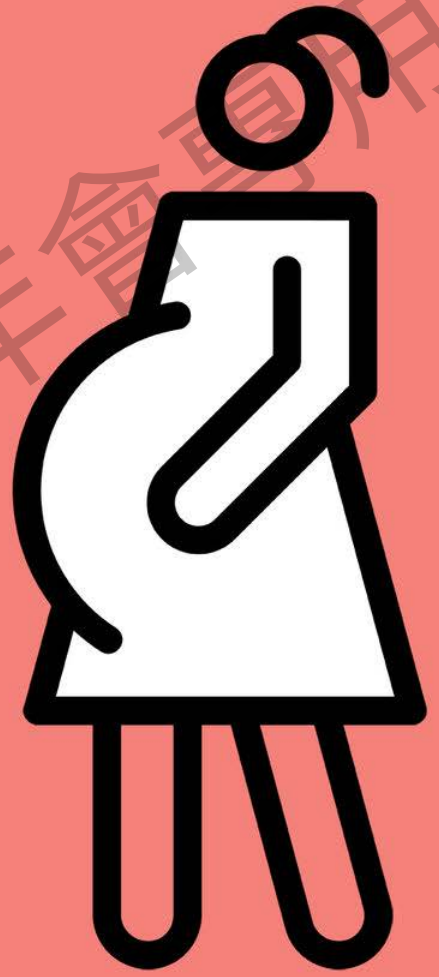
Preeclampsia and Peripartum Cardiomyopathy

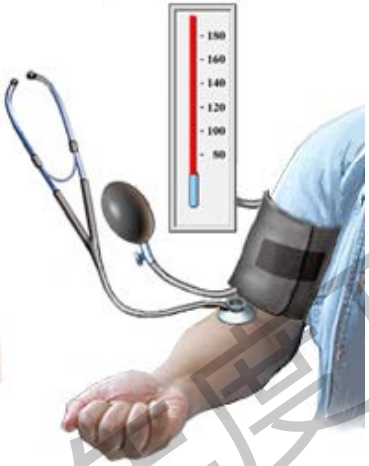


台大醫院婦產部
康巧鈺 醫師
2022/8/13

Preeclampsia

Sudden weight gain

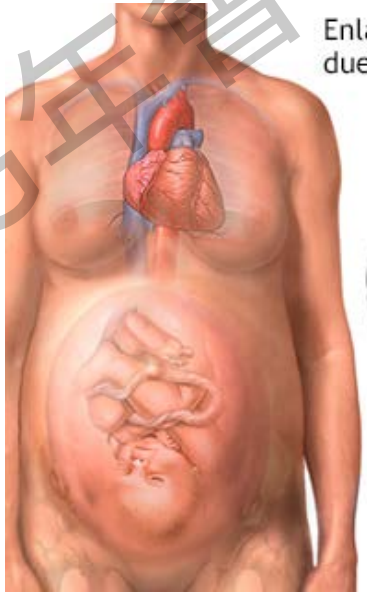
High blood pressure

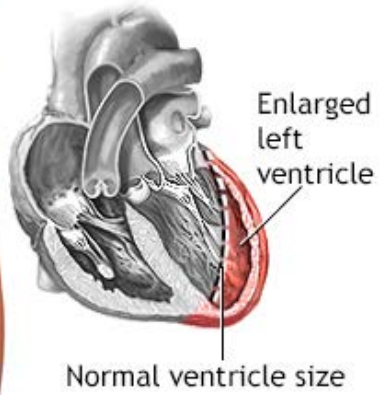


Edema

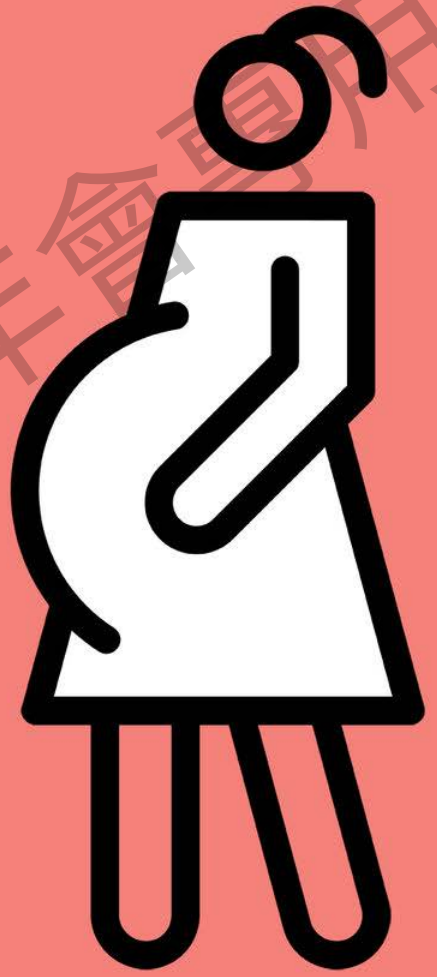
Peripartum cardiomyopathy

Enlargement of left ventricle due to dilated cardiomyopathy





Preeclampsia



Preeclampsia

- Preeclampsia is a **multiorgan disease** characterized by the development of **hypertension**, along with **proteinuria or end organ dysfunction**
- Preeclampsia complicates **2–8%** of pregnancies globally
- Leading cause of **maternal and perinatal morbidity and mortality**
- **Early and late onset** preeclampsia

Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020 Jun;135(6):e237-e260.

Diagnosis criteria

Hypertension

- SBP > 140mmHg, DBP > 90mmHg (x2, at least 4 hours)
- SBP > 160mmHg, DBP > 110mmHg

1

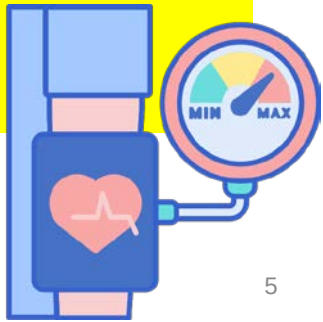
Proteinuria

- ≥ 300mg/24hr urine collection
- Protein/creatinine ratio ≥ 0.3
- Dipstick +2

2

No Proteinuria

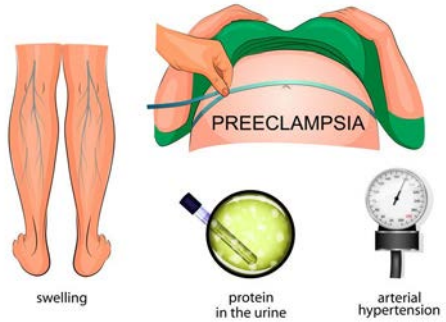
- **Thrombocytopenia**: ≤ 100,000/uL
- **Renal insufficiency**: Cr 1.1 mg/dL or ↑2X
- **Impaired liver function**: liver transaminases ↑ 2X
- **Pulmonary edema**
- **New-onset headache**



Risk Factors for Preeclampsia

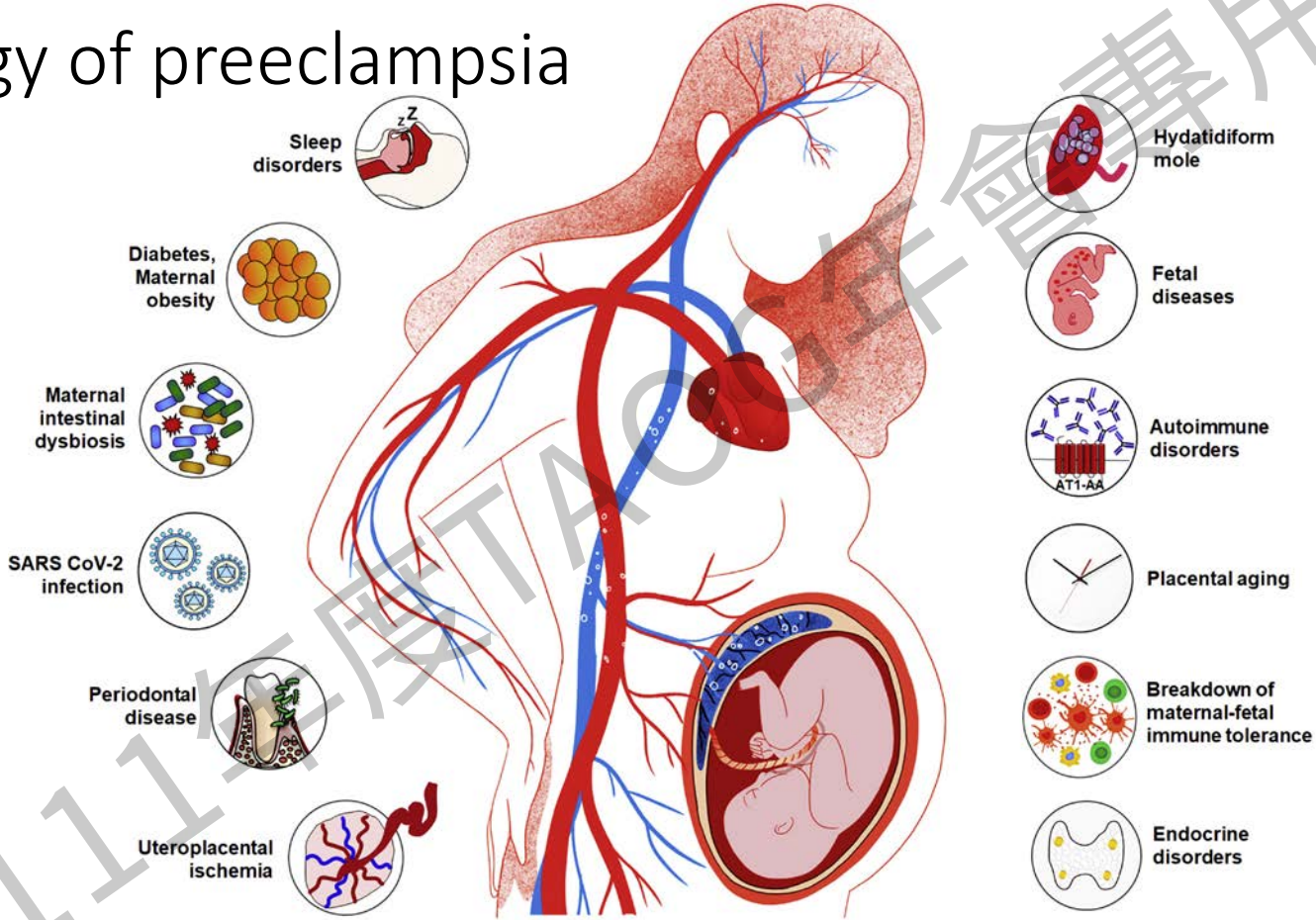
Box 1. Risk Factors for Preeclampsia

Nulliparity
Multifetal gestations
Preeclampsia in a previous pregnancy
Chronic hypertension
Pregestational diabetes
Gestational diabetes
Thrombophilia
Systemic lupus erythematosus
Prepregnancy body mass index greater than 30
Antiphospholipid antibody syndrome
Maternal age 35 years or older
Kidney disease
Assisted reproductive technology
Obstructive sleep apnea



Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020 Jun;135(6):e237-e260.

Etiology of preeclampsia



Jung E. et al. Am J Obstet Gynecol. 2022

Atherosis and PE

Abnormal placentation

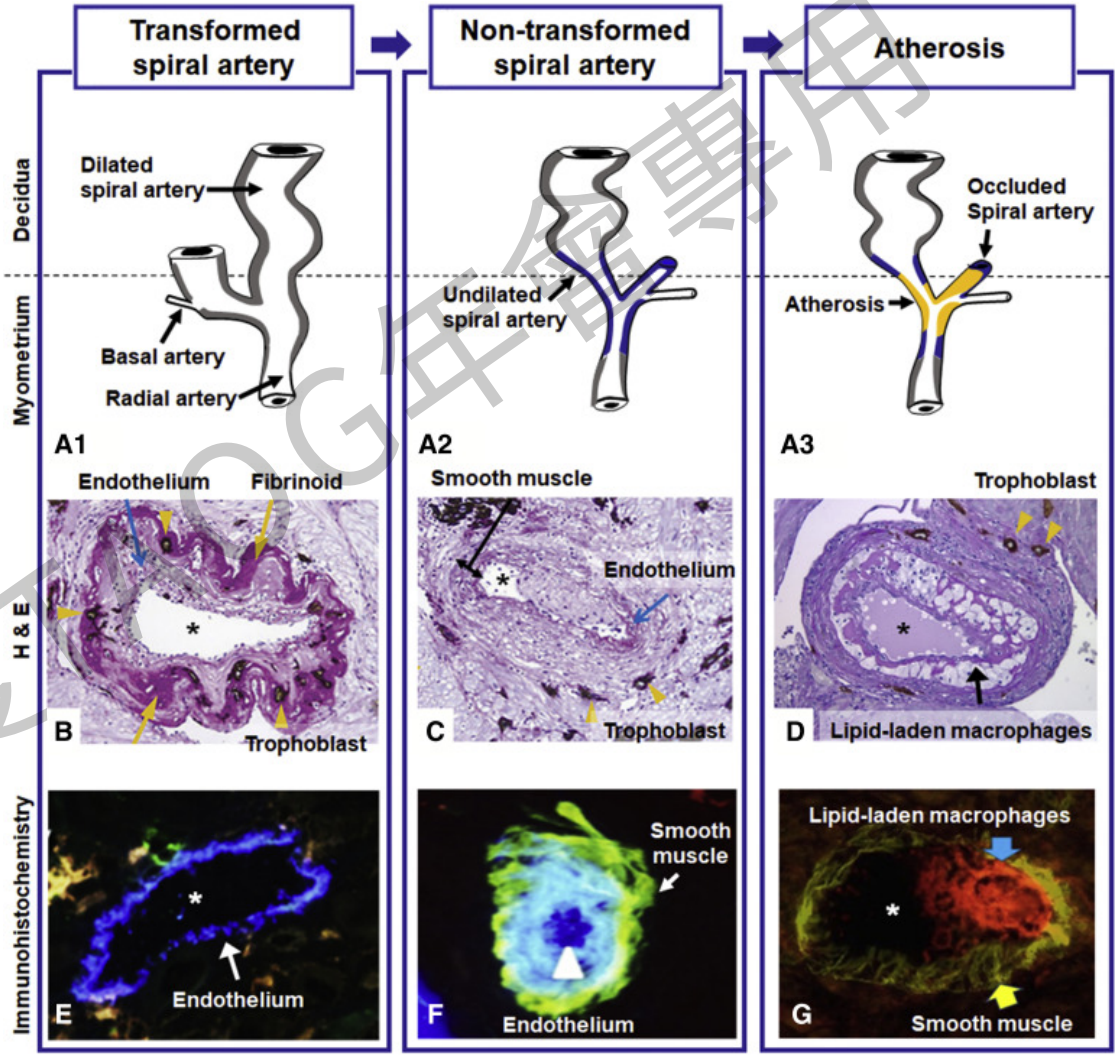
↓

Placental ischemia

↑

endothelial dysfunction

Dysfunctional maternal cardiovascular system



Jung E. et al. Am J Obstet Gynecol. 2022

The role of maternal infection?

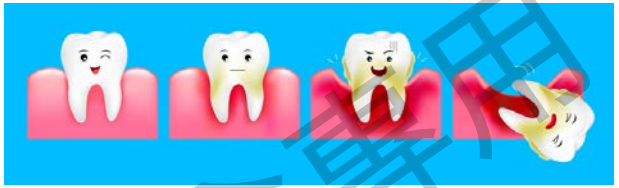
- Preeclampsia and eclampsia →
  X present the typical features of an infectious disease

- Microorganisms may be involved in the genesis of preeclampsia and eclampsia recurs in the literature every few years

- Periodontal disease, urinary tract infection, SARS-CoV-2 infection, or maternal gut dysbiosis…

Jung E. et al. Am J Obstet Gynecol. 2022

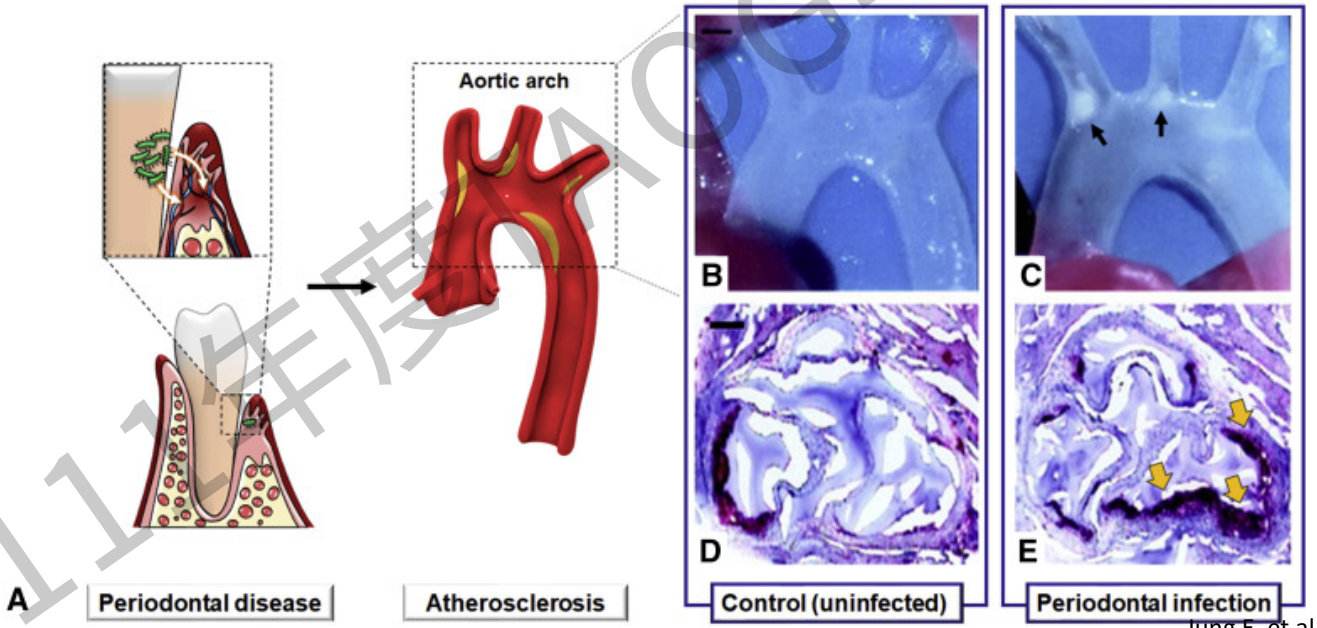
Periodontal disease VS PE



- Risk factor for atherosclerotic cardiovascular diseases

(atherosclerosis, coronary artery disease, stroke, and atrial fibrillation)

- Elevated CRP → systemic inflammatory process → ↑PE



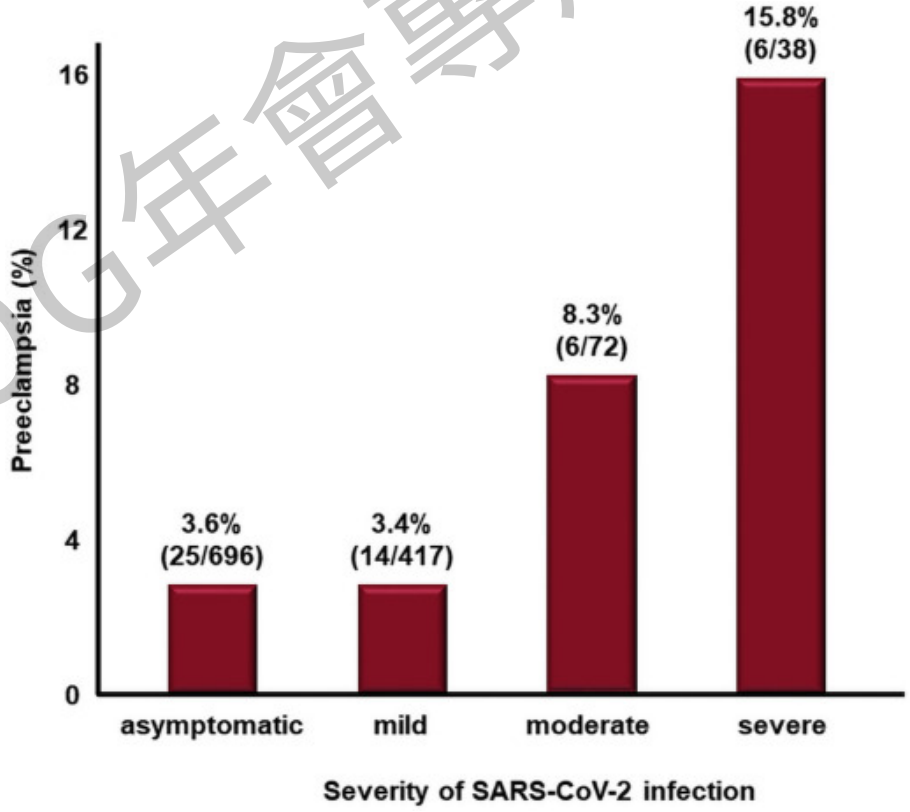
Jung E. et al. Am J Obstet Gynecol. 2022

SARS-CoV-2 infection VS PE

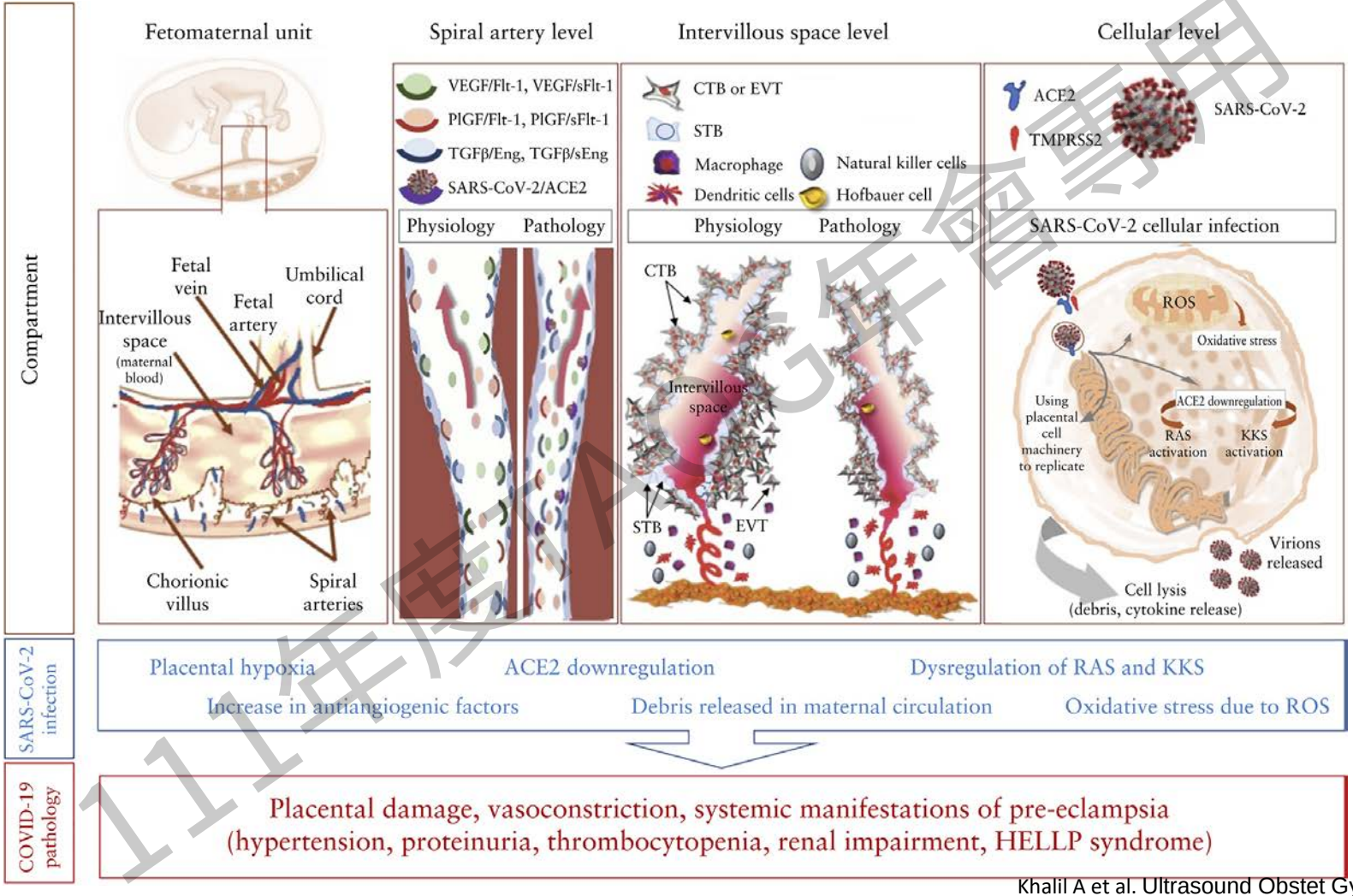
- **Increased risk of PE**
  - ↑ Preeclampsia (OR, 1.58; 95% CI, 1.39–1.8)
  - ↑ Preeclampsia with severe features (OR, 1.76; 95% CI, 1.18–2.63)
  - ↑ Eclampsia (OR, 1.97; 95% CI, 1.01–3.84)
  - ↑ HELLP syndrome (OR, 2.01; 95% CI, 1.48–2.97)

- Patients with severe COVID-19

→ 5X risk of preeclampsia than those with asymptomatic COVID-19



Conde-Agudelo A. et al. Am J Obstet Gynecol. 2021
Lai J. et al. Am J Obstet Gynecol. 2021

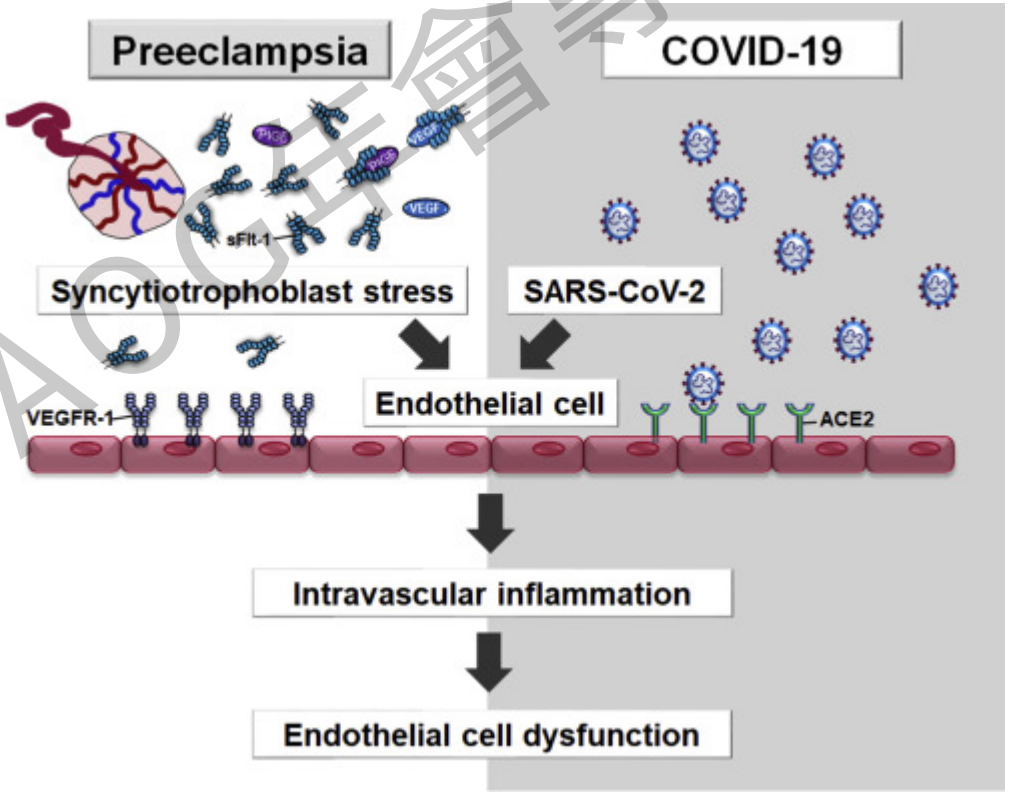


Khalil A et al. Ultrasound Obstet Gynecol. 2022

SARS-CoV-2 infection VS PE

- **Infect endothelial cells**

→ Endotheliitis
→ Activation of thrombin, intravascular inflammation
→ Damage of the microvasculature in target organs
→ Multisystemic dysfunction

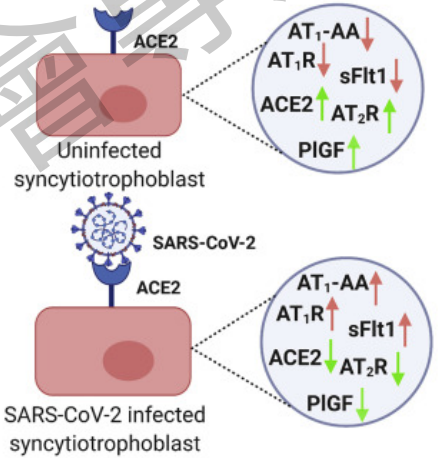


Jung E. et al. Am J Obstet Gynecol. 2022

SARS-CoV-2 infection VS PE

- Nonpregnant patients with COVID-19 →
  Serum and plasma sFlt-1 ↑

- Pregnant women with severe COVID-19 →
  - ↑ maternal plasma sFlt-1
  - High sFlt-1/PlGF ratio



- *Recovery from COVID-19*

→ Disappearance of hypertension and proteinuria without delivery of fetus and placenta

→ Placental involvement or endothelial cell dysfunction and intravascular inflammation

Mendoza M. et al. BJOG. 2020; 127: 1374-1380
Espino-Y-Sosa S.et al. Viruses. 2021; 13: 1906

Risks of subsequent cardiovascular disease

- **Preeclampsia ↑**
  - Cardiovascular (hypertension, myocardial infarction, congestive heart failure)
  - Cerebrovascular events (stroke)
  - Peripheral arterial disease
  - Cardiovascular mortality
- **Graded relationship between the severity of preeclampsia or eclampsia and the risk of cardiac disease**
  - 4-8 times higher for recurrent ecclampia, early onset or preterm delivery
- Mechanism
  - **Endothelial dysfunction**
  - Cardiovascular changes alead to cardiovascular remodeling

McDonald SD, et al. Am Heart J. 2008;156:918–30
Mongraw-Chaffin ML. et al. Hypertension. 2010;56:166–71

Prediction of preeclampsia

Traditional screening

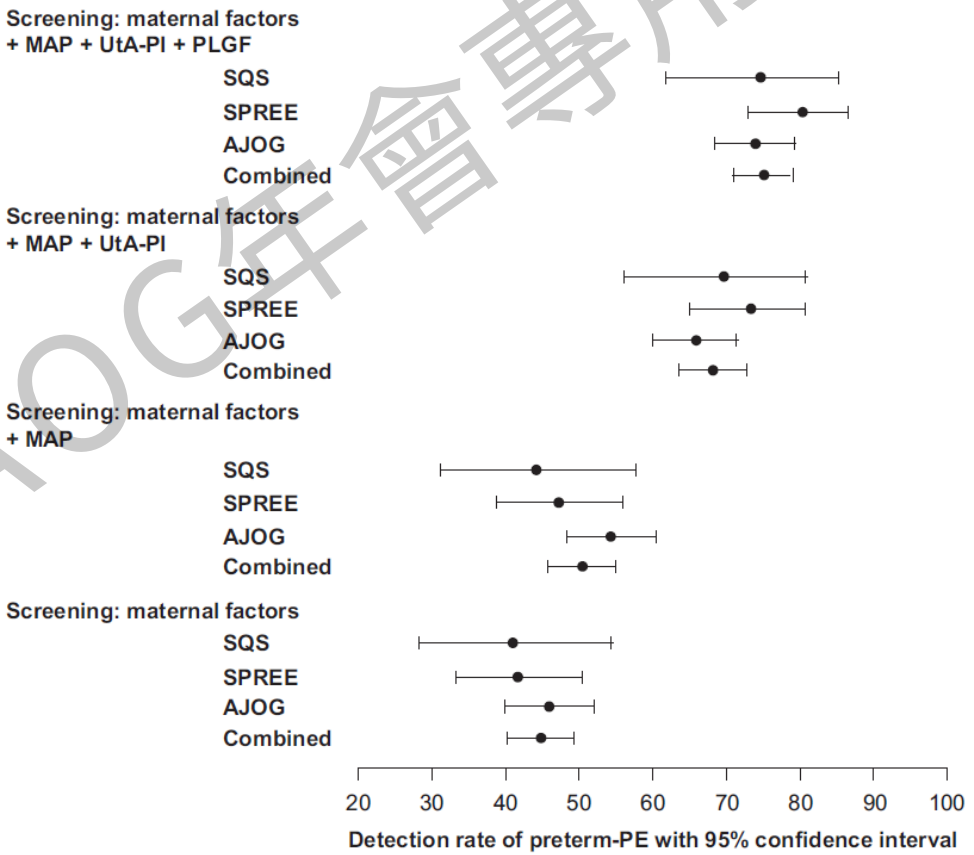
- Assessment of clinical risk factors
- Low detection rate:

Preterm: 40%; Term: 35%

Multivariable models

- FMF model: 90% of early PE
- Two-step screening

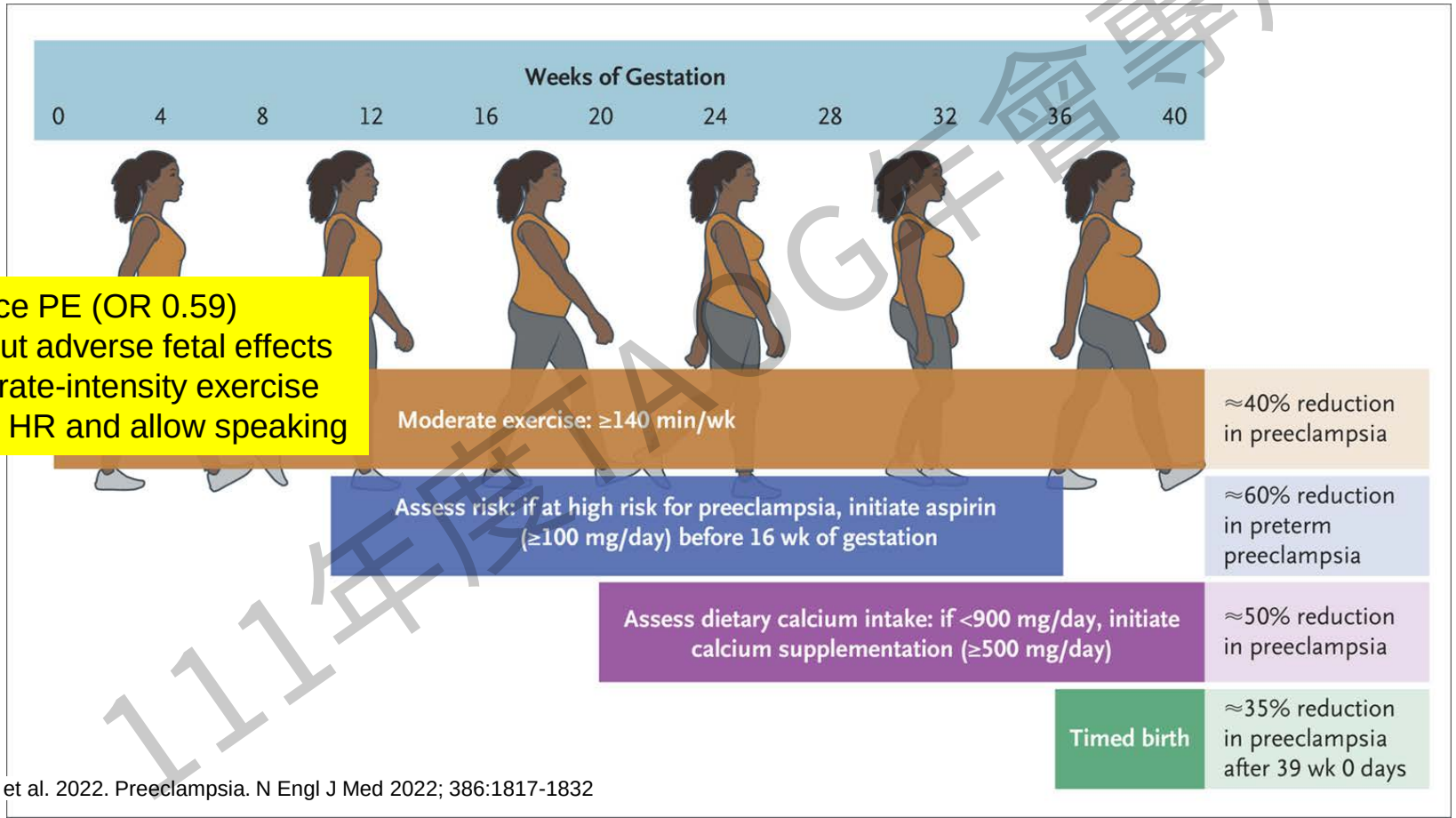
Detection rate of preterm-PE



Magee L. et al. 2022. Preeclampsia. N Engl J Med. 2022; 386:1817-1832
Wright D. et at. AJOG. 2020;223(1):12-23

Prevention Strategies

Reduce PE (OR 0.59)
Without adverse fetal effects
Moderate-intensity exercise
Raise HR and allow speaking



Magee L et al. 2022. Preeclampsia. N Engl J Med 2022; 386:1817-1832

Prevention

Aspirin usage

- **Meta-analysis of 60 trials** [1]

→ 50-162 mg/day

→ ↓PE, maternal complication, preterm birth, SGA, fetal/newborn death

- **ASPRE trial** [2]

→ 150 mg/day, GA11-13wks ~ GA36wks

→ ↓60% preterm PE

- **Meta-analysis of 16 trials** [3]

→ ≥100 mg/day, ≤GA16wks

→ ↓preterm PE

At least 100mg/day
As early as possible
Prevent peterm PE

1. Duley L. et al. Cochrane Database Syst Rev. 2019;10:CD004659
2. Rolnik DL. et al. N Engl J Med. 2017;377:613-22
3. Roberge S, et at. AJOG. 2018;218(3):287-293

Table 1. Clinical Risk Factors and Aspirin Use*

Level of Risk	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (ie, systemic lupus erythematosus, the antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	• Nulliparity • Obesity (body mass index greater than 30) • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age 35 years or older • Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020 Jun;135(6):e237-e260

Medication treatment for BP control

Nonsevere Hypertension

Manifestation: Systolic BP 140–159 mm Hg or diastolic BP 90–109 mm Hg
Objective: Systolic BP 135 mm Hg and diastolic BP 85 mm Hg
Management: Start with one of the three classes of drugs and use a low–medium dose
If BP control is not achieved within a week with a medium dose, consider adding a low–medium dose from another class, rather than a high dose of the same medication, for a maximum of three medications
Consider expectant care if antenatal

First-Line Drug	Formulation	Low–Medium Dose	High Dose	Maximum Dose
Labetalol		100–200 mg, 3 or 4 times daily	300 mg, 3 or 4 times daily	1200 mg/day
Nifedipine	Intermediate-acting (PA/MR)	10–20 mg, 2 or 3 times daily	30 mg, 2 or 3 times daily	120 mg/day
	Long-acting (XL/LA)	30 mg, 1 or 2 times daily or 60 mg daily	30 mg every morning and 60 mg every evening	120 mg/day
Methyldopa		250–500 mg, 3 or 4 times daily	750 mg, 3 times daily	2500 mg/day

Magee L et al. Preeclampsia. N Engl J Med. 2022; 386:1817-1832.

Severe Hypertension

Manifestation: Systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg
Objective: Systolic BP <160 mm Hg and diastolic BP <110 mm Hg within 180 min
Management: Choose one of the following four classes of drugs and the preferred route and timing of administration
If BP control is not achieved despite maximal doses, move to another class of medication
If BP control is not achieved by 360 min despite 2 medications, consult critical care, consider ICU admission, stabilize and deliver (if undelivered)

First-Line Drug	Route of Administration and Dosage Units	0 Min	30 Min	60 Min	90 Min	120 Min	150 Min
Labetalol	Oral — mg	200	—	200	—	200	—
	Intermittent IV — mg	10–20	20–40	40–80	40–80	40–80	40–80
	IV infusion — mg/min	0.5–2.0	→	→	→	→	→
Nifedipine	Oral capsule — mg	5–10	10	—	10	—	10
	Oral tablet (PA/MR) — mg	10	—	10	—	10	—
Hydralazine	Intermittent IV — mg	5	5–10	5–10	5–10	—	—
Methyldopa	Oral (if other medications unavailable or for in utero transfer without monitoring) — mg	1000	—	—	—	—	—

Magee L et al. 2022. Preeclampsia. N Engl J Med. 2022; 386:1817-1832.

Box 4. Conditions Precluding Expectant Management

Maternal

- Uncontrolled severe-range blood pressures (persistent systolic blood pressure 160 mm Hg or more or diastolic blood pressure 110 mm Hg or more not responsive to antihypertensive medication
- Persistent headaches, refractory to treatment
- Epigastric pain or right upper pain unresponsive to repeat analgesics
- Visual disturbances, motor deficit or altered sensorium
- Stroke
- Myocardial infarction
- HELLP syndrome
- New or worsening renal dysfunction (serum creatinine greater than 1.1 mg/dL or twice baseline)
- Pulmonary edema
- Eclampsia
- Suspected acute placental abruption or vaginal bleeding in the absence of placenta previa

Clinical management

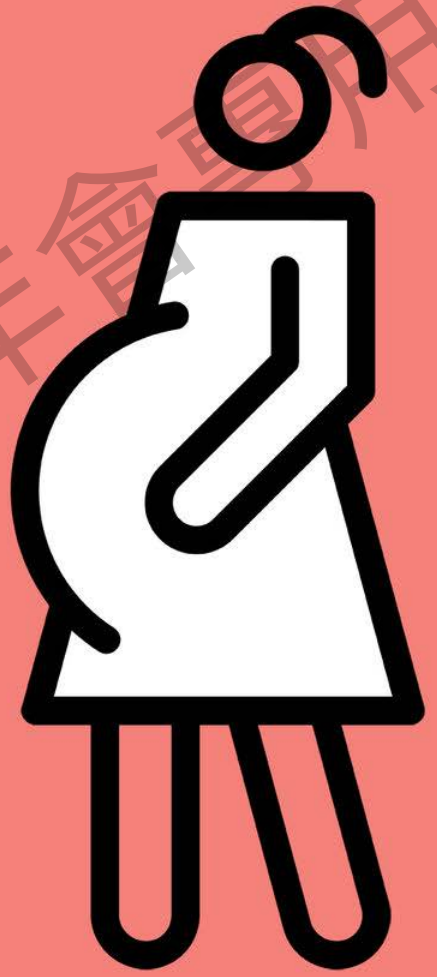
Be aware!!!

Fetal

- Abnormal fetal testing
- Fetal death
- Fetus without expectation for survival at the time of maternal diagnosis (eg, lethal anomaly, extreme prematurity)
- Persistent reversed end-diastolic flow in the umbilical artery

ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020 Jun;135(6):e237-e260.

Peripartum Cardiomyopathy



Case Summary

37 y/o ,G1P1

- Pregnant at 36+1 weeks with DCDA twin via IVF

1. Past history: GERD, GDM
2. Family history: no known relatives with cardiomyopathy
3. Prenatal exam:
   - GDM: 75g OGTT 94→178→145mg/dL
   - PIH after GA 30 weeks → dyspnea and edema aggravated

Chronic nocturnal cough since GA 34 wks

- 10/26 GA 35 wks, BP: 146/91mmHg, BW: 82.6kg
- 11/02 GA 36 wks, BP: 169/109mmHg, BW: 86kg
  - T/P/R: 37.2/80/19
  - U/A: protein: 600mg/dl

Admission for severe preeclampsia

BUN: 15mg/dL, CRE: 1.24mg/dL
AST: 30 U/L, ALT: 17U/L, INR: 0.84
Hb 10.4g/dL, Plt 144k/uL

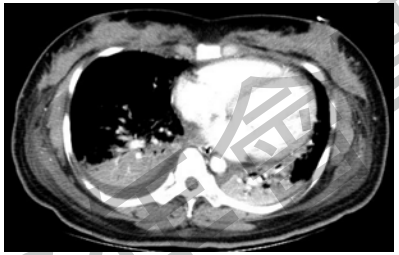
- 14:03 C/S
  - Female, breech at 14:05, BW: 2990gm, A/S: 8-9
  - Male, breech at 14:06, BW: 2235gm, A/S: 8-9
  - MgSO4 given postpartum

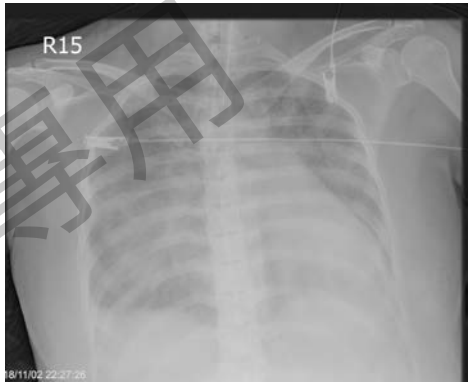
17:20 Dyspnea, persist cough, orthopnea

Hypoxemia under O2 10L mask

Breathing sound: bil. rales

CXR: acute pulmonary edema





BP 152/120mmHg ;P/R: 149/37

→BP 70/50mmHg after intubation

→SpO2 84% / O_2 10L (mask)

VBG: pH 7.235, PCO2 45.2, PO2 46.3,
HCO3 18.7, Base -8.8, LA: 2.0

D-dimer >35.2, CKMB 27.85ng/mL,
pro-BNP 2325pg/mL, Troponin-T 2304ng/L

ECG: ST, no ischemic change

CXR: cardiomegaly with lung edema

CT: bil. pleural effusion with partial atelectasis, multiple GGO and consolidations in both lungs

ICU BP: 105/75mmHg, SpO2: 92%(60%,L,VCR)

Bedside UCG: four chamber dilatation with poor LVEF (estimated LVEF:20% with global hypokinesia), MR(+), no pericardial effusion.

Dilated cardiomyopathy, favor peripartum cardiomyopathy
With cardiogenic shock with multiorgan involvement

Lasix 40mg Q6H, fentanyl pump sedation and ventilator support
Dopamine for low BP on 11/3

	11/3			11/4	11/5	11/6	11/7	11/8
CKMB(ng/mL)	51.99	79.40	68.86	42.98	10.69	5.12	4.99	4.67
CPK(U/L)	2608	3074	2840	2229	866	383	285	201
proBNP(pg/mL)	8874	9935	10493	8391	4115	3160	2139	1664

BW: 80.6->64kg (11/3 to 11/10)

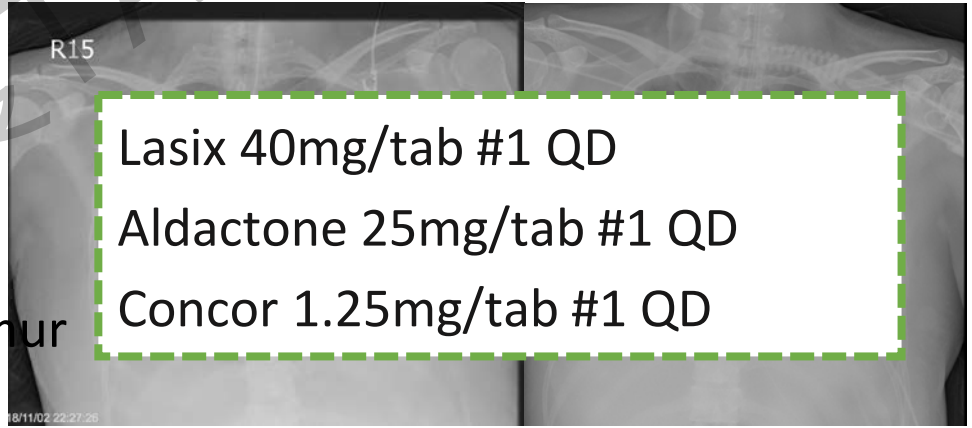
11/5

UCG: Borderline dilated LV (LVEDD 52 mm),
Improved LVEF 46%,
focal akinesia at mid anterior wall,
MR, mild, with eccentric posteriorly directed jet, TR, mild

11/7 extubation

OPD BP: 110/74 BW:62kg
Chest: bil clear BS
Heart: RHB, no murmur

11/2 11/6

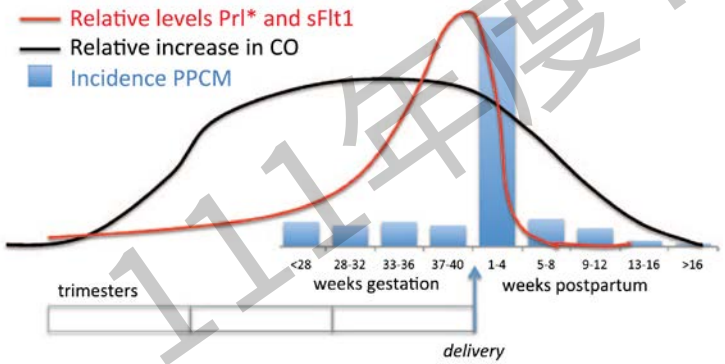


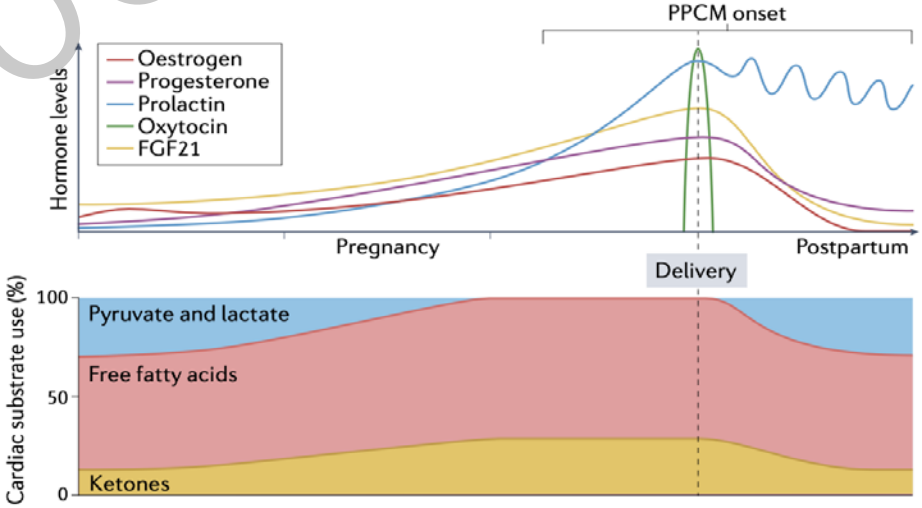
Lasix 40mg/tab #1 QD
Aldactone 25mg/tab #1 QD
Concor 1.25mg/tab #1 QD

Definition

- Idiopathic cardiomyopathy
- Heart failure secondary to **LV systolic dysfunction**
- Occurs **towards the end of pregnancy** or **in the months following delivery**
- No other cause of heart failure is found

→ ***A diagnosis of exclusion***





Sliwa K et al. Eur J Heart Fail 2010
Davis MB et al. Journal of the American College of Cardiology 2020

Epidemiology

- Incidence increased from 2004 to 2011 in the US.

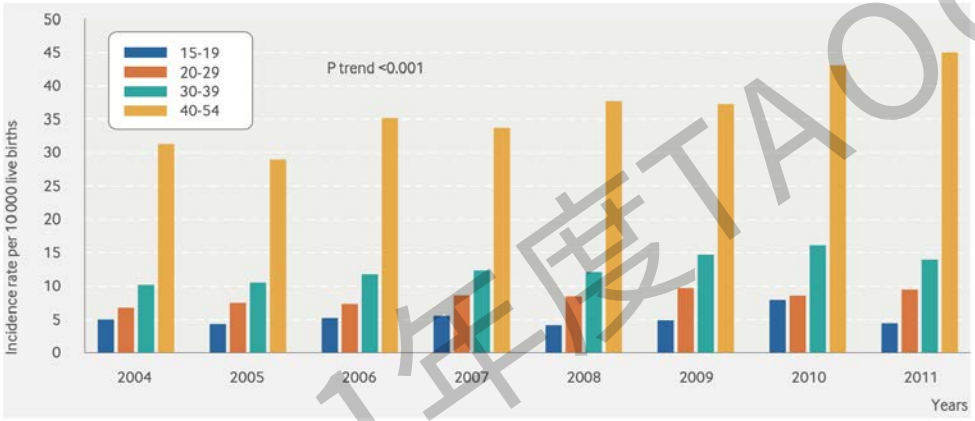


Fig 1 | Temporal trend in the incidence of peripartum cardiomyopathy in the United States. Coloured bars indicate different maternal age groups (see legend). Adapted from Kolte and colleagues.[12]

- **Possible cause ???**
  - Advanced maternal age
  - Multiple gestation
  - Increasing prevalence of cardiovascular risk factors
  - Growing recognition of PPCM

Honigberg MC et al. *BMJ 2019*

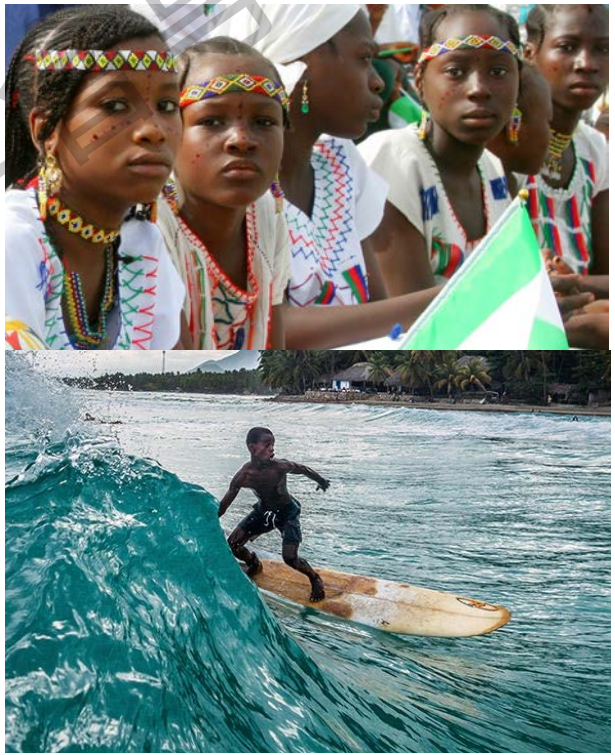
Epidemiology

Genetic background ?
Environmental factors ?

Table 1 | Worldwide variation in incidence of peripartum cardiomyopathy

Country/ Region	Incidence (per live births)	Reference	Data source
Nigeria	1/102	Isezuo et al[18]	Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria
Haiti	≈1/300	Fett et al[19]	Hospital Albert Schweitzer PPCM Registry
China	1/346	Huang et al[20]	Liaocheng People's Hospital, Shandong Province, China
United States	1/968	Kolte et al[12]	US Nationwide Inpatient Sample
South Africa	1/1000	Desai et al[21]	King Edward VIII Hospital, Durban, South Africa
California, US	1/2066	Gunderson et al[11]	Kaiser Permanente Northern California hospitals
Malaysia	1/2941	Chee et al[22]	University Malaya Medical Centre
Sweden	1/5719*	Barasa et al[23]	National Inpatient, Cause of Death, and Medical Birth Registries
Denmark	1/10 149	Ersbøll et al[24]	Danish National Birth and Patient Registers
Japan	≈1 in 20 000	Kamiya et al[25]	Japanese Nationwide Survey of Peripartum Cardiomyopathy

*Heart failure in late pregnancy and the postpartum period.



Honigberg MC et al. *BMJ 2019;* Zolt et al. Circulation 2016

Risk factors

Family history
Anemia
Asthma
Autoimmune disease
Substance misuse

Multigestation

7%-14.5% of PPCM patients VS 3% in USA overall population

HTN and preeclampsia

– *15% to 68% of PPCM patients* VS 8% in all USA
– Frequently found **associated with eclampsia (OR:12.9 -27.9)**

Age

– >60% >30 y/o
– >40 y/o VS <20 y/o (OR: 10)

Race

– African American (3-16X)
– Younger, higher prevalence of HTN, later onset, lower LVEF recovery rate

Honigberg MC et al. *BMJ 2019*

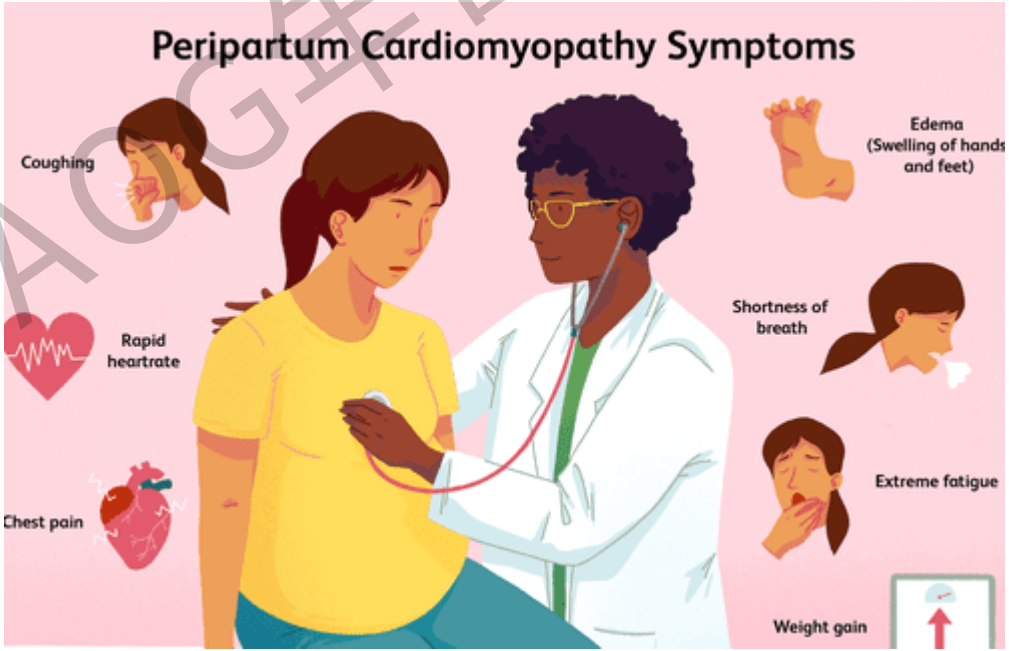
Clinical Presentation

Physical examination
- Tachypnea
- Tachycardia
- Elevated jugular vein pressure
- Pulmonary rales
- Peripheral edema

- Typical symptoms of heart failure
  - Dyspnea
  - Exercise intolerance
  - Orthopnea
  - Paroxymal noctural dyspnea
  - Edema
  - Chest tightness

Dyspnea Cough Fatigue

- Uncommon presentation
  - Cardiogenic shock
  - Severe arrhythmia
  - Thromboembolic complication



Davis MB et al. Journal of the American College of Cardiology 2020

Diagnosis

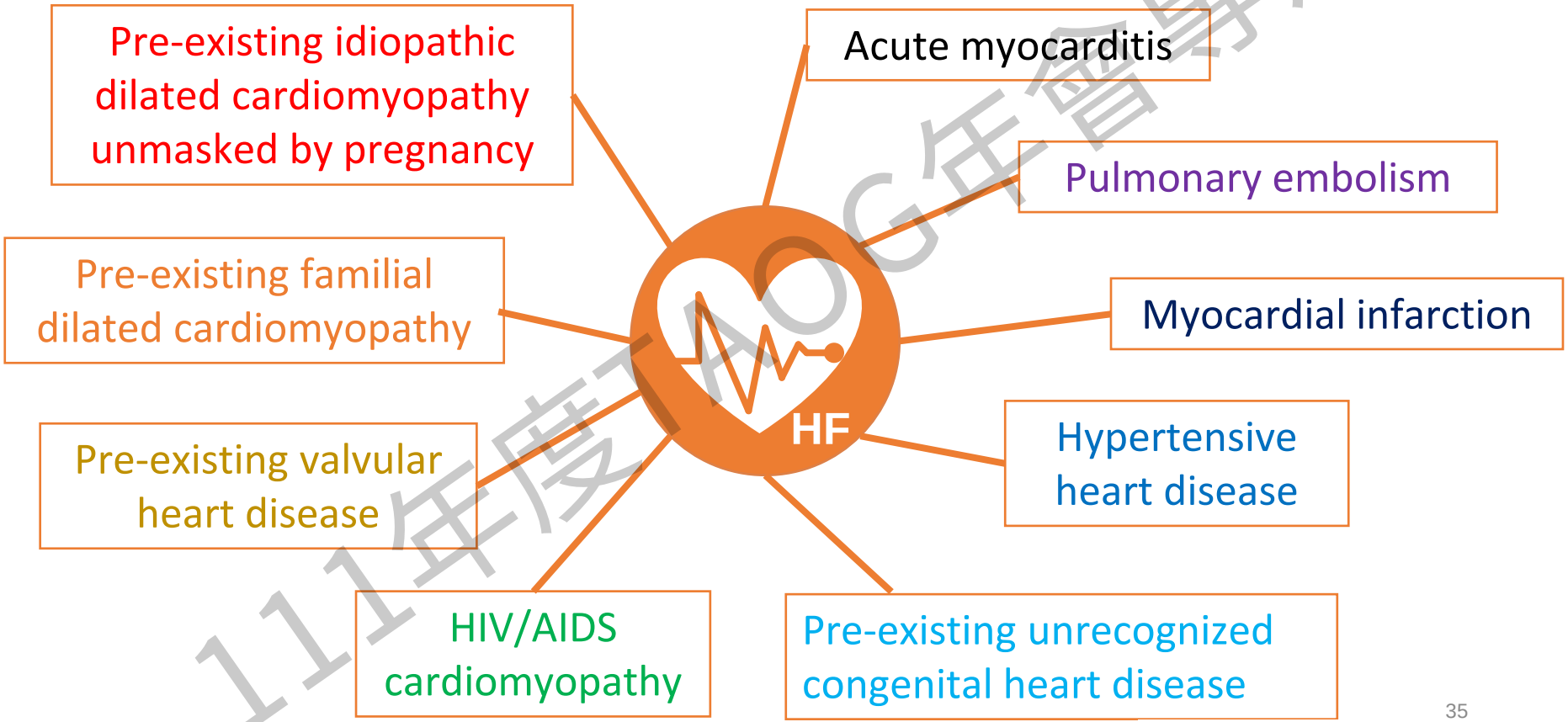
- ★ Echocardiography
  - ***LV dysfunction (LVEF <45%)*** / *LV dilatation*
- X Cardiac MRI
  - Accurate EF and measurement
  - Gadolinium crosses the placenta and may be teratogenic
- X Endomyocardial biopsy
  - No diagnostic histologic findings
  - Generally not indicated
- ★ Laboratory studies
  - **NT-pro-BNP**

Table 1. Diagnostic testing for peripartum cardiomyopathy

Blood test
Complete blood cell count
Urea, creatinine, electrolytes
Cardiac enzymes, including troponin
BNP or N-terminal BNP
Liver function test
Thyroid-stimulating hormone
Chest radiograph
Electrocardiogram
Transthoracic echocardiogram
Cardiac magnetic resonance imaging (if needed)

Davis MB et al. Journal of the American College of Cardiology 2020

Differential diagnosis



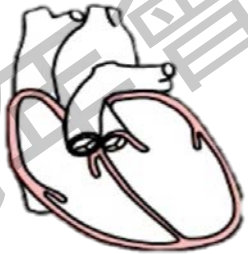
Honigberg MC et al. *BMJ 2019;* Zolt et al. Circulation 2016

Etiology

Activation of protective cardiac myocyte signaling pathways

Normal

Normal

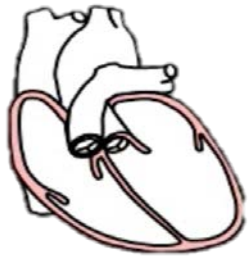


PPCM

Normal

Pregnancy associated hypertrophy

- Stress, autoimmune
- Malnutrition
- Myocardial inflammation
- Vasculo-hormonal hypothesis
  -Prolactin
  -sFLT1
- Genetic factors



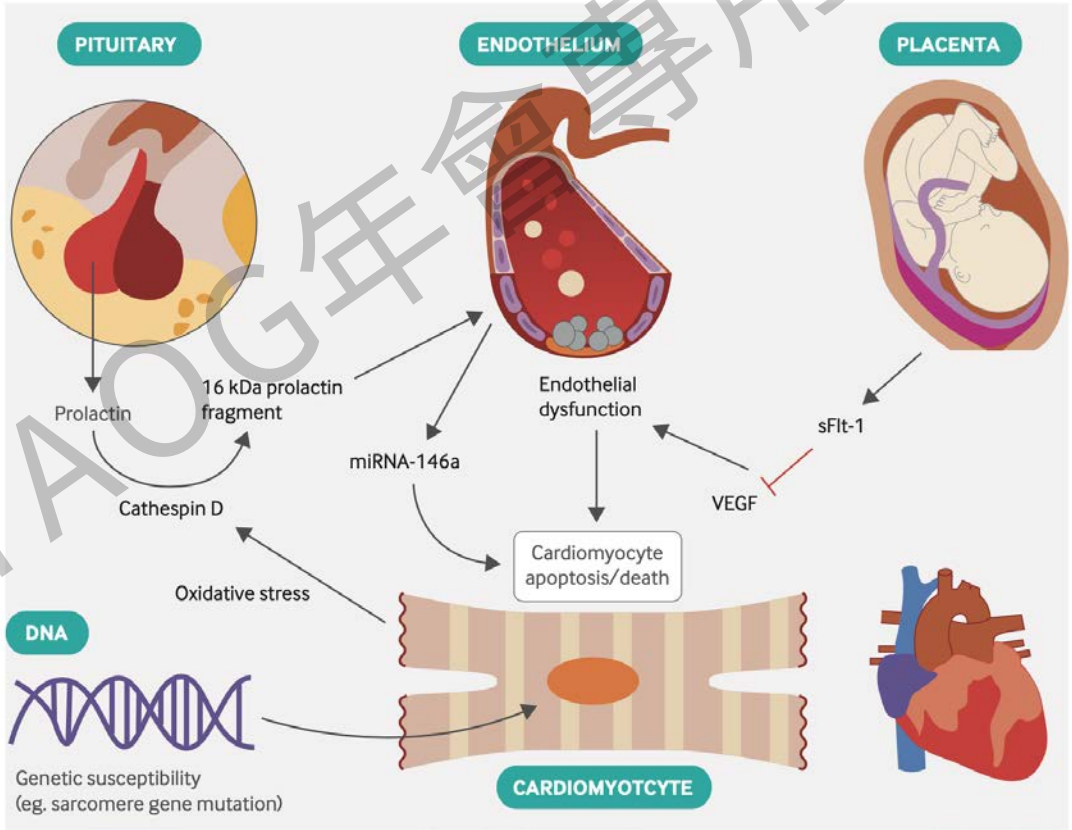
Irreversible dysfunction

Honigberg MC et al. *BMJ 2019;* Zolt et al. Circulation 2016; Hoes MF et al. Cardiology 2022

Pathophysiology

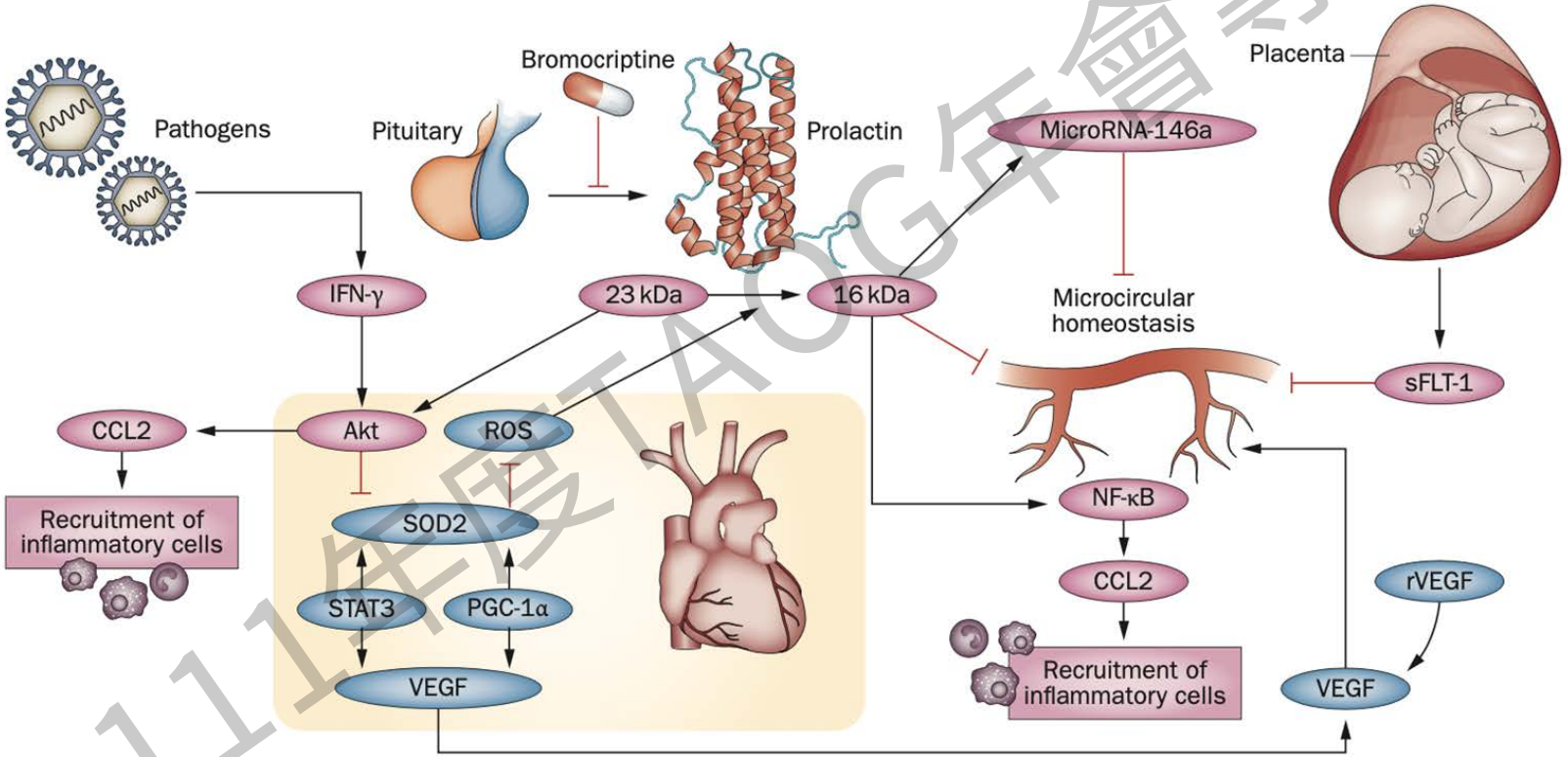
- Multifactorial
  - Endothelial (vascular) dysfunction
  - Cardiomyocyte injury / death

- A “multiple-hit” model
  - Genetic predisposition
  - Vascular-hormonal changes during pregnancy



Honigberg MC et al. *BMJ 2019*

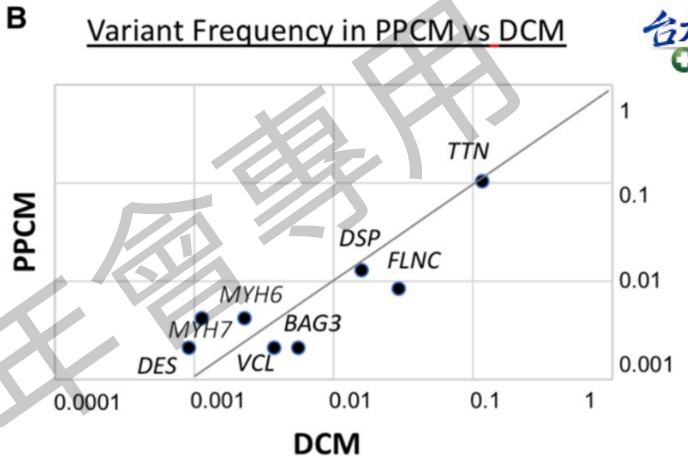
Pathophysiology



Hilfiker-Kleiner D et al. Cardiology 2014

Pathophysiology - Genetics

BAG3	BAG family molecular chaperone regulator 3
DSP	desmoplakin
FLNC	filamin C
LMNA	lamin A/C
MYH6	myosin 6
MYH7	myosin 7
TNNC1	cardiac troponin C
TTN	titin
VCL	vinculin



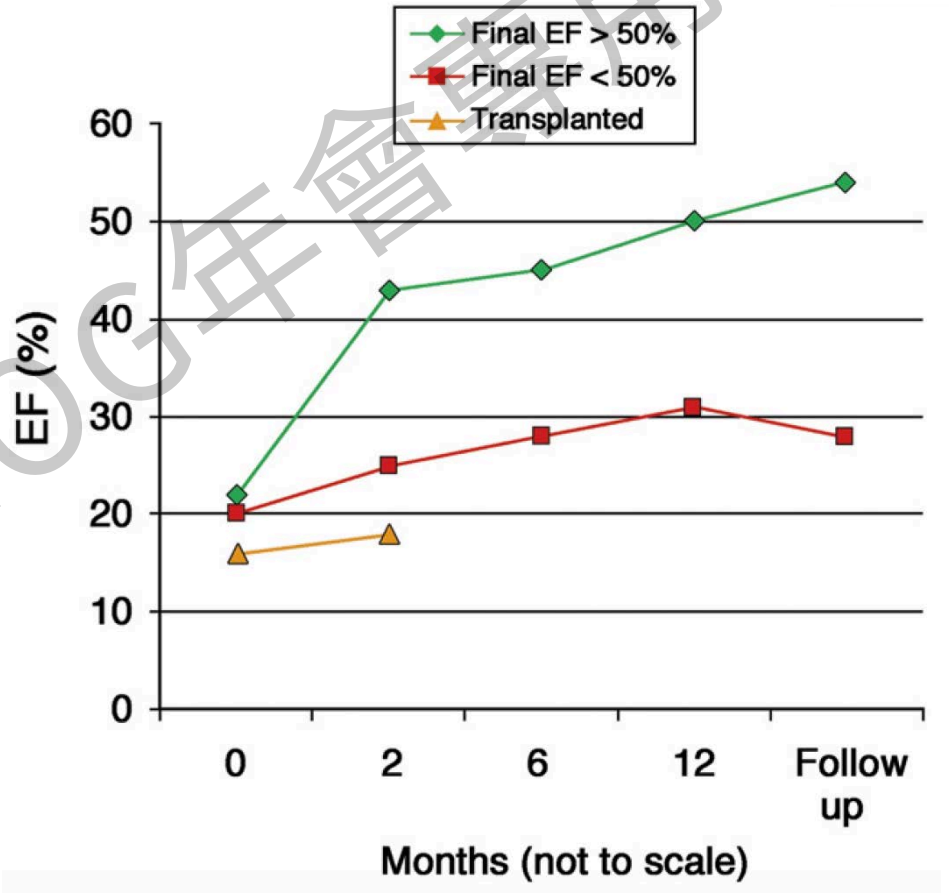
- **Genetic similarity between PPCM and DCM**
- LVEF at presentation was significantly lower in patients with **truncating variants in TTN (TTNtvs)**

→ *Not correlate with worse rates of recovery, with lower LVEF at 1 year, or with adverse outcomes*

Hoes MF et al. Nature reviews. Cardiology 2022; Elkayam U et al. Circulation 2021

Prognosis & Outcomes

- **Higher rate of recovery**
- **Highly variable** from complete recovery to cardiac death
- **23% to 72% had full recovery of normal LV systolic function**
  - Often within 2-6 months
  - Median time to recovery: 8 months
  - May delayed to 5 years

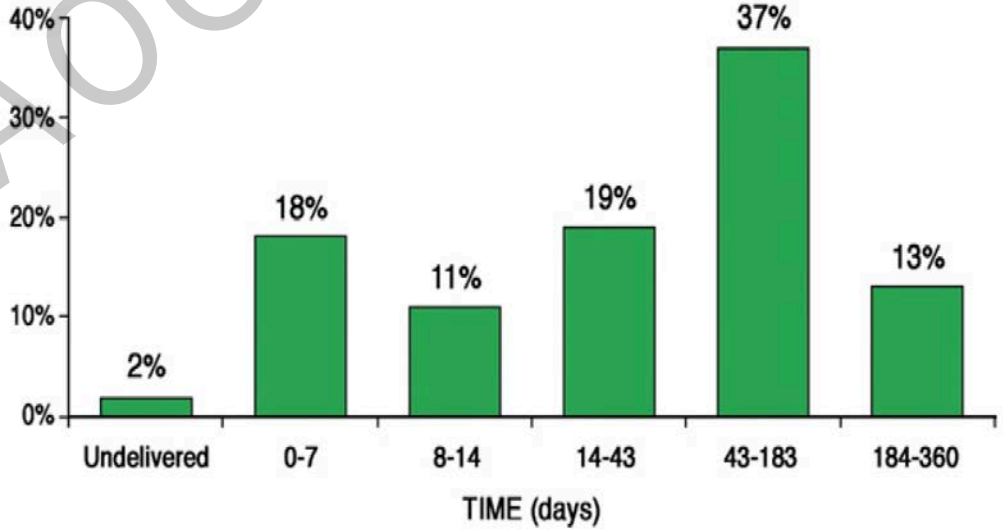


Amos et al. Am Heart J 2006; Davis MB et al. Journal of the American College of Cardiology 2020

Prognosis & Outcomes

- **20% to 25% of patients progress to end-stage HF**
- 4% to 11% receive cardiac transplantation or LV assist device treatment

- Mortality 3.3% to 30%
  - 18% within 1 week, 87% within 6 months
  - Mortality still high in young, previously healthy women.

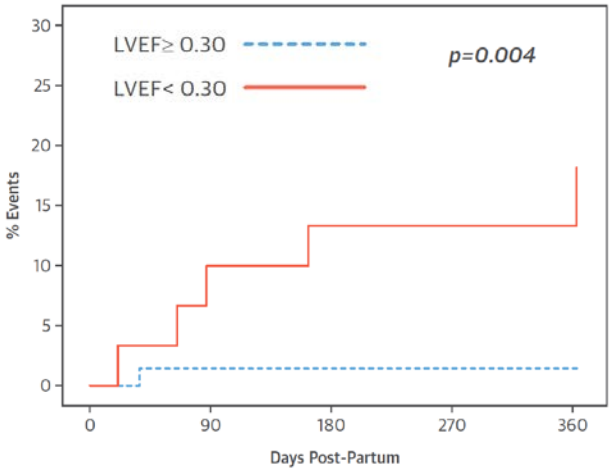


Whitehead et al. Obstet Gynecol 2003

Predictors of recovery

- **Concomitant pre-eclampsia** has been associated with lower 1-year survival, but higher rates of LV recovery in survivors
- **LVEF and LV size at the time of diagnosis** most strongly predict adverse events and long-term recovery
  - In the IPAC cohort, LVEF <30% was associated with lower rates of recovery and increased risk of adverse events.

Clinical characteristic	*P*
EF at 2 m	<.001
LVEDd <5.6 cm	.01
LV thrombus	.03
African-American race	.03



Davis MB et al. Journal of the American College of Cardiology 2020; Amos et al. Am Heart J 2006; Results of the IPAC Study. J Am Coll Cardiol. 2015

Management

ESC European Society of Cardiology
European Heart Journal (2018) 39, 3165–3241
doi:10.1093/eurheartj/ehy340
ESC GUIDELINES

2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

- **BOARD label:**

Bromocriptine, Oral HF therapies, Anticoagulants, Vasorelaxing agents, and Diuretics

- **Bromocriptine** (2.5 mg once daily) for at least 1 week may be considered in uncomplicated cases
  - Prolonged treatment (2.5 mg twice daily for 2 weeks, then 2.5 mg once daily for 6 weeks) may be considered in patients with EF <25% and/or cardiogenic shock
- Must always accompany with **anticoagulation with heparin** (LMWH or UFH)

Management – HF medications

MEDICATION	DURING PREGNANCY	POTENTIAL ADVERSE EFFECTS	INDICATIONS	DURING LACTATION
HEART FAILURE MEDICATIONS				
Loop diuretics	Yes	Caution for hypovolemia or hypotension that may lead to decreased placental perfusion	For signs and symptoms of congestion and fluid overload.	Yes, but over-diuresis can lead to decreased milk production.
Beta blockers (metoprolol tartrate used most commonly)	Yes	IUGR; fetal bradycardia and hypoglycemia	For standard treatment of HF; consider treatment of women with subsequent pregnancy.	Yes
Hydralazine/nitrates	Yes	Caution with hypotension	Use for afterload reduction during pregnancy (instead of ACE-I/ARB) when needed.	Yes, but ACE-I/ARB typically chosen post-partum
Digoxin	Yes	No associated congenital defects	Can be used with symptomatic heart failure and/or systolic dysfunction during pregnancy, or afterwards per guidelines.	Yes

Honigberg MC et al. *BMJ 2019;* Davis MB et al. Journal of the American College of Cardiology 2020

Management – Anticoagulants

- Anticoagulation

  → ***LMWH***

ANTICOAGULANTS				
Low molecular weight heparin	Yes	Caution at time of delivery and with neuraxial anesthesia; does not cross placenta; consider the need for monitoring anti-Xa levels	For prevention and treatment of thromboembolic complications during pregnancy and as bridge to warfarin postpartum.	Yes
Warfarin	Avoid	Warfarin embryopathy and fetopathy	For prevention and treatment of thromboembolic complications postpartum.	Yes

- ESC
  - LVEF <35%
  - Received bromocriptine

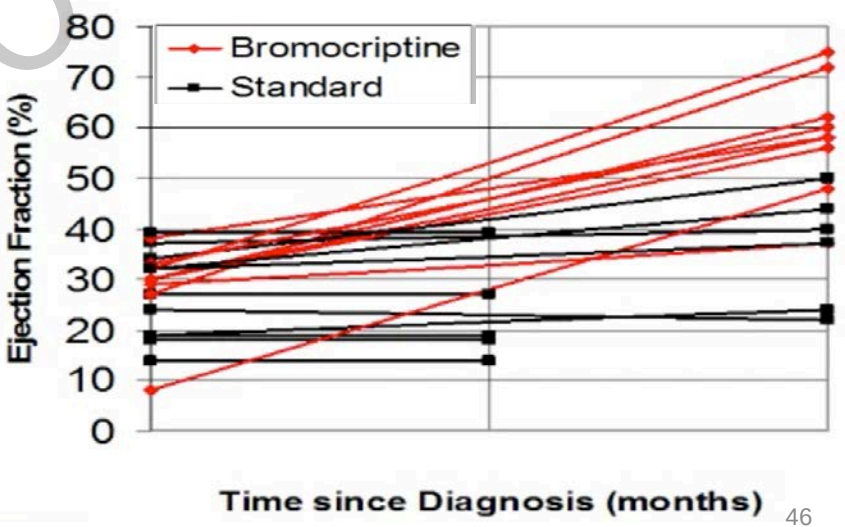
- AHA
  - LVEF <30%

Honigberg MC et al. *BMJ 2019;* Davis MB et al. Journal of the American College of Cardiology 2020

Management - Bromocriptine

- **Prolactin inhibitor → dopamine D2 agonist**
  - **Greater improvement in LVEF at 6 months**
  - No significant difference in overall rates of recovery
- Bromocriptine 2.5mg BID for 2 weeks → 2.5mg QD for 6 weeks

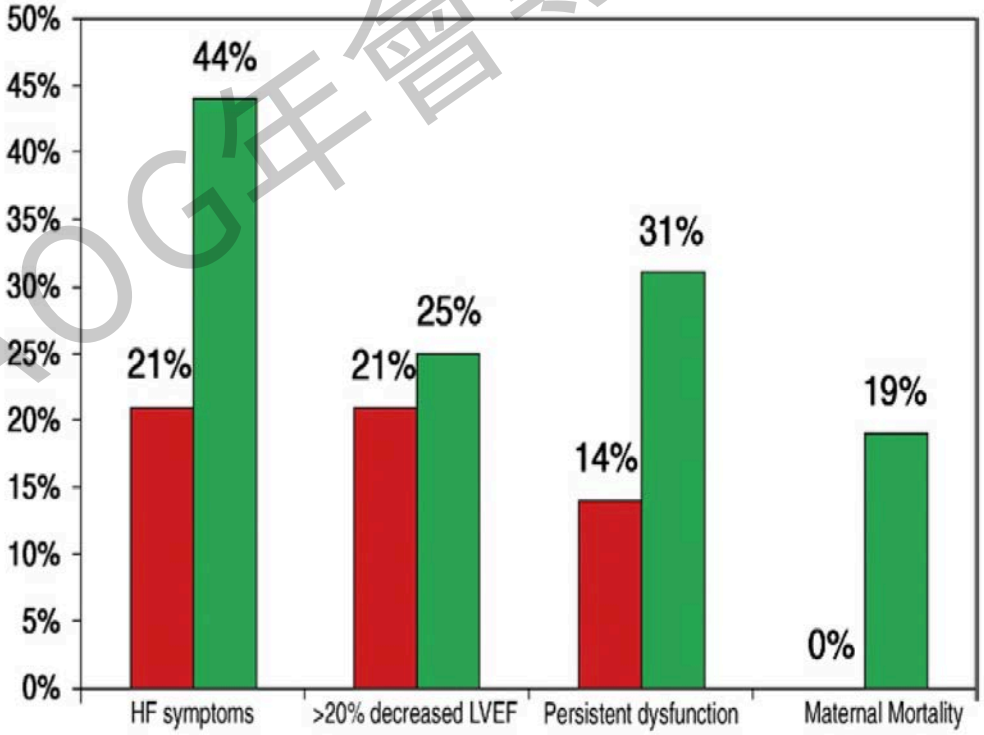
- LVEF
  - PPCM Br vs Std: 28-56% : 28-36%, p=0.06
- Mortality:
  - PPCM Br 10%
  - PPCM Std: 40%



Silwa et al. Circulation 2010; Honigberg MC et al. *BMJ 2019;* Davis MB et al. Journal of the American College of Cardiology 2020

Recurrence with subsequent pregnancy

- **30% to 50% risk of recurrent PPCM**
- Termination may not prevent onset of PPCM
- **Prepregnancy LVEF not guarantee a normal outcome**
- Contraception with IUD
  - **Estrogen-based oral pill is not recommended**



Honigberg MC et al. *BMJ 2019;* Davis MB et al. Journal of the American College of Cardiology 2020

Management - Subsequent Pregnancy

- **LVEF before the subsequent pregnancy** is the strongest predictor of outcomes
  - LVEF <50% → 50% risk of acute heart failure with worsening cardiomyopathy
    25-50% risk of mortality

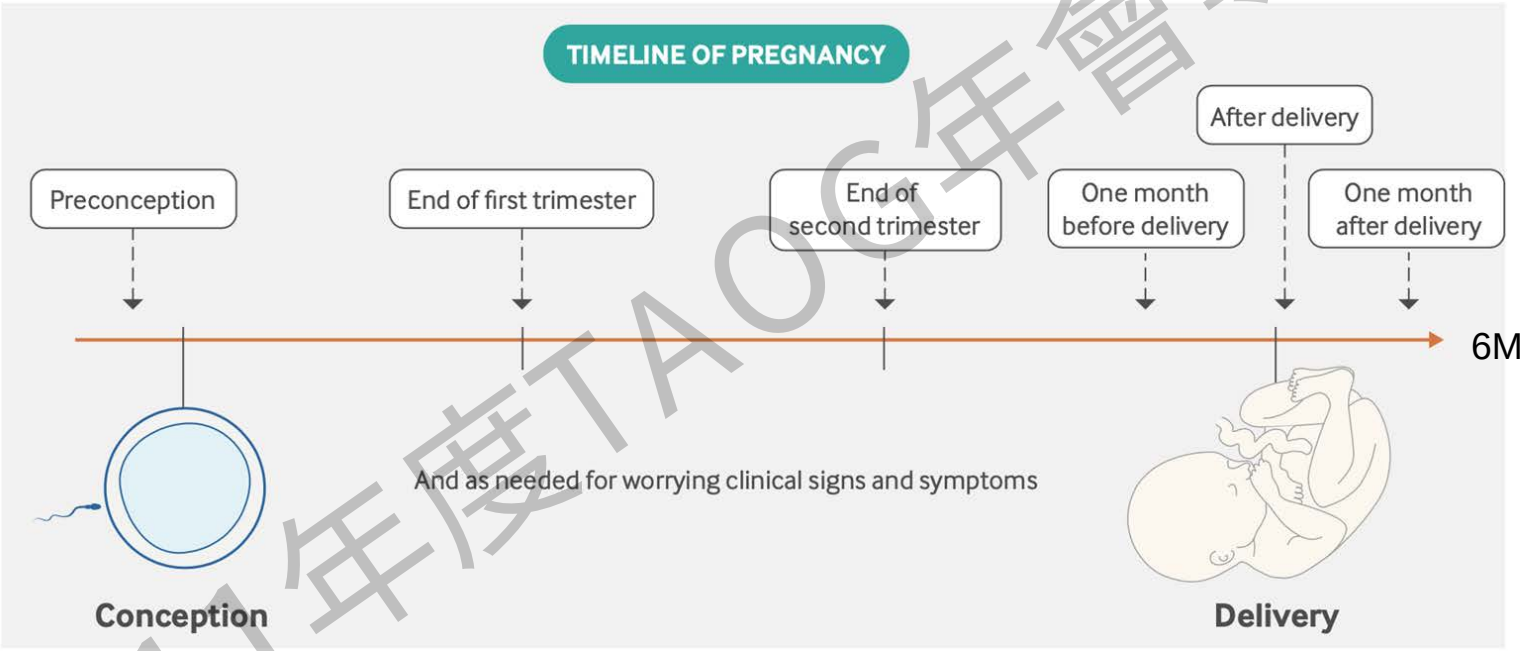
- **Persistent LV dysfunction → Stillbirth, abortion, and preterm delivery**

- No evidence based strategies are available for stratifying risk in women with recovered LV function who wish to conceive again.

Women with hx should be informed of significant risk for recurrent PPCM and even death !

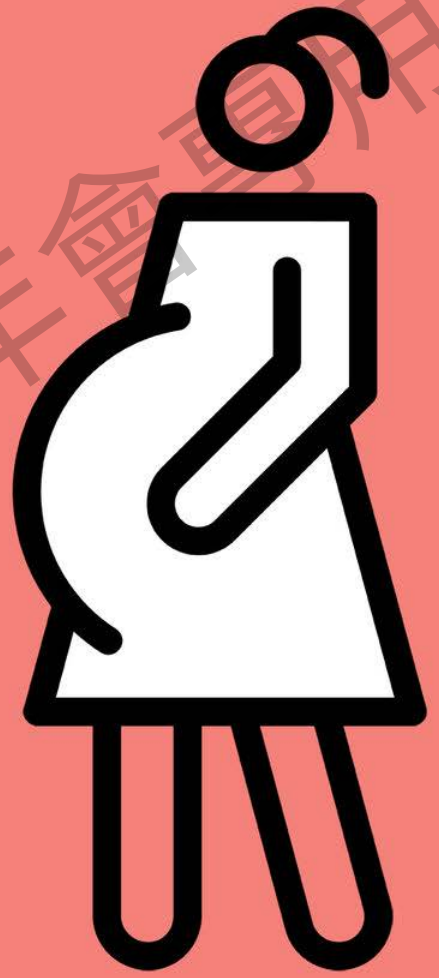
Honigberg MC et al. *BMJ 2019;* Davis MB et al. Journal of the American College of Cardiology 2020

Management - Subsequent Pregnancy



Honigberg MC et al. *BMJ 2019;* Davis MB et al. Journal of the American College of Cardiology 2020

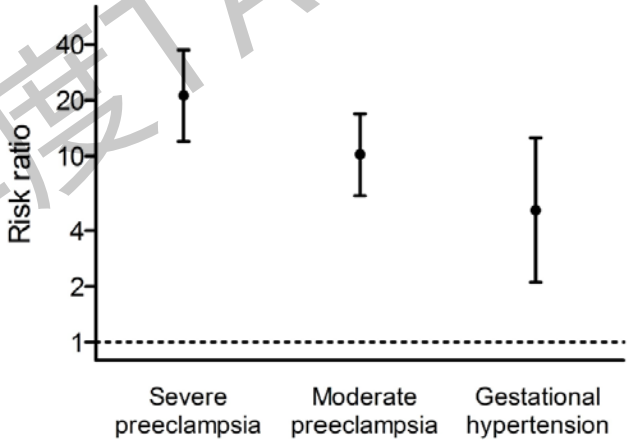
Association between Hypertensive Disorders of Pregnancy & Peripartum Cardiomyopathy



Introduction

- Meta-analysis → **women with PPCM → 3-5X to have PE**

- Hypertensive disorders of pregnancy (HDP)
  - Associated with *substantial increases in PPCM risk*
  - PPCM risk in women with HDP dramatically *increase with HDP severity* (5–21X)
  - Most risk factors of PPCM are also linked to HDP



Behrens I et al. PLoS ONE 2019

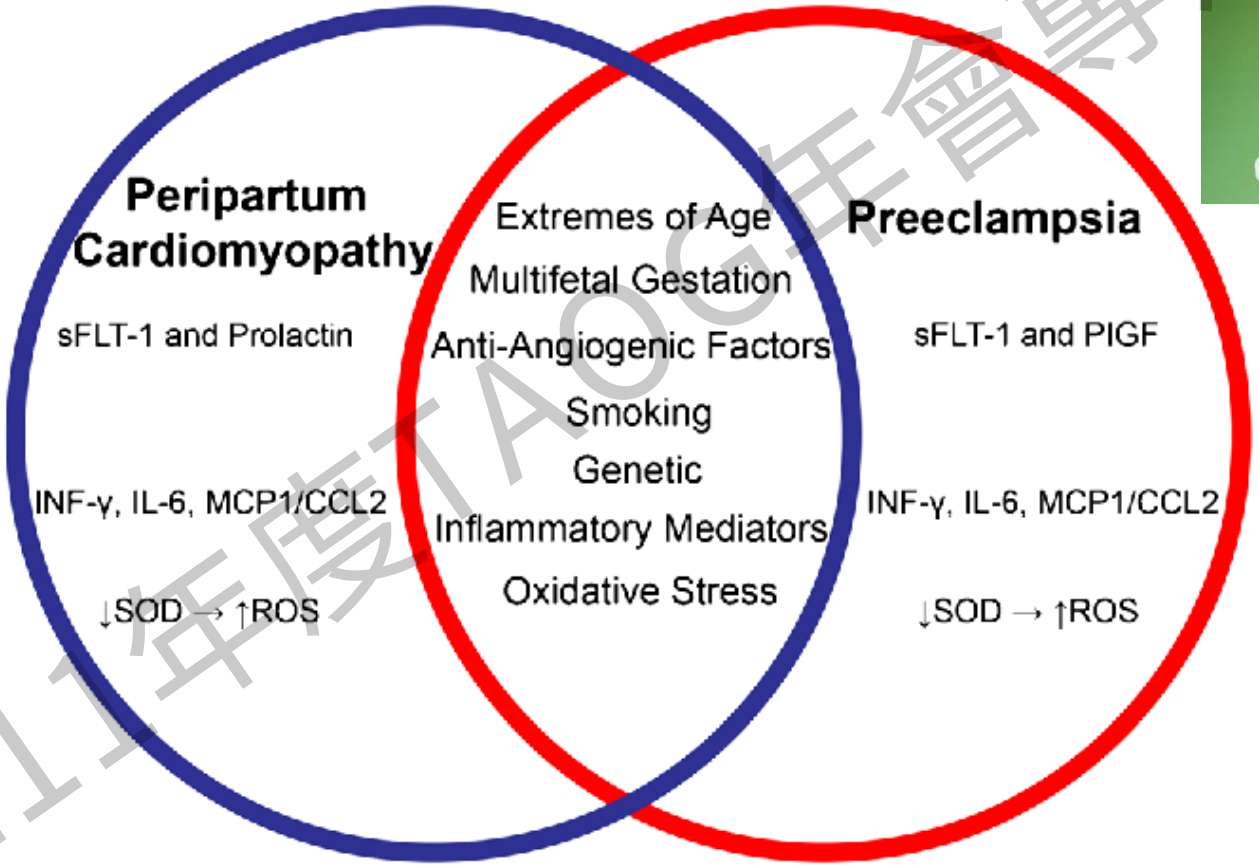
Table 1 Comparison of heart failure in peripartum cardiomyopathy and heart failure in preeclampsia

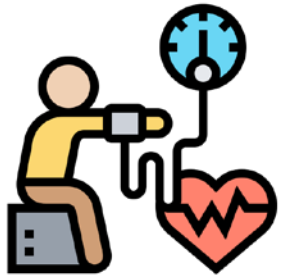
	Peripartum cardiomyopathy	Preeclampsia
Pathological mechanism	Systolic dysfunction	Diastolic dysfunction
Additional features		
Hypertension	No	Yes
Proteinuria	No	Often
Associated features		
Haemolysis	No	Yes
Abnormal liver function	No	Yes
Thrombocytopenia	No	Yes
Seizures	No	Yes
Renal dysfunction	No	Yes (proteinuria)
Vascular thrombus	Yes*	Not reported
Arrhythmia	Yes^	Not reported
Mitral regurgitation	Yes	Not reported
Echocardiography features		
Cardiac volumes and structure		
Left atrium volume	Dilated	Normal
Left ventricular volume	Dilated	Normal
Right ventricular volume	Dilated	Normal
Pericardial effusions	Infrequent and small	Frequent and larger
Left ventricular hypertrophy	No†	Frequent
Cardiac function		
Left ventricular systolic function	Reduced	Preserved¶
Contractility	Reduced	Preserved
Cardiac output	Reduced	Preserved/increased
Myocardial tissue Doppler systolic velocities	Reduced	Normal range¶
Ejection fraction	Reduced	Preserved¶
Right ventricular systolic function	Reduced	Not affected
Diastolic function	Normal†	Abnormal/reduced
Initial pharmacological treatment		
Inotropic agents	Commonly used	Uncommonly used
Systemic anticoagulation	Yes	Uncommonly used
Antihypertensive agents	No	Yes
Parenteral magnesium sulphate	No	Yes

*Reported with severe ventricular dysfunction; ^Atrial fibrillation, ventricular tachycardia and ectopics reported; †Unless hypertension present before pregnancy; ¶Systolic function may be reduced in the presence of malignant hypertension.

Dennis AT et al. International Journal of Obstetrics Anesthesia 2014

Mutual risk factor



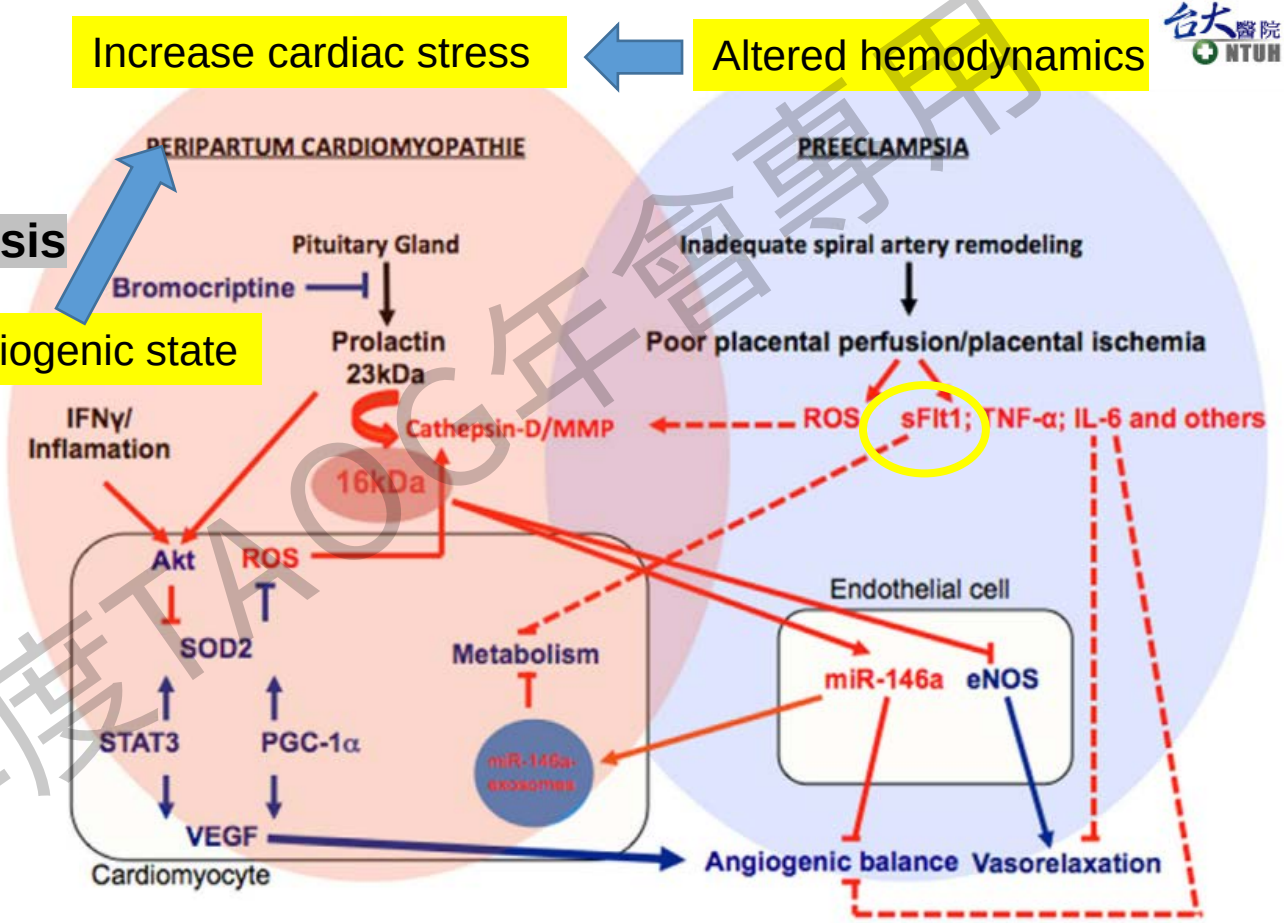


Parikh P et al. Current Hypertension Reports 2018

Pathophysiology

Inflammation / Angiogenesis

- PE
  - *Placentation deficiency*
  - *Cytotrophoblast ↓*
  - *Spiral artery ↓*
  - *Perfusion of placenta ↓*
  - *Oxidative stress ↑*
  - *Antiangiogenic factors↑*
  - *TNF-α, IL-1&6, sFlt-1↑*
  - *Endothelial dysfunction*
  - *HDP ↑*



* TNF: tumor necrosis factor
* sFlt-1: soluble fms-like tyrosine kinase-1
* HDP: hypertensive disorders of pregnancy

Pfeffer T et al. Current Problems in Cardiology 2018

Genetically

- **Women with PE** → more likely to carry protein-altering mutations in genes associated with cardiomyopathy, particularly in **TTN**
- **Mutations promoting cardiomyopathy are prevalent in preeclampsia, idiopathic cardiomyopathy, and PPCM** → Important risk factors for a widening spectrum of CVD

Gene variants associated with idiopathic and PPCM are also associated with PE

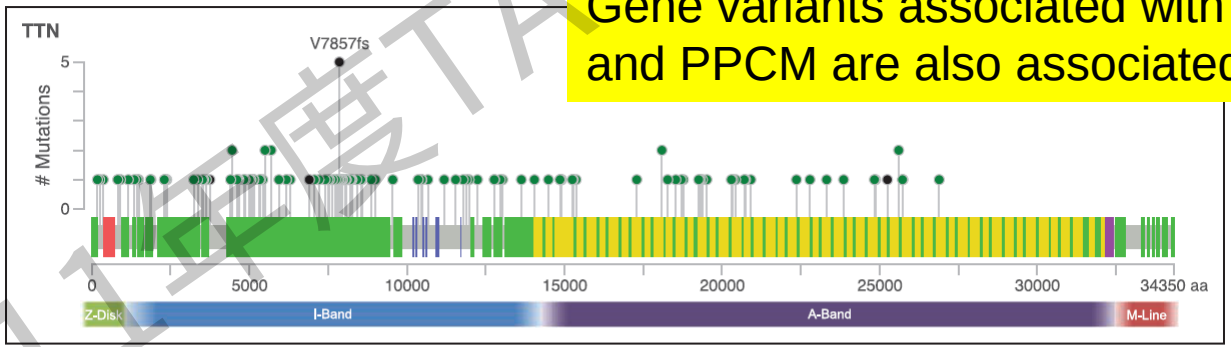


Figure 2. Distribution of rare damaging/truncating mutations in preeclampsia subjects along the protein structure of *TTN*.
The green colored dots represent damaging missense mutations, and the black dots show truncating mutations. The distinct bands of *TTN* gene are depicted below the protein schematic, based on data from Schwarz et al.[32] The mutations in preeclampsia subjects are predominantly clustered in the I-Band of *TTN*.

Gammill HS et al. Circulation 2018

Take Home Message

- PE
  - A relationship between the **severity of SARS-CoV-2 infection and PE**
  - Aspirin prevention: **≥100 mg/day, ≤GA16wks** → preterm PE
- PPCM
  - An idiopathic cardiomyopathy → *A diagnosis of exclusion*
  - Mimic typical symptoms of pregnancy / early post-partum period that can be easily overlook
  - **LVEF before the subsequent pregnancy** is the strongest predictor of outcomes
  - Women should be informed of significant risk for recurrent PPCM and death
- **sFlt-1** is believed to be the connection between HDP and PPCM

Thank you!