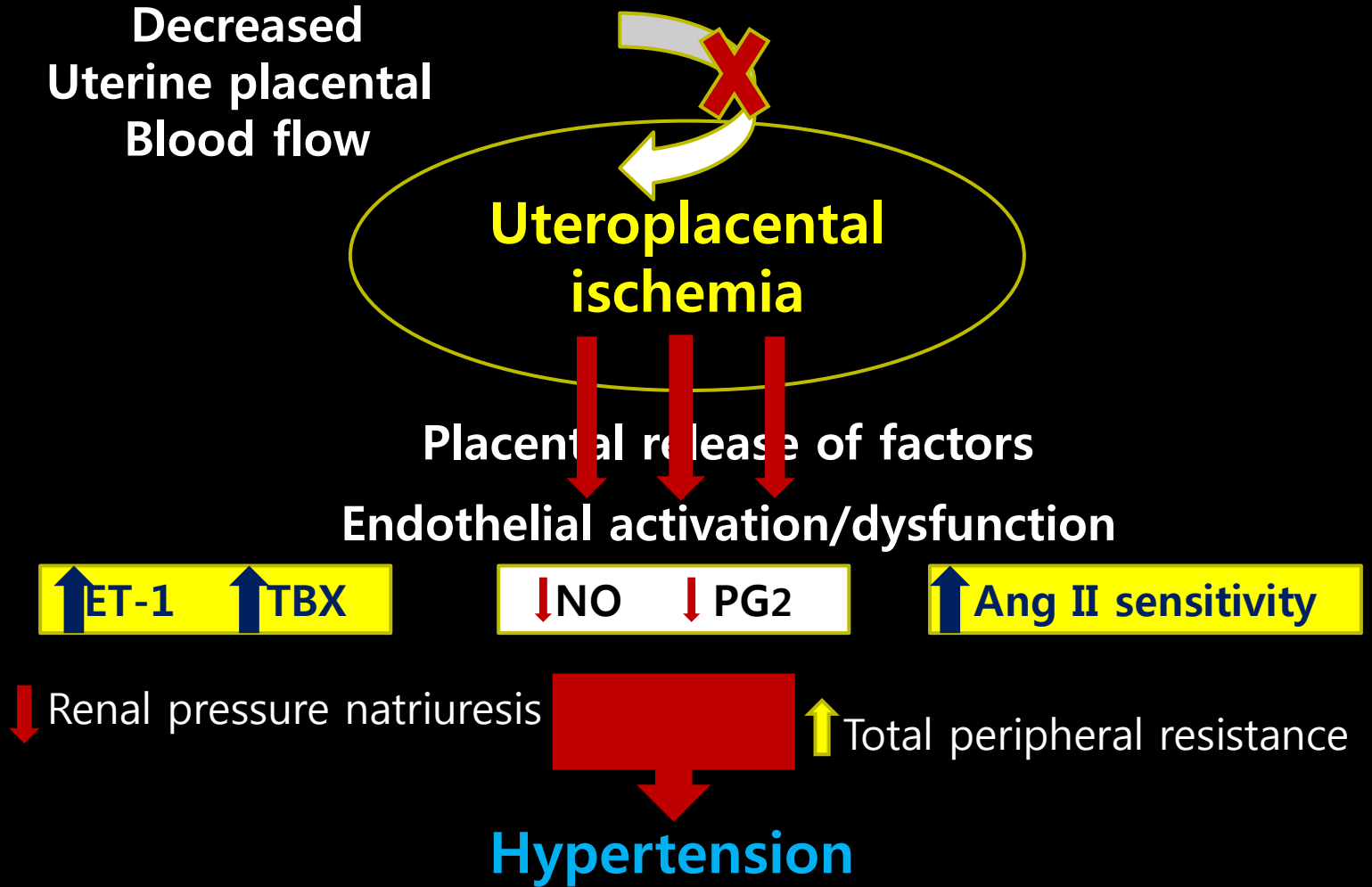
- Placental abruption
- Placental insufficiency
- Still births
- Prematurity
- Intrauterine growth restriction

Proposed scheme of cellular mechanisms underlying pregnancy and relaxin-induced vasodilation and hyperfiltration and reduced myogenic reactivity



K.P. Conrad et. Al, Endothelium,2005 12:57

Potential mechanisms whereby chronic reductions in uteroplacental perfusion may lead to hypertension



Granger, J. P. et al. Hypertension 2001;38:718-722

Management of Hypertension in Pregnancy

Subclass by symptoms in HP

- **Severity**
- **Mild**

-systolic BP >140mmHg but not exceeding 160mmHg &/or
-diastolic BP >90mmHg but not exceeding 110mmHg &/or
-Proteinuria >300mg/day but not exceeding 2g/day

- **Severe**

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(24hour urine sample should be used
random urine sample; repeated test results of 3+ are considered to be severe)

JSH 2009

Treatment of mild to moderate hypertension

Antihypertensive drug therapy for mild to moderate hypertension during pregnancy.

Abalos E, Duley L, Steyn DW, Henderson-Smart DJ.

Centro Rosarino de Estudios Perinatales, Pueyrredon 985, Rosario, Santa Fe, Argentina, 2000. crep@crep.com.ar

Comment in:

ACP J Club. 2007 Jul-Aug;147(1):9.

Evid Based Med. 2007 Aug;12(4):116.

Update of:

Cochrane Database Syst Rev. 2004;(3):CD002252.

Antihypertensive tx
-insufficient data to Determine the benefit and risks

Abstract

BACKGROUND: Mild to moderate hypertension during pregnancy is common. Antihypertensive drugs are often used in the belief that lowering blood pressure will prevent progression to more severe disease, and thereby improve outcome.

OBJECTIVES: To assess the effects of antihypertensive drug treatments for women with mild to moderate hypertension during pregnancy.

SEARCH STRATEGY: We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2006), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2005, Issue 3), MEDLINE (1966 to November 2005), LILACS (1984 to November 2005) and EMBASE (1974 to November 2005).

SELECTION CRITERIA: All randomised trials evaluating any antihypertensive drug treatment for mild to moderate hypertension during pregnancy defined, whenever possible, as systolic blood pressure 140 to 169 mmHg and diastolic blood pressure 90 to 109 mmHg. Comparisons were of one or more antihypertensive drug(s) with placebo, with no antihypertensive drug, or with another antihypertensive drug, and where treatment was planned to continue for at least seven days.

DATA COLLECTION AND ANALYSIS: Two review authors independently extracted data.

MAIN RESULTS: Forty-six trials (4282 women) were included. Twenty-eight trials compared an antihypertensive drug with placebo/no antihypertensive drug (3200 women). There is a halving in the risk of developing severe hypertension associated with the use of antihypertensive drug(s) (19 trials, 2409 women; relative risk (RR) 0.50; 95% confidence interval (CI) 0.41 to 0.61; risk difference (RD) -0.10 (-0.12 to -0.07); number needed to treat (NNT) 10 (8 to 13)) but little evidence of a difference in the risk of pre-eclampsia (22 trials, 2702 women; RR 0.97; 95% CI 0.83 to 1.13). Similarly, there is no clear effect on the risk of the baby dying (26 trials, 3081 women; RR 0.73; 95% CI 0.50 to 1.08), preterm birth (14 trials, 1992 women; RR 1.02; 95 % CI 0.89 to 1.16), or small-for-gestational-age babies (19 trials, 2437 women; RR 1.04; 95 % CI 0.84 to 1.27). There were no clear differences in any other outcomes. Nineteen trials (1282 women) compared one antihypertensive drug with another. Beta blockers seem better than methyldopa for reducing the risk of severe hypertension (10 trials, 539 women, RR 0.75 (95 % CI 0.59 to 0.94); RD -0.08 (-0.14 to 0.02); NNT 12 (6 to 275)). There is no clear difference between any of the alternative drugs in the risk of developing proteinuria/pre-eclampsia. Other outcomes were only reported by a small proportion of studies, and there were no clear differences.

AUTHORS' CONCLUSIONS: It remains unclear whether antihypertensive drug therapy for mild to moderate hypertension during pregnancy is worthwhile.

Treatment of Severe Hypertension

- Indication of treatment
  ≧ 160/110mmHg to prevent intracranial hemorrhage and maternal death
- Woman with hypertensive encephalopathy, hemorrhage, eclampsia

→ parenteral agents to lower mean BP by 25% over minutes to hours

→ further lower BP to 160/100mmHg over subsequent hours

- Aggressive lowering may cause fetal distress
- Agents

  - Labetalol(IV), Hydralazine(IV), Nifedipine(T), Diazoxide(IV)
    relative contraindicated nitroprusside

Hypertensive medications for use during pregnancy

Drug	Route	Dose	Activity Time	Action	Side Effects
First-line agent					
Methyldopa (B)	PO	0.25-1.5 g twice per day	3-5 d	False neurotransmitter	Orthostasis, sleepiness
Second-line agent					
Labetalol (C)	PO/IV	200-1200 mg/d 2 or 3 times per day in divided doses 20-40 mg IV every 30 min as needed	2-4 h/5 min	Nonselective ß-blockade	Tremulousness, headache
Nifedipine (C)	PO	30-120 mg/d	30 min	Calcium channel blocker	Edema, orthostasis, dizziness
Hydralazine (C)	PO/IV	50-300 mg/d 2 or 3 times per day 10 mg IV every 2 h as needed	1-2 h/20-30 min	Direct vasodilator	Lupus-like syndrome with chronic use
HCTZ (C)	PO	12.5-25 mg daily	3-5 d	Diuretic	
Selective ß-blockers (C)	PO	Variable	1-2 wk	Selective ß-blocker	Generally safe; bradycardia; may decrease uteroplacental perfusion, neonatal hypoglycemia at higher doses
Metoprolol (C)	PO/IV	25-150 mg daily	3-5 d	Selective ß-blocker	Bradycardia
Emergency Medications					
IV labetalol as noted above					
IV hydralazine as noted above					
Nifedipine (C) as noted above					
Diazoxide (C)	IV	30-50 mg IV every 5-15 min	2-4 min	Direct vasodilator	Hypotension, hypoglycemia
Nitroprusside (C or D)	IV	0.25-5 µg/kg/min	1-2 min	Direct vasodilator	Hypotension, cyanide toxicity if used > 4 h

IV = intravenously; PO = by mouth; HCTZ = hydrochlorothiazide.

Contraindication ; ACEI, ARB, Direct renin inhibitor in 2nd and3rd trimester

Scott RY, et al. Am J Med 2009;122:890

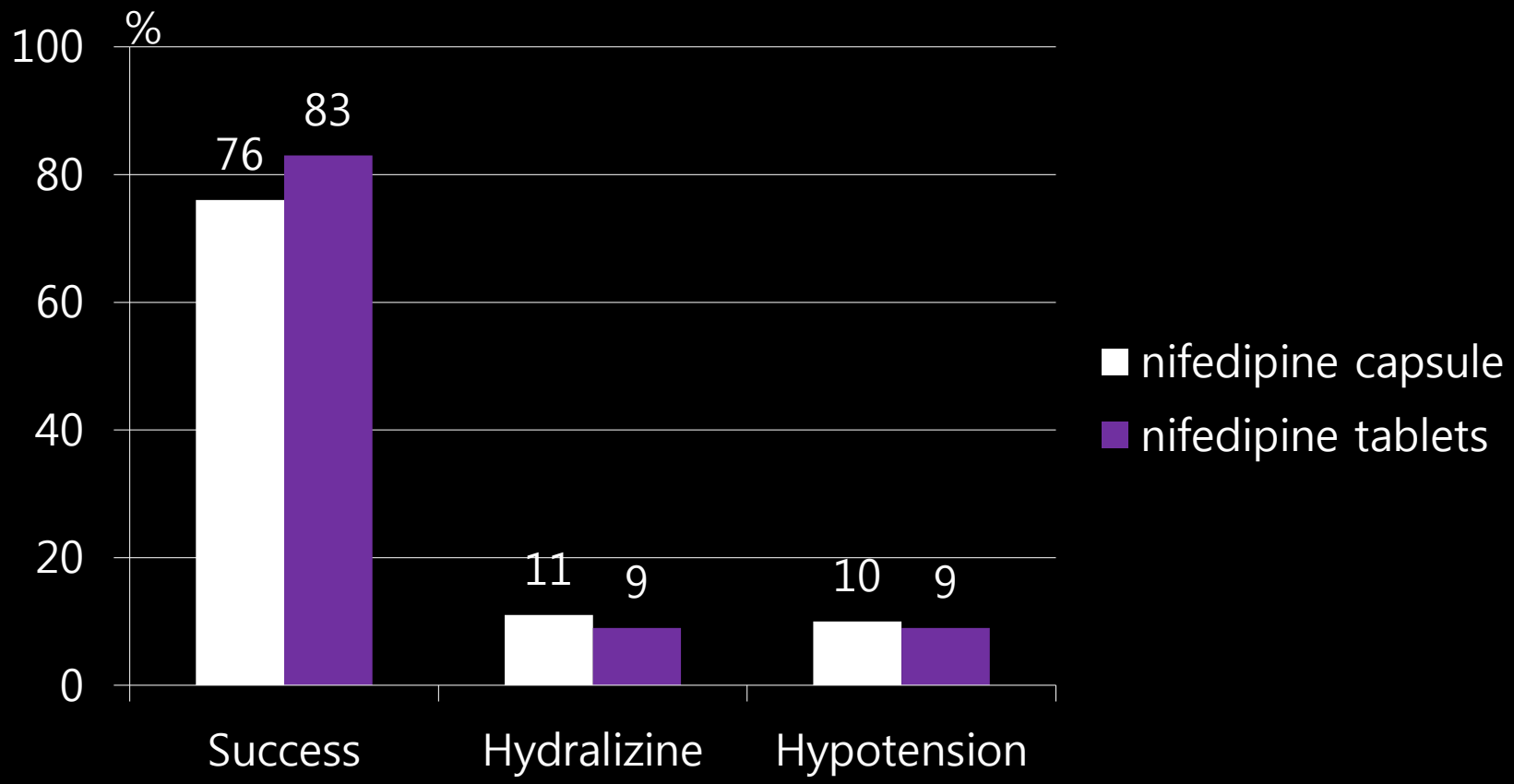
Calcium Channel Antagonists

- **nifedipine**
- nicardipine
- isradipine
- felodipine
- verapamil
- amlodipine ?

Tima P, et al Hypertension 2008;51:960

Percentage of women who received nifedipine capsule or tablets who had successful lowering of blood pressure, who required intravenous hydralazine, or who had hypotension at the end of the 90minute period after treatment for severe hypertension

(10mg nifedipine capsule and tablet, 64 women in second half of pregnancy BP 170/110mmHg)



Mark AB, et al. Am J Obstet Gynecol 2002;187:1046

Maternal and fetal outcomes in women who received nifedipine capsules of tablets for the treatment of severe hypertension in pregnancy

Outcome	Capsules	Tablets	P value
Preeclampsia(%)	53	78	0.04
Entry caused by severe SBP(%)	81	65	0.04
Severe DBP(%)	64	65	0.88
Severe SBP and DBP(%)	45	31	0.13
Medication score	3 3	4	0.21
Fetal death(n)	0	0	
Birth weight(g)	2812	2484	0.1
Small for gestational age: 3rd percentile(n)	3	16	0.1
Small for gestational age: 10th percentile(n)	14	29	0.15

BP; blood pressure
SBP; systolic BP, DBP;diastolic BP

Vanessa AR, et al. atherosclerosis, 2004;175:189

Exposure to Amlodipine in the First Trimester of Pregnancy and During Breastfeeding

(Case report-3 cases)

Case	Ultrasound	Triple test	Birth Weight	Follow -up
1	정상	정상	3,570g	At 3 month old 6.3 kg healthy
2	Ascites, small Gastric chamber	정상	2,600g	At 20months old Weakness of left Arm and intelectual delay
3	G. Sac without Cardiac activity			

Ahn HY et al, Hyper Pre 2007;26:179

Maternal Antihypertensive Medications Usually Compatible With Breastfeeding

- Methyldopa/Labetalol
- Nifedipine/Diltiazem/Verapamil
- Hydralazine
- Hydrochlorothiazide/**spironolactone**
- **Captopril/Enalapril**
- **Nadolol/Oxprenolol/Propranolol/Timolol**

(⟷ atenolol, metoprolol)

Tima P, et al Hypertension 2008;51:960

Alternative Analyses of Risk of Major Congenital Malformations Among Study Infants With Fetal Exposure to ACE Inhibitors during the First Trimester Alone

(cohort of 29,507 infants enrolled in Tennessee Medicaid, born between 1985-2000)

Alternative Analysis	Any Malformation	Cardiovascular Marformation	CNS Marformation
	Risk ratio(95% confidence interval		
Entry study group	2.71(1.72-4.27)	3.72(1.89-7.30)	4.39(1.37-14.02)
ACE inhibitor prescription Filled >14 days after last mentrual period	2.96(1.83-4.79)	4.04(1.98-8.25)	5.45(1.69-17.64)
Broader definition of diabetes	2.77(1.76-4.37)	3.81(1.94-7.49)	4.48(1.40-14.38)
Patent ductus arteriosus excluded	2.51(1.54-4.09)	3.35(1.55-7.27)	4.39(1.37-14.02)

Cooper, W. et al. N Engl J Med 2006;354:2443-2451

Chronic Hypertension

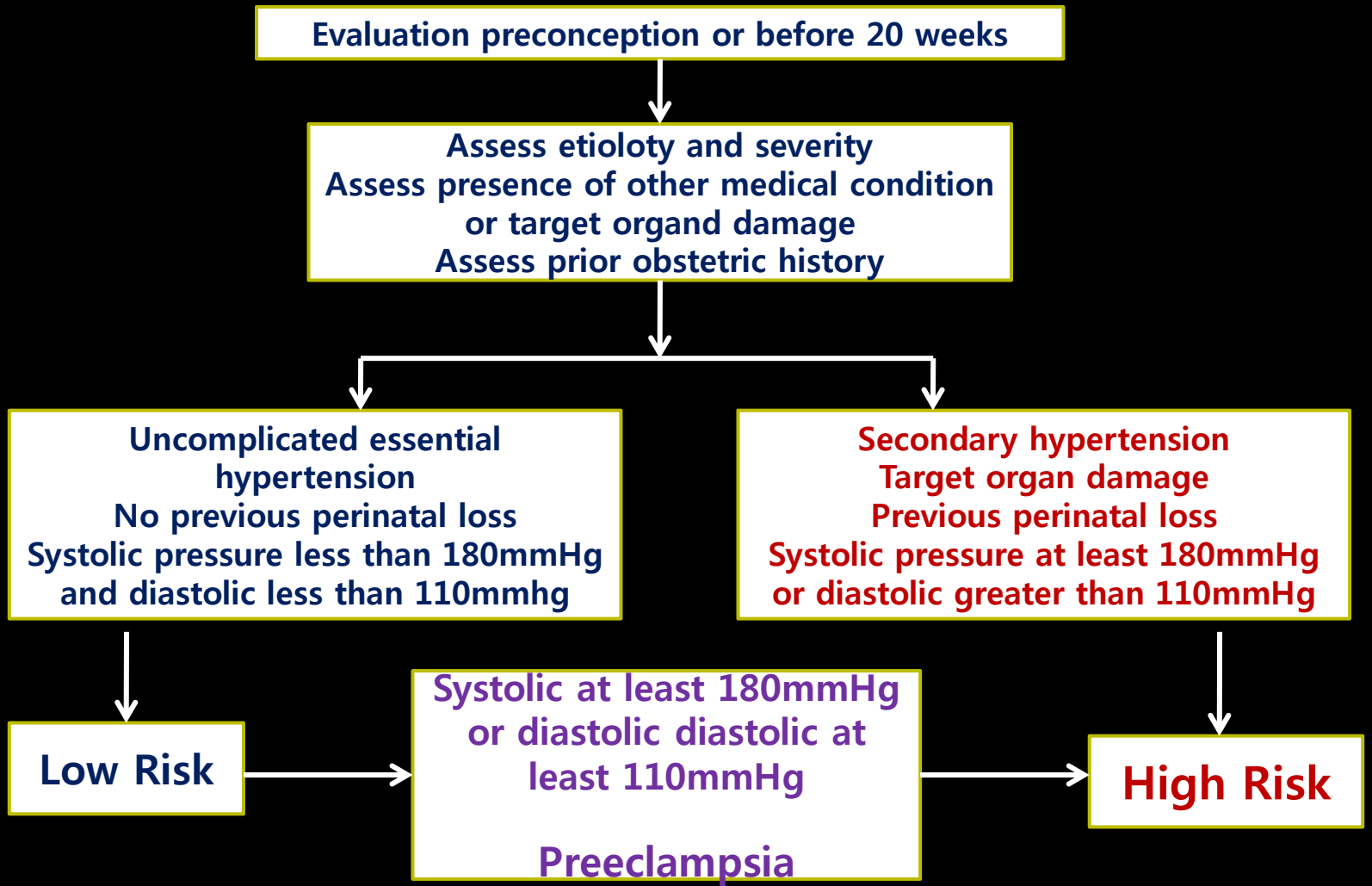
- **Incidence**

  -3% of pregnancy

- **Adverse pregnancy outcomes**

  - superimposed preeclampsia(10-25%/50%)
  - placental abruption(0.7-1.5% / 5-10%)
  - preterm birth prior to 37 weeks(12-34%/62-70%)
  - fetal growth restriction(8-16%/31-40%)

Initial evaluation of women with CH



Target organ damage: left ventricular dysfunction, retinopathy
dyslipidemia, materal age above 40y, microvascular disease, stroke

Baha MS, Obstret Gynecol 2002;100:369

Antepartum management of CH

Pregnant women with chronic hypertension

Low Risk

- No antihypertensive drugs
- Ultrasound examination at 16-20weeks, repeat at 30-32 weeks and monthly after that until term

1. Antihypertensive drugs if severe hypertension develops
2. If preeclampsia develops, if antihypertensive drugs are used, or if there is abnormal fetal growth, then begin immediate fetal testing with non-stress test of biophysical profile. Continue serial testing until delivery

High Risk

- Hospitalization at initial visit
- Antihypertensive drugs are needed to keep systolic below 140mmHg and diastolic below 90mmHg(for women with TOD)
- Ultrasound examination at 16-20 weeks, repeat at 28 weeks and then every 3 weeks until delivery
- Non-stress test and/or biophysical profile at 28weeks and then weekly

1. Hospitalization if there is exacerbation to severe hypertension, if there is preeclampsia, or if there is evidence of abnormal fetal growth
2. Frequent evaluation of maternal and fetal well –being
3. Consider delivery at 36-37 weeks

Target organ damage: left ventricular dysfunction, retinopathy, microvascular disease, stroke, **dyslipidemia, maternal age above 40y**

Baha MS, Obstret Gynecol 2002;100:369

Aims of treatment of CH

- **No evidence that treatment prevents the adverse pregnancy conditions of superimposed preeclampsia and abruption or improves fetal and maternal outcomes**

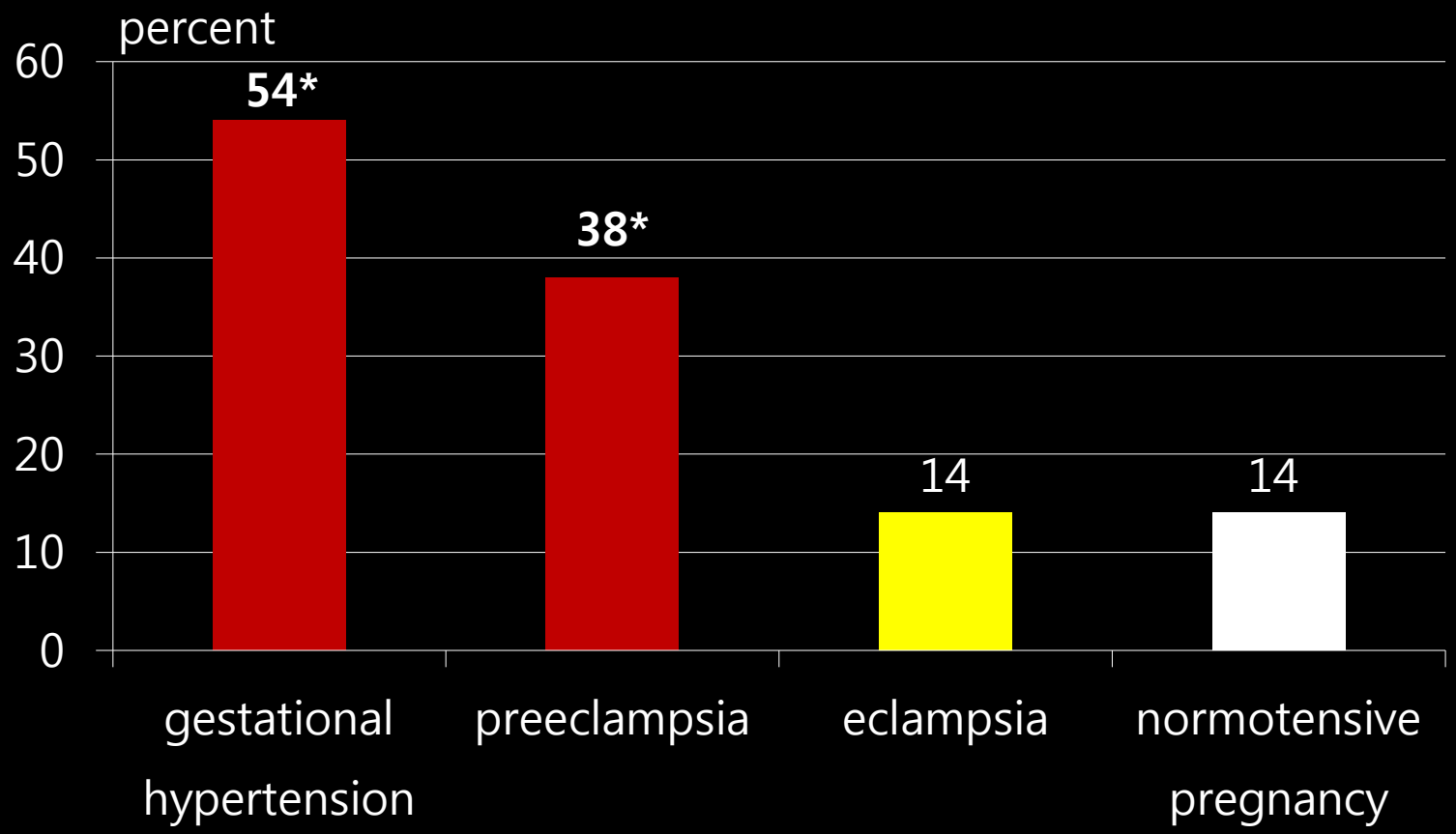
- **Treatment reduces in the development of severe hypertension later in pregnancy.**
- **There are benefits for the reduction of BP <160/110mmHg, above which is a strong risk of stroke. And Maternal morbidity such as renal failure and heart failure in secondary hypertension is improved .**

- **Mean arterial pressure in the first and second trimester is better predictor of subsequent preeclampsia than SBP, DBP, or increase in BP.**

Hypertension in pregnancy, Cambridge clinical guide, 2010

Pregnancy as a window for future health

Long-term hypertension prevalance in the different types of pregnancy-induced hypertension and normotensive pregnancies
(prospective study 1973 to 1991, 702 patients(HP-476 NP-226)



Rafael M, et al. Hyper Pre,2000;19(2):199

Maternal history of PET/eclampsia and risk of cardiovascular disease

Author	Disease	RR(95% CI)
Hannaford et al.	Hypertensive disease	2.35(2.08-2.65)
	Acute MI	2.24(1.42-3.53)
	Chronic IHD	1.74(1.06-2.86)
	Angina pectoris	1.53(1.09-2.15)
	All IHD	1.65(1.26-2.16)
	VTE	1.62(1.09-2.41)
Van Walraven et al.	Thromboembolism	2.2(1.3-3.7)
Wilson et al.	Hypertension	3.98(2.82-5.61)

MI; myocardial infarction, IHD ischemic Heart disease
VTE;venous thromboembolism
PET; preeclampsia

Vanessa AR, et al. atherosclerosis, 2004;175:189

Risk of maternal premature cardiovascular disease, accoording to type of maternal placental syndrome and concomitant presence of poor fetal growth or intrauterine fetal death

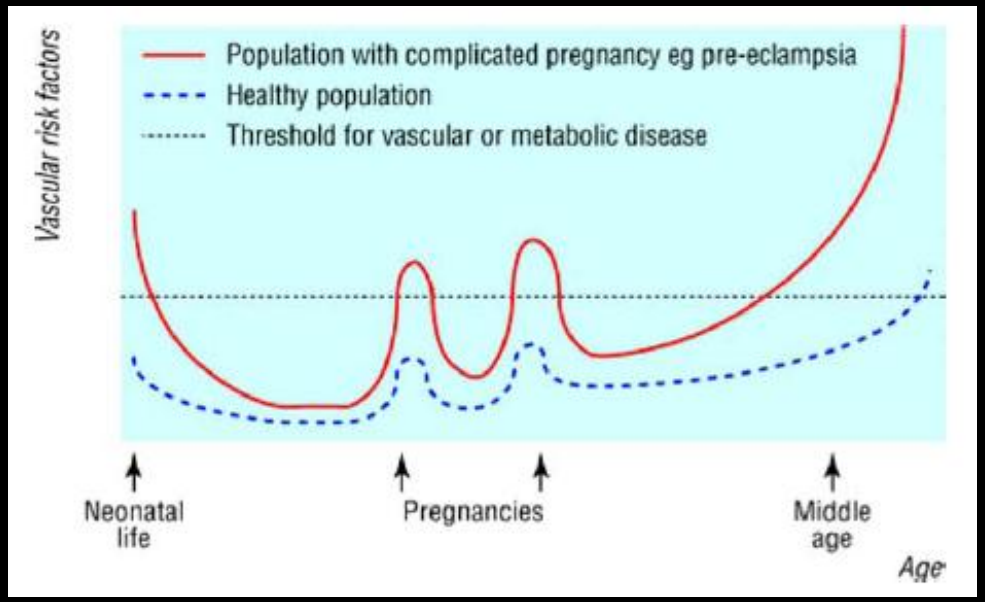
(CHAMPS:population based retrospective cohort study)

	Adjusted HR(95% CI)* For cardiovascular disease
Maternal placental syndrome(n=75380) *	2.0(1.7-2.2)
Placental abruption(n=11156)	1.7(1.3-3.2)
Or infarction(n=9303)	
Gestational hypertension(n=20942)	1.8(1.4-2.2)
Preeclampsia(n=36982)	2.1(1.8-2.4)
Maternal placental syndrome and Poor fetal growth(n=4390)	3.1(2.2-4.5)
Maternal placental syndrome and Intrauterine fetal death(n=1171)	4.4(2.4-7.9)

Joel GR, et al. Lancet 2005;366:1797

Commen hypothesis underlying metabolic syndrome and preeclampsia

- Endothelial dysfunction and activation
- Insulin resistance
- Oxidative stress
- Inflammation



Risk factors for vascular disease are identifiable During excursions into the metabolic syndrome of pregnancy

Vanessa AR, et al. atherosclerosis, 2004;175:189

Take Home messages

- 임신성 고혈압의 빈도가 증가되고 있고 비만 임산부와, 고령 산모의 증가로 가임기 여성을 대상으로 임신 전 혈압 측정이 필요하다.

- 항고혈압제로 methydopa, labetalol이 안정적이나 현실적으로 칼슘길항제에 대한 고려가 필요하다. (nifedipine)

- 합병증이 동반되었던 임산부를 대상으로 심혈관계 질환에 대한 추적 관찰이 필요할 수 있다.