Hypertension in Pregnancy

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Introduction

- Hypertensive disorders of pregnancy are one of the leading causes of maternal mortality
- Worldwide: 50,000 women die each year

Hemodynamic Changes in Normal Pregnancy

- Systemic vascular resistance decreases
- Plasma volume and cardiac output increase
- There is a physiological drop in BP detectable before the end of the first trimester due to vasodilation

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American Heart Association.

AHA SCIENTIFIC STATEMENTS

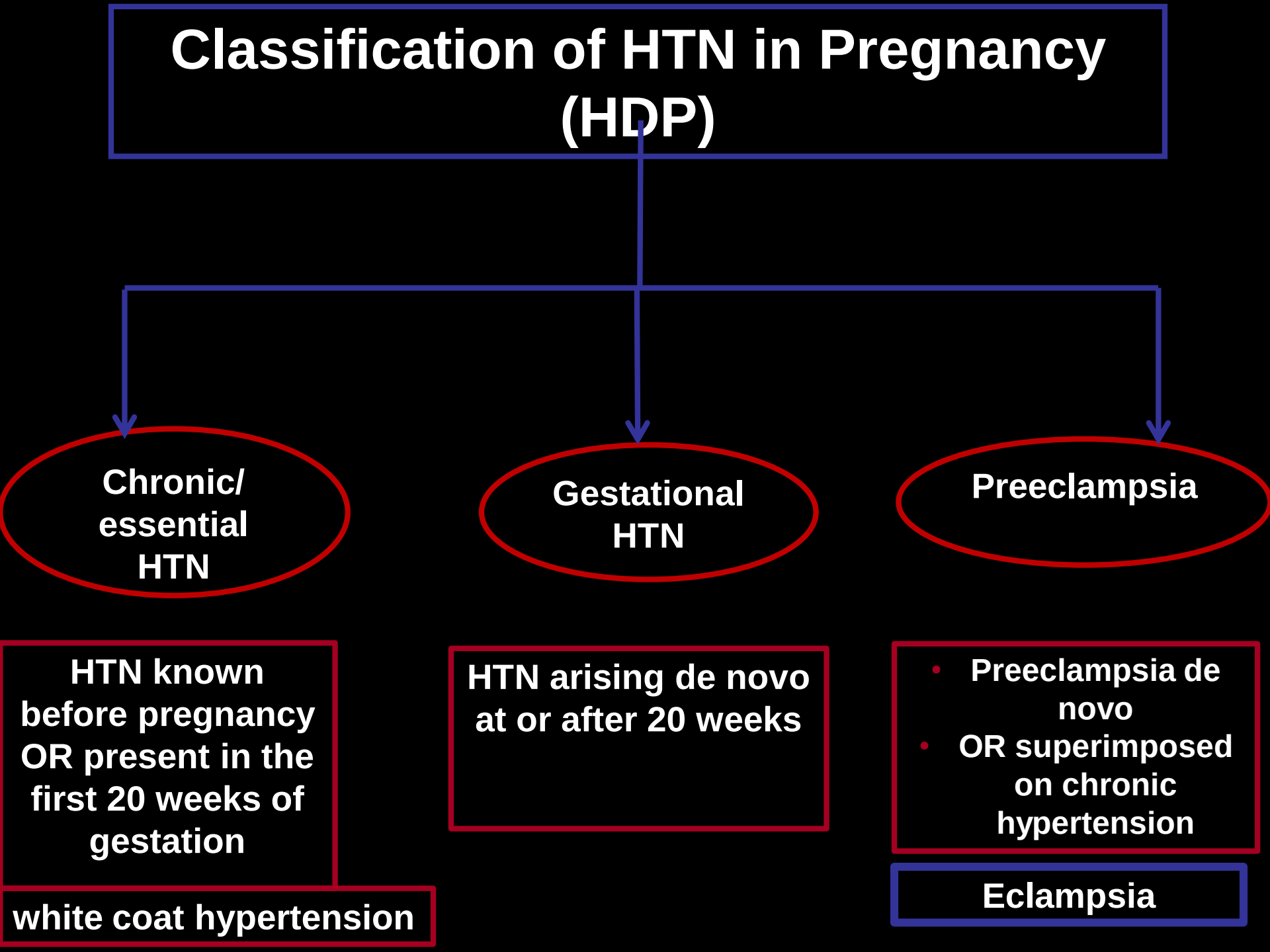
Hypertension in Pregnancy: Diagnosis, Blood Pressure Goals, and Pharmacotherapy: A Scientific Statement From the American Heart Association

- Hypertension one the most common medical complication in pregnancy
- Major cause of maternal/fetal and neonatal morbidity and mortality

- Hypertension is systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mmHg on ≥2 occasions 4 hours apart

- Proteinuria is the presence of ≥300 mg of protein in a 24-hour collection of urine
- OR urinary protein to creatinine ratio of ≥30 mg/mmol 0.3 mg /dl
- OR two readings of at least ++ on dipstick analysis of a midstream or catheter urine specimen

Classification of HTN in Pregnancy (HDP)



Chronic hypertension

- Diagnosed prior to pregnancy or before 20 weeks gestation (and persisting 12 weeks after pregnancy)
- Has doubled in prevalence over the last decade and now complicates at least 100,000 pregnancies (2.36%) in the United States each year
- The diagnostic criteria for hypertension in pregnancy were similar to those for non-pregnant individuals and included a systolic blood pressure (SBP) of ≥ 140mm Hg or a diastolic blood pressure (DBP) of ≥ 90mm Hg on at least 2 separate occasions more than 4 hours apart for <u>mild hypertension</u>
- SBP ≥ 160 mm Hg or a DBP ≥ 110 mm Hg for <u>severe hypertension</u>

Classification of chronic hypertension

- **Primary (idiopathic) or essential**
- **Secondary due to**

Renal :glomerulonephritis, renal artery stenosis ,Polycystic kidneys .. etc

Endocrine: crushing's syndrome ,Conn's syndrome ,Phaeochromocytoma , Thyrotoxicosis..etc

Vascular: coarctation of the aorta

What are the effects of HTN on Pregnancy

- **Maternal :**
- **Preeclampsia up to 50 % of those with severe chronic HTN**
- **Placental abruption up to 10%**
- **Cesarean delivery**
- **Cerebrovascular accidents**
- **Acute renal failure**
- **Congestive heart disease**
- **Liver failure**
- **DIC**
- **Death**

Fetal complications :

Fetal growth restriction

Preterm birth

Perinatal mortality

Gestational hypertension

Hypertension after 20 weeks of gestation with no proteinuria
High BP>=140/90 in 2 reading 4 hours apart

Preeclampsia

- **Multisystem syndrome developing during the second half of pregnancy**
- **characterized by hypertension and proteinuria OR in the absence of proteinuria the finding of maternal organ dysfunction**

Preeclampsia superimposed on chronic hypertension

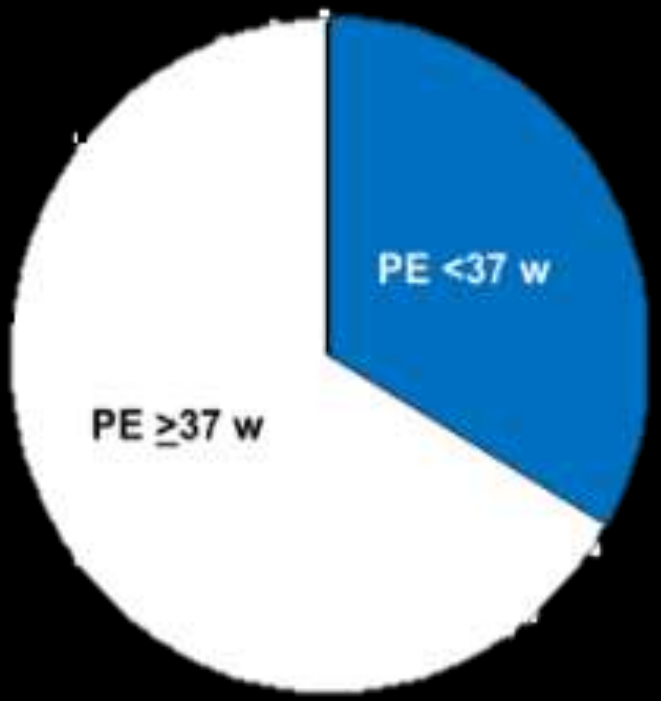
PET superimposed on chronic hypertension :
History of hypertension before conception
the presence of hypertension before 20 weeks
Gestation and proteinuria OR maternal organ dysfunction should develop after 20 weeks gestation

Maternal organ dysfunction

- Renal insufficiency – serum creatinine ≥ 90 µmol/L or 1,04 mg/dl
- Hepatic dysfunction – high serum hepatic transaminase levels (≥2 times the upper limit of normal) and / or severe persistent upper abdominal pain unresponsive to medication
- Neurological complications - eclampsia, stroke, confusion, hyperreflexia accompanied by clonus, severe headache accompanied by hyperreflexia, blindness or persistent visual scotomata
- Hematological complications - platelet count <100,000/dL
- Disseminated intravascular coagulation (DIC) or hemolysis
- Pulmonary edema

Prevalence

- In 2-5% of pregnancies
- The rate depends on the demographic characteristics of the population in Black women the rate is 2-3 times higher than in White women



In one third of the cases the condition leads to delivery at <37 weeks' gestation (preterm PE) and in two thirds delivery occurs at ≥37 weeks (term PE)

Maternal complications of Preeclampsia

- Eclampsia (convulsions or coma in a woman with PET
- Brain hemorrhage or stroke
- Disseminated intravascular coagulation (DIC)
- HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets)
- Other severe complications include:
  - Brain edema
  - Blindness
  - Renal failure
  - Hepatic failure
  - Pulmonary edema
  - Death

Long term complications

Doubling in lifetime risk of cardiovascular disease (CVD)
Including: Hypertension
Ischemic heart disease
Stroke
Death from CVD

Fetal complications

- Reduced blood supply to the placenta
- Impairment in fetal growth oxygenation and increased risk of stillbirth
- Premature delivery for maternal and / or fetal indications
- Babies are subjected to the additional risks arising from prematurity: - neonatal death
  -brain hemorrhage
  -seizures
  -respiratory and feeding difficulties, jaundice, retinopathy, and prolonged hospitalization

PEt and eclampsia are implicated in about 25% of stillbirths and neonatal deaths and 15% of growth restricted neonates

Childhood compications

Children exposed to PE before birth compared to those born after normal pregnancy have

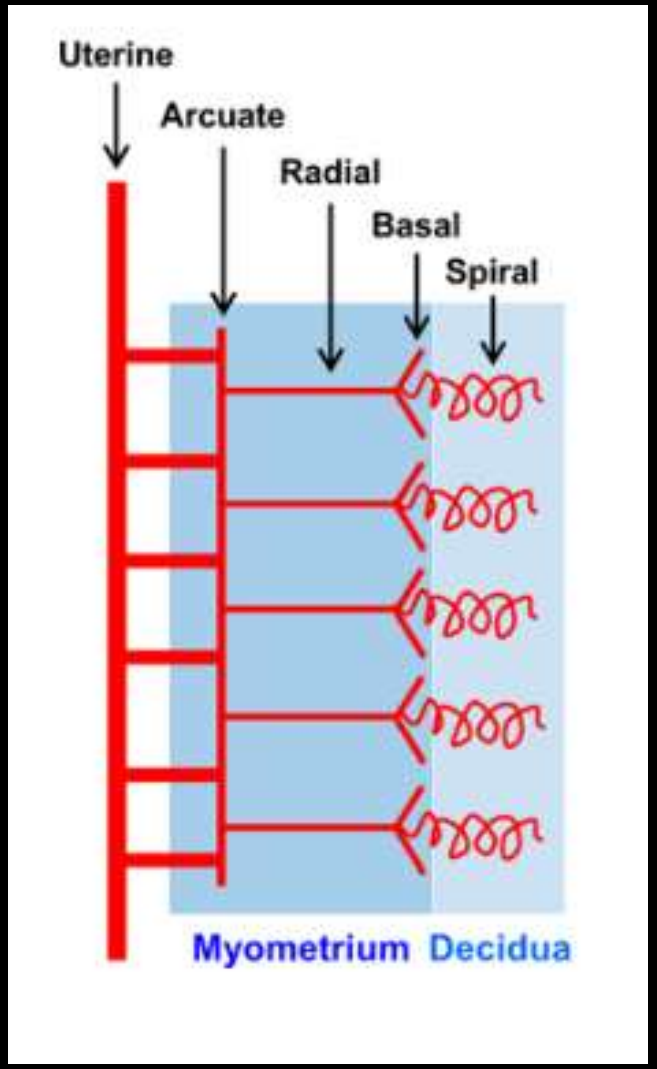
- **a doubling in risk of cerebral palsy**

(this risk is mediated through premature birth growth restriction or both)

- **Higher blood pressure**
- **Body mass index**
- **Increased risk for CVD**
- **Diabetes in adult life**

Pathogenesis

- In pregnancy the blastocyst implants into the maternal endometrium
- The outer layer of the blastocyst develops into the trophoblast
- This differentiates into villous trophoblasts and extravillous trophoblasts



- Villous trophoblasts give rise to chorionic villi that transport nutrients and oxygen between the fetus and the mother
- Extravillous trophoblasts which invade and transform the spiral arteries

The trophoblasts replace the endothelial lining and destroy the musculoelastic tissue in the walls of the spiral arteries

so that they are converted from tortuous narrow muscular vessels into large non-muscular channels thereby increasing maternal blood flow to the placenta

This physiological process occurs in two stages:

- **The first wave of trophoblastic invasion involves the spiral arteries in the decidua (endometrium of pregnancy) and starts at 8 weeks of gestation**
- **The second involves the spiral arteries in the inner third of the myometrium and occurs at 14-18 weeks**

In PEt ⇒ the physiologic process of placentation is impaired
There is trophoblastic invasion in 50-70% of spiral arteries
does not extend into the myometrial segments and is confined to the decidual part of the vessels

- **The spiral arteries are less dilated than the normally transformed arteries and the blood supply the placenta is reduced**
- **The reason why in some pregnancies there is failed placentation is unknown but genetic and immunological reasons may be implicated**

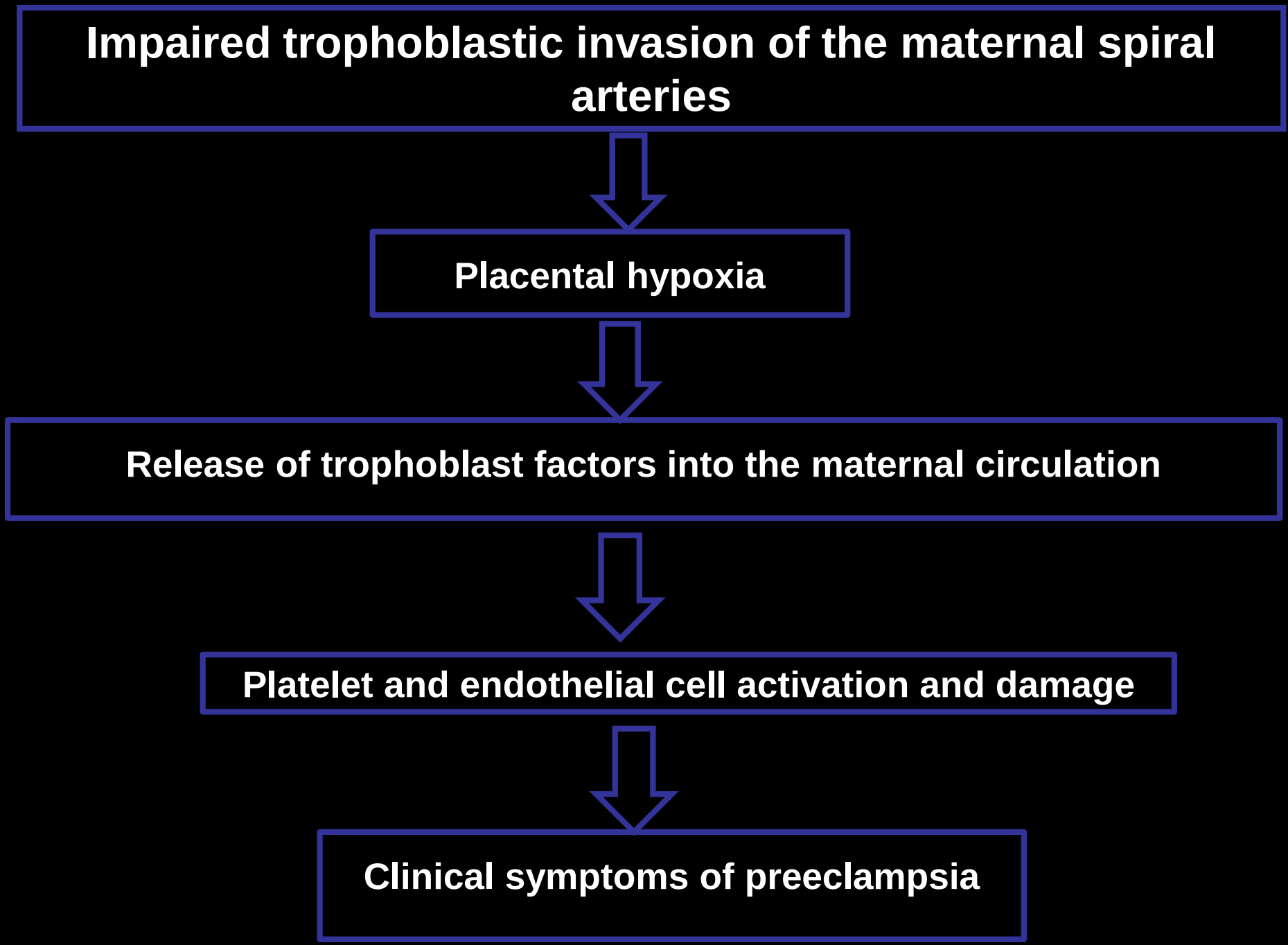
Reduced perfusion of the placenta causes oxidative stress ⇒ release of trophoblast-derived factors ⇒ enter the maternal circulation and cause endothelial cell damage in:

- The kidney
- liver
- brain and placenta

** exaggerated inflammatory response which underlines many of the changes observed in PE

Placental-derived factors released in response to stress include :
the anti-angiogenic protein sFLT1(which is increased in PEt) whereas the circulating concentration of the angiogenic placental growth factot (PlGF) is reduced in PE This angiogenic imbalance results in increased maternal vascular inflammation and generalized endothelial dysfunction

- In preterm PEt which is characterized by impaired placentation
- In term PEt placentation is usually normal
- In women with medical disorders, such as chronic hypertension, there is endothelial dysfunction even before pregnancy in such cases PE can develop in the absence or lower degree of impaired placentation


Impaired trophoblastic invasion of the maternal spiral arteries
Placental hypoxia
Release of trophoblast factors into the maternal circulation
Platelet and endothelial cell activation and damage
Clinical symptoms of preeclampsia

Prevention of preeclampsia

- In 1543 BC the Egyptians used extracts from the willow tree for pain relief
- In 400 BC Hippocrates used powder made from the bark and leaves of the willow tree for headaches, pains and fevers
- In 1828 Johann Buchner at the University of Munich, extracted the active ingredient of the willow plant and called it salicin (Latin term for willow)
- In 1915 Bayer developed aspirin tablets
- In 1979 Crandon and Isherwood reported that women who had taken aspirin regularly during pregnancy were less likely to have PE than women who had not

Prevention of preeclampsia

The rate of PE is not reduced by

1. **bed rest**
2. **restriction of physical activity or dietary manipulations, including restriction of salt intake or supplementation with magnesium, zinc, folate vitamins C, D and E or fish oil**

- **Dietary calcium supplementation in women with low calcium diets may halve the rate of PE**
- **Preliminary data suggest that prophylactic use of pravastatins may also benefit women at high-risk of PEt**

Low dose aspirin

- The prophylactic use of low-dose aspirin in the prevention of PE has been studied extensively
- A meta-analysis of trials showed that the administration of low-dose aspirin in high-risk pregnancies resulted in a 10% lower incidence of PE However in most studies aspirin was started after 16 weeks' gestation and at a dose of <100 mg/day
- Other meta-analyses showed that aspirin started before 16 weeks resulted in halving the rate of PE, whereas aspirin started after 16 weeks did not have a significant benefit
- In addition, the beneficial effect of aspirin was dose dependent, with a greater reduction in the incidence of PE being associated with a dose of >100 mg/day

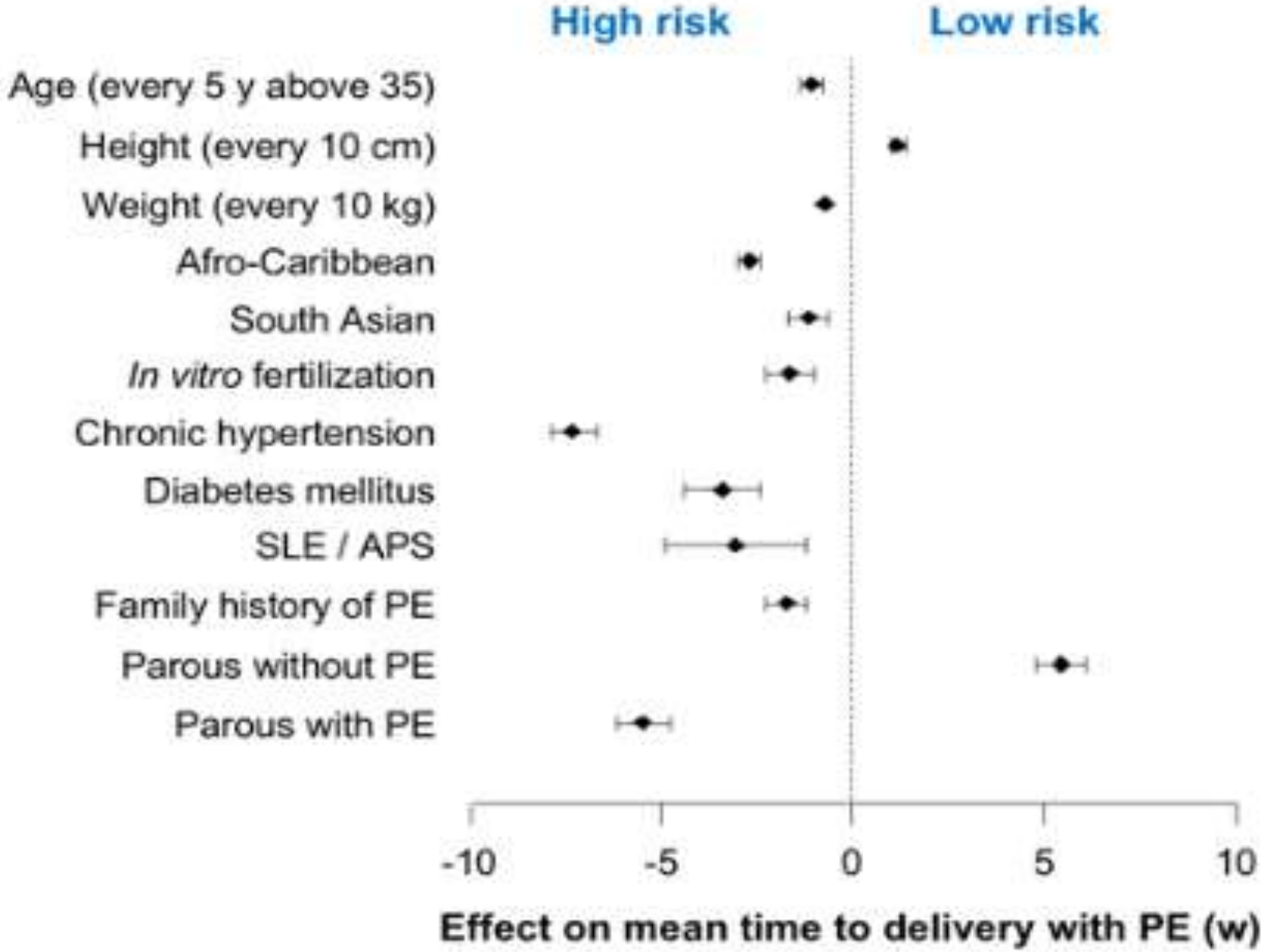
ASPRE trial

- International multicenter study
- Routine screening for preterm PE was carried out at 11-13 weeks gestation by the FMF algorithm that combines maternal factors and biomarkers in about 27,000 singleton pregnancies

Use of aspirin was associated with a 62% reduction in the incidence of preterm PE and 82% reduction in the incidence of PE at <34 weeks' gestation

Maternal risk factors

- Advancing maternal age
- Increasing weight
- Afro-Caribbean and South Asian racial origin
- Medical history of chronic hypertension
- Diabetes mellitus
- Systemic lupus erythematosus or antiphospholipid syndrome
- Conception by in vitro fertilization
- family history or personal history of PE
- The risk of PE in women in their first pregnancy is three times higher than in women with previous pregnancies that were not complicated by PE
- Women who had PE in a first pregnancy are up to 10 times more likely to develop PE in a second pregnancy
- The risk for PE is lower in tall than in short women
- Decreased in parous women with no previous PE
- The protective effect against PE of a previous pregnancy without PE, decreases with the time interval between the previous and the current pregnancy so that after 15 years the risk of PE is about the same as that in nulliparous women


High risk
Low risk
Age (every 5 y above 35)
Height (every 10 cm)
Weight (every 10 kg)
Afro-Caribbean
South Asian
In vitro fertilization
Chronic hypertension
Diabetes mellitus
SLE / APS
Family history of PE
Parous without PE
Parous with PE
-10
-5
0
5
10
Effect on mean time to delivery with PE (w)

Screening at 11-13 weeks

Combined screening by maternal risk factors, mean arterial pressure MAP, uterine arteries UTPI and PLGF predicts about 90% of early PE (<34 weeks), 75% of preterm PE (<37 weeks) and 45% of term PE (≥37 weeks)

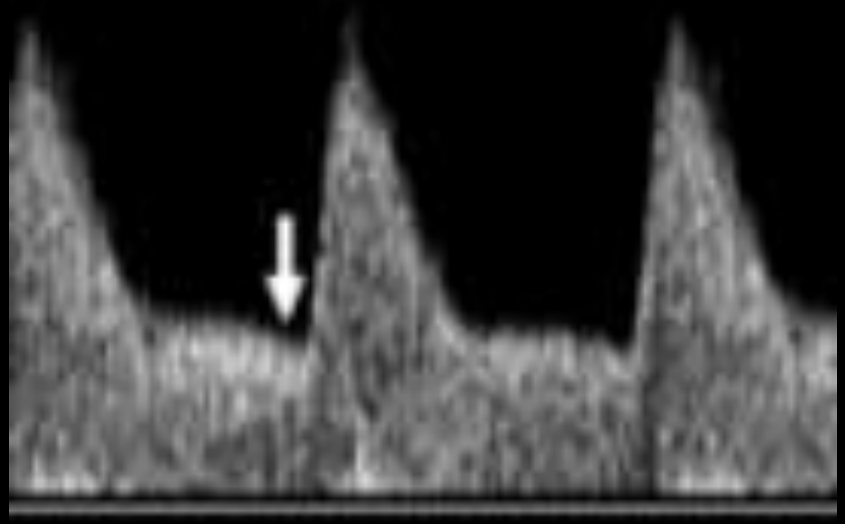
Mean arterial pressure (MAP)

In the prediction of PE measurement of MAP is more useful than measurement of systolic and diastolic blood pressure

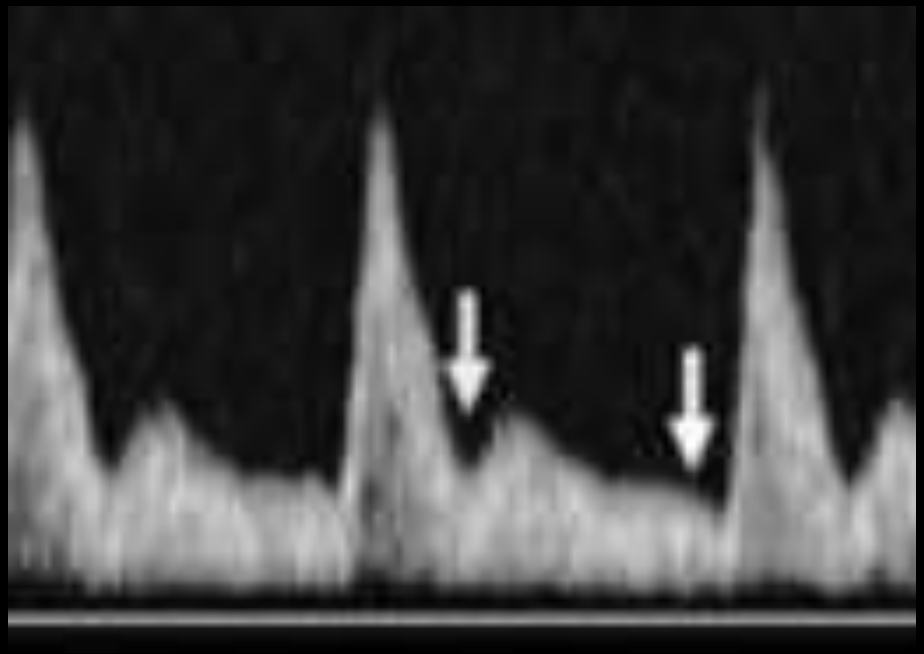
The MAP is defined as the average arterial pressure during a single cardiac cycle and is calculated from the following formula: MAP = 2/3 diastolic blood pressure + 1/3 systolic blood pressure

Measurement of uterine artery PI (UTPI)

The UTPI can be measured by either transabdominal or transvaginal sonographey



Waveform has good end-diastolic flow



shows high resistance of flow with early diastolic notch and low end-diastolic flow

Placental growth factor PIGF

- Measure the amount of PIGF in blood plasma or serum

PIGF is a protein involved in placental angiogenesis (the development of new blood vessels)

- In normal pregnancy PGIF levels rise and peak at 26-30 weeks
- PIGF levels do not rise during pregnancy may be placental dysfunction
- In Preeclampsia level of PIGF can be abnormally low

Soluble FMS-like tyrosine kinase-1 (sFlt-1)

- an anti-angiogenic factor that is thought to play a central role in the pathogenesis of PE
- Exogenous sFLT-1 administered to pregnant rats induces hypertension, proteinuria, and glomerular endotheliosis

Pregnancy associated plasma protein-A (PAPP-A)

PAPP-A is produced by the placenta and is thought to play an important role in placental growth and development

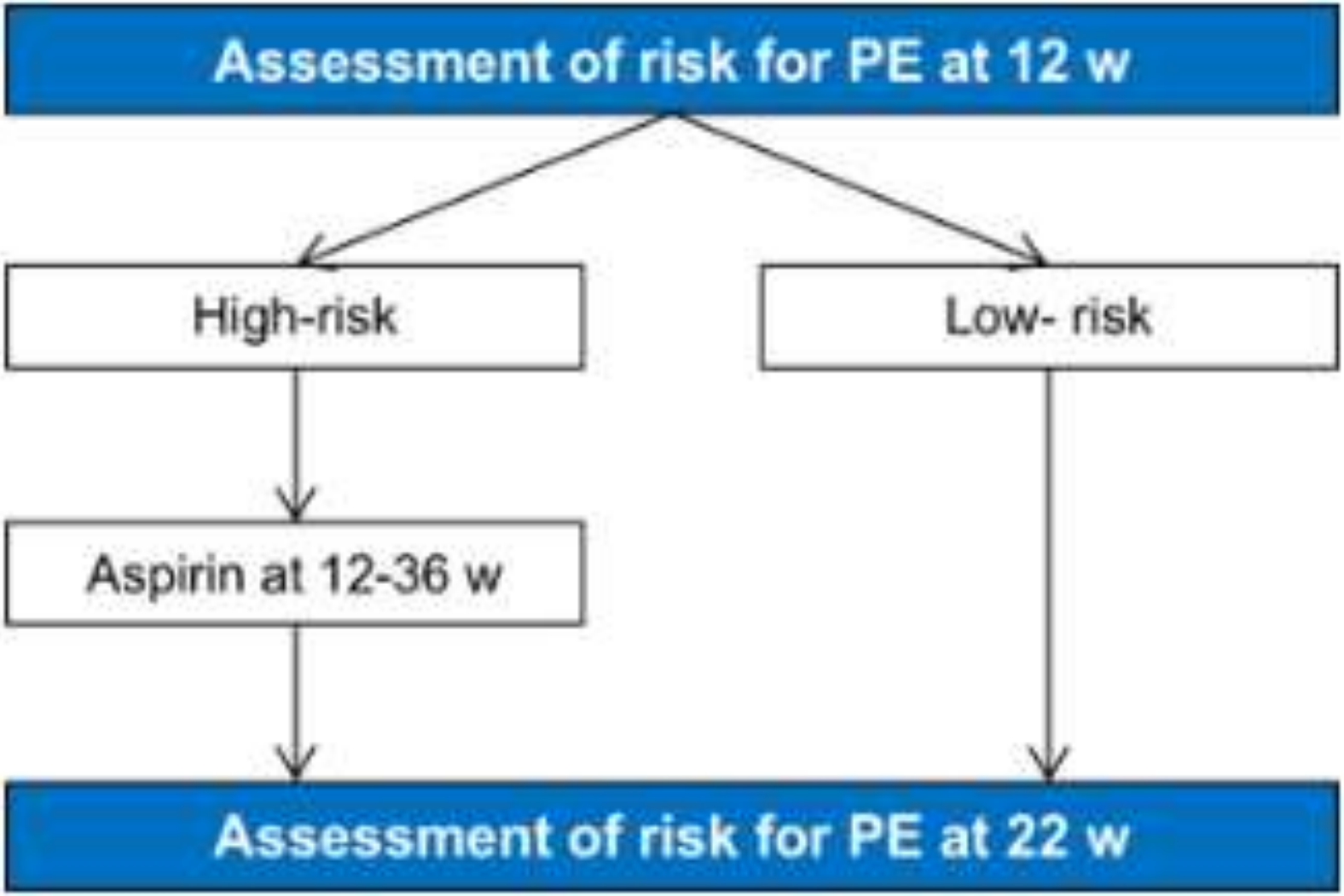
Maternal serum levels of PAPP-A in the first-trimester of pregnancy are decreased in pregnancies with fetal trisomies 21, 18 and 13

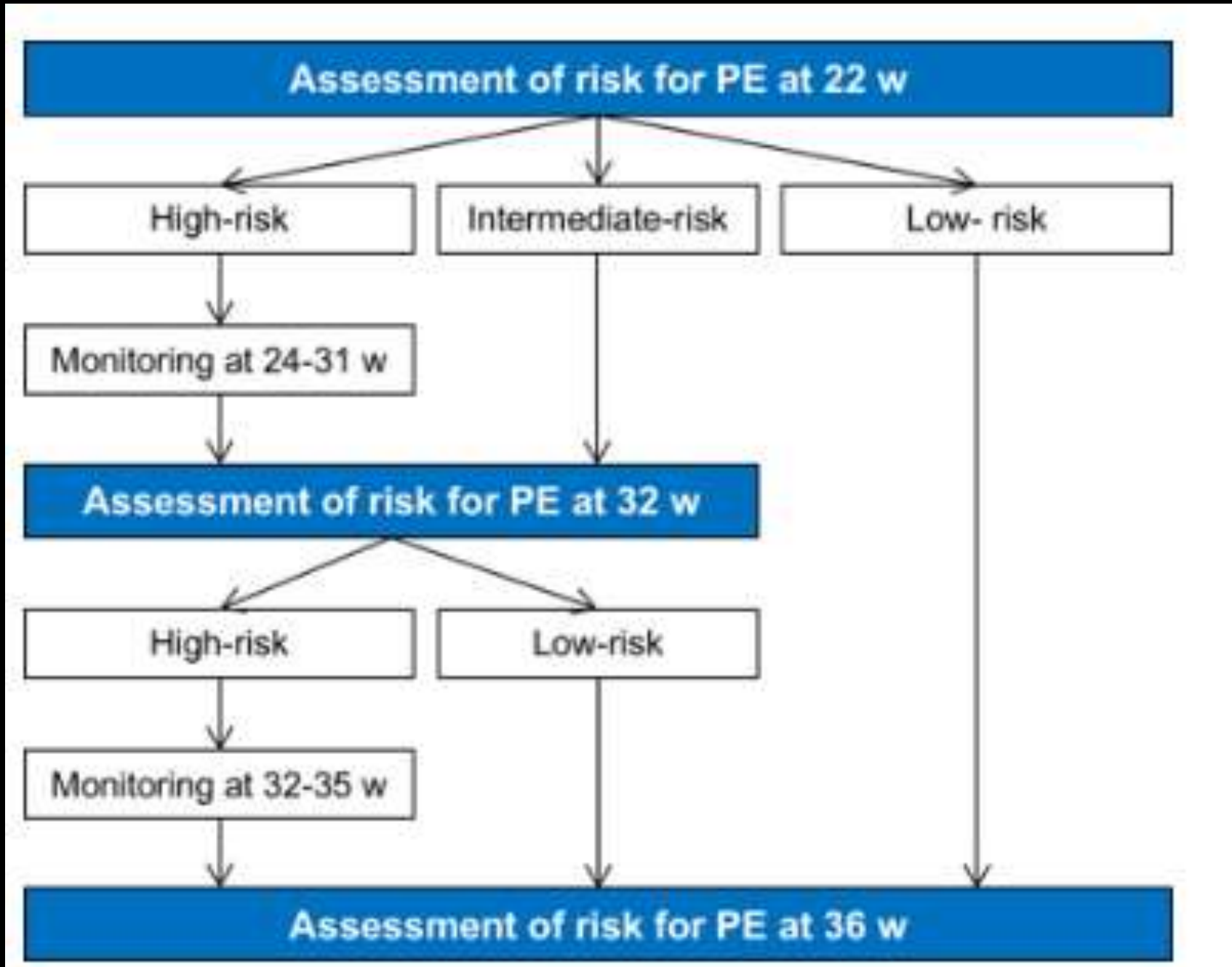
In pregnancies that develop PE, compared to unaffected pregnancies, maternal serum PAPP-A is decreased during the first-trimester, not significantly different in the second-trimester and increased in the early third-trimester

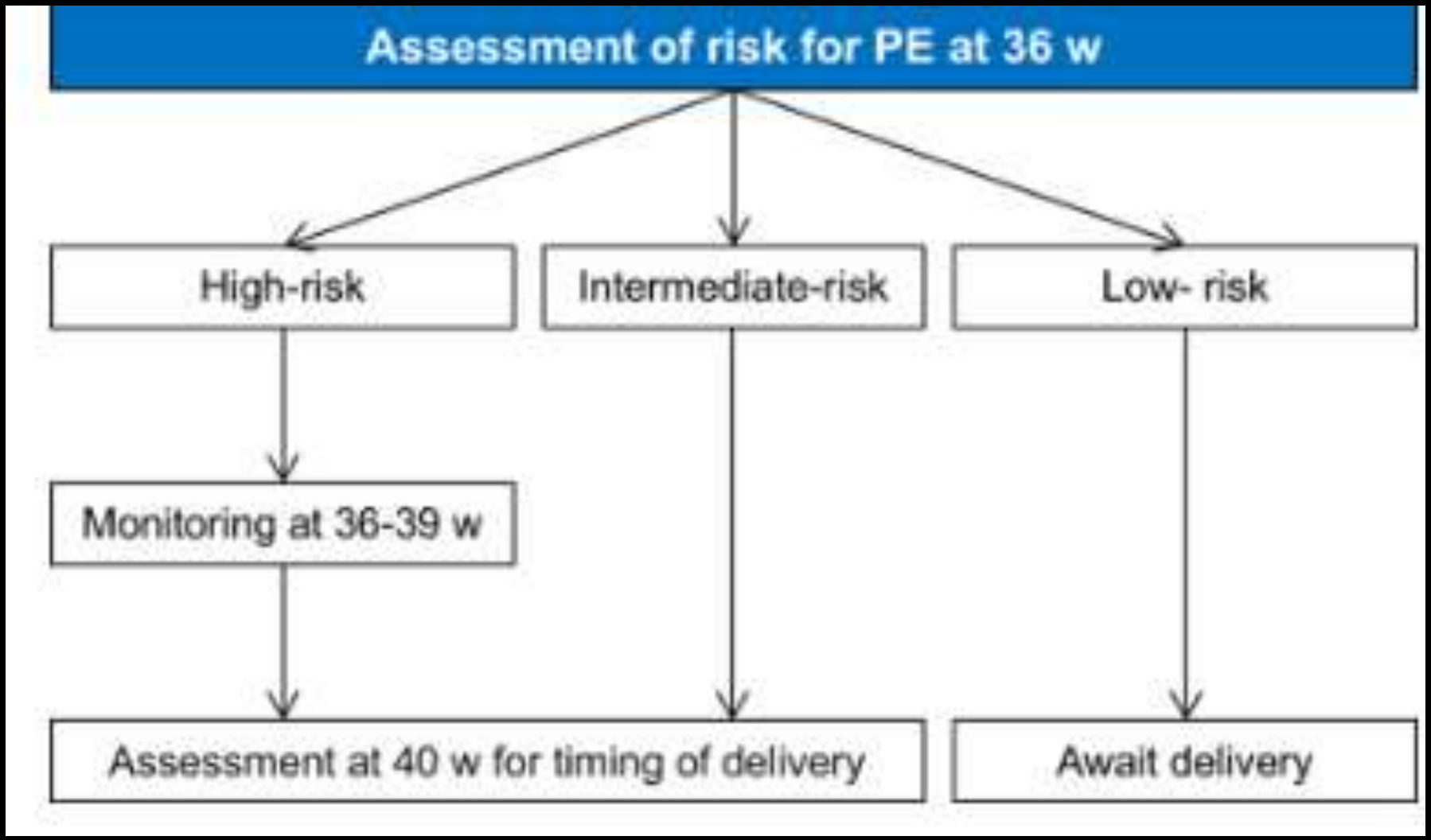
Screening at 20-24 weeks

Screening at 30-34 weeks

Method of screening	Detection rate		
	PE <34 w	PE <37 w	PE ≥37
Maternal factors	52%	47%	36%
Maternal factors plus:			
MAP	72%	60%	44%
MAP, UTPI	96%	80%	44%
MAP, PLGF	94%	75%	44%
MAP, sFLT-1	77%	65%	44%
MAP, UTPI, PLGF	94%	85%	45%
MAP, UTPI, PLGF, sFLT-1	100%	85%	45%


Assessment of risk for PE at 12 w
High-risk
Low- risk
Aspirin at 12-36 w
Assessment of risk for PE at 22 w


Assessment of risk for PE at 22 w
High-risk
Intermediate-risk
Low- risk
Monitoring at 24-31 w
Assessment of risk for PE at 32 w
High-risk
Low-risk
Monitoring at 32-35 w
Assessment of risk for PE at 36 w


Assessment of risk for PE at 36 w
High-risk
Intermediate-risk
Low- risk
Monitoring at 36-39 w
Assessment at 40 w for timing of delivery
Await delivery

Managements

Chronic hypertension:

- **STOP :**
- **ACE inhibitors or ARBs (within 2 days of notification of pregnancy**
- **Diuretics**

ACE case fetal renal damage
ARB cases fetal renal failure lung dysplasia cranial hypoplasia
Limb contractures and fetal death

All these outcomes may de due to fetal hypotension and reduced renal blood flow perfusion
kidney ischemia – anuria --- oligohydramnios

Antenatal appointments

Weekly if HTN poorly controlled or admission

Every 2 to 4 weeks if well controlled

Laboratory findings

- Urine analysis ---proteinuria
- Microangiopathic hemolytic anemia---elevated serum lactate dehydrogenase LDH or decreased serum Hepatoglobin
- Elevated hematocrit ---due to third spacing fluid
- Elevated serum creatinine
- Elevated serum uric acid
- Elevated serum transaminases
- Thrombocytopenia
- Prolonged prothrombin and partial thromboplastin
- Decreased fibrinogen
- Increased fibrin degradation products

Treatment of chronic hypertension in pregnancy

- Start antihypertensive SBP>= 140 mmHg , DBP>=90 mmHg
- Consider labetalol
- Consider Nifedipne for women in whom labetalol is not suitable
- Consider methyldopa if both labetalol and Nifedipne are not suitable
- Offer pregnant women with chronic hypertension aspirin 75 mg-150 mg once at night from 12 week

Antihypertensive therapy:

Treating the hypertension is mainly to reduce the maternal complications

It will not improve fetal condition

Acute treatment of severe hypertension:

Hydralazine: 5mg IV repeated every 20-30 min.

Nifedipine: 10mg orally repeated at 30 min. IV infusion can be used in severe cases.

Labetalol:10-20mg IV .

The dose can be doubled every 10 minutes if proper response is not achieved.

Magnesium Sulphate should be given in the management of all cases of severe preeclampsia to prevent eclampsia

Time of delivery

In chronic hypertension no induce delivery before 37 weeks if
BP lower 160/110
After 37 weeks depends on senior obstetrician decision

If early birth is necessary offer :
Antenatal corticosteroids
Magnesium sulfate

HELLP syndrome

- **Hemolysis : identified by burr cells and schistocytes**
- **Thrombocytopenia**
- **Elevated liver function tests**

Eclampsia

The occurrence of tonic-clonic convulsions (without any neurological disease) in a woman with pre-eclampsia

Incidence: 5 in 10 000 deliveries and 1-2% of severe PE cases
High maternal and fetal mortality
It can occur antenatally, intra-partum and post-partum
The pathophysiology is cerebral vasospasm leading to ischemia and cerebral edema

Management of eclampsia

- During seizure: Maintain airway, Administer oxygen and avoid supine hypotension
- Anticonvulsant therapy:
- Magnesium sulfate 4-6 g IV followed by a maintenance infusion of 1-2 g / h
- Diazepam 20mg IV followed by a maintenance infusion as required
- Phynenton
- Anticonvulsant should be continued for at least 24 h after the last convulsion
- CS is indicated unless the mother is in active labour

Magnesium Sulfate ($MgSO_4$)

- It can be given IV or IM or SC
- The therapeutic level is 4-7mEq/L
- The total dose of $MgSO_4$ should not exceed 24 gms in 24 hours
- The dose of $MgSO_4$ is monitored by:
- Preserved patellar reflex. (7-10 mEq/L)
- Respiratory rate >16/min. (10-13 mEq/L)
- Urine output >100ml/4hours. (15-25 mEq/L)
- Serum Mg++ level.
- Is stopped 24 hours after delivery
- Antidote is ca gluconate

Thank you