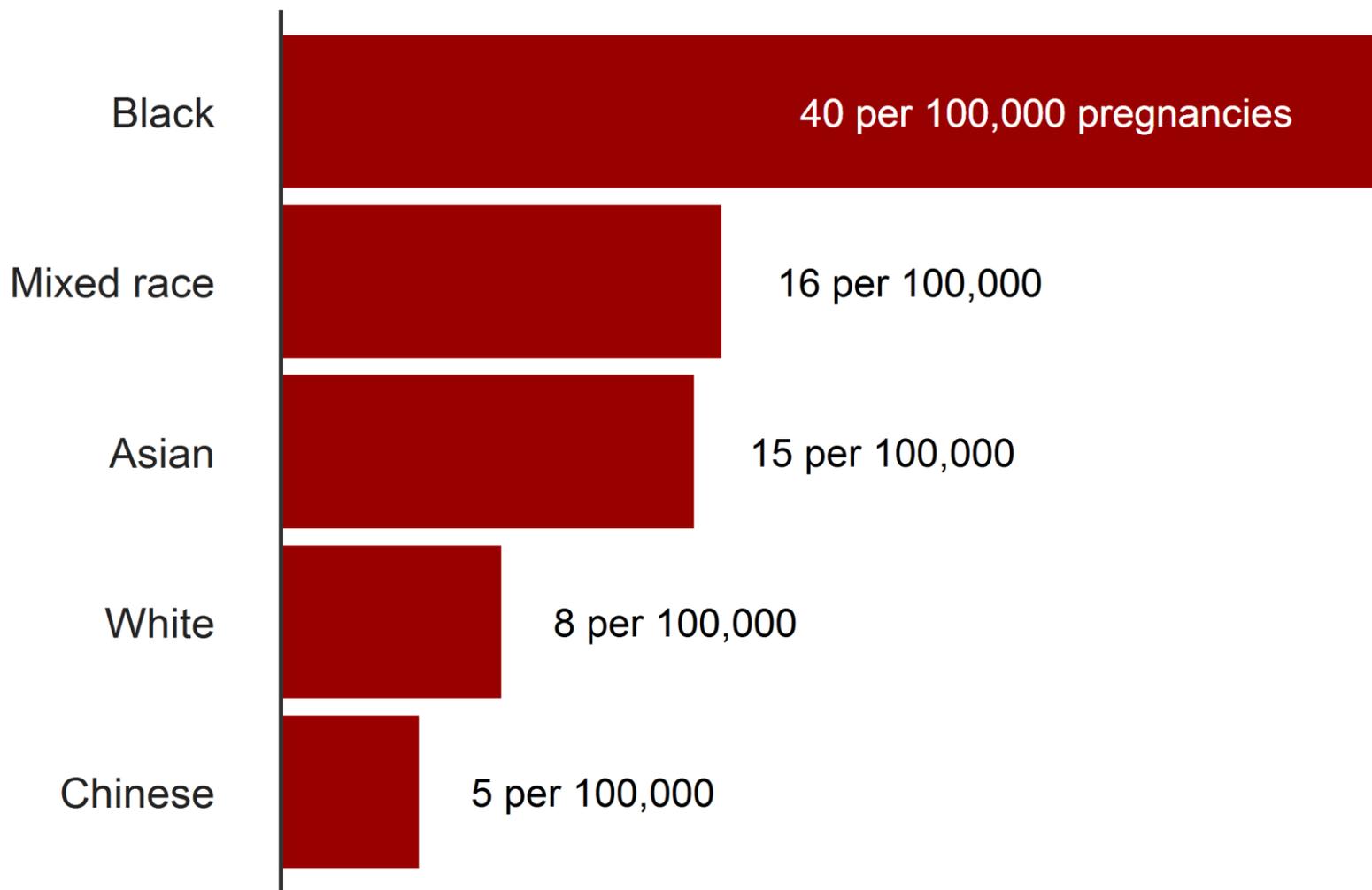


***Hematologic and Vascular
Concepts and Considerations in
the Management of Pregnancy***

Kenneth Braunstein, MD

Maternal death rates in the UK, 2014 to 2016

Race of women dying during or up to six weeks after pregnancy

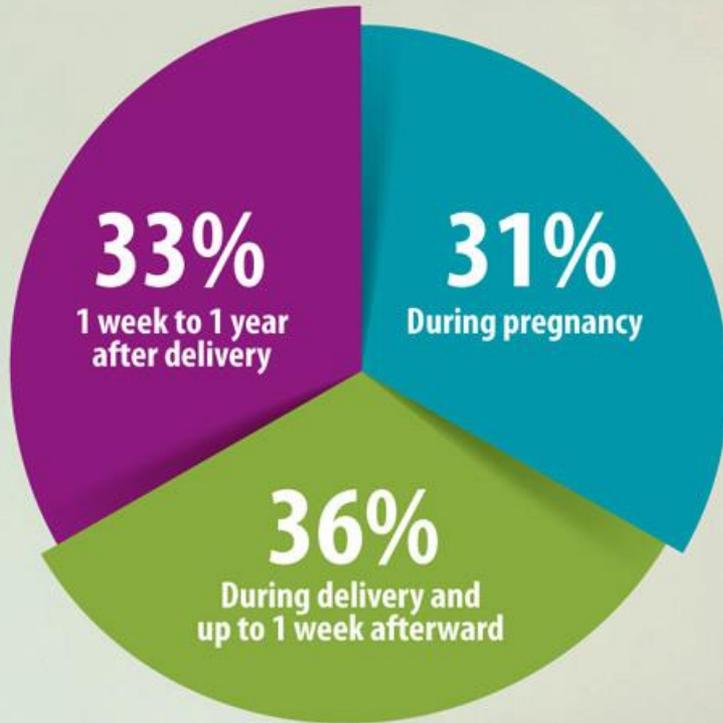


Note: Researchers used England figures to calculate UK rates

MAJOR CAUSES FOR MATERNAL MORBIDITY OR DEATH IN PREGNANCY (APPROXIMATELY 60% OF PREGNANCY-RELATED DEATHS ARE DEEMED PREVENTABLE)

- **Cardiomyopathy**
- **Venous Thrombosis And Embolization**
- **Cerebral Vascular Accidents**
- **Preeclampsia/Eclampsia**
- **Hemorrhage And Pulmonary Edema**

Death can happen up to a year after delivery.



EIGHT SUGGESTED MEASURES TO LOWER MORBIDITY AND MORTALITY IN 2020

1. Measure and monitor BNP levels for heart issues and preeclampsia.
2. Follow the YEARS algorithm with D-Dimer level for DVT and pulmonary emboli detection.
3. Evaluate and treat for the angiogenic cause(s) of preeclampsia (once FDA approved), evidence of posttraumatic stress syndrome, and the presence of insomnia to lower cerebral vascular events.
4. Pending FDA approval, measure sFlt-1 and PlGF levels and the sFlt-1/PlGF ratio to predict who will be having preeclampsia and, thus, who are also at highest risk of cerebral vascular event.
5. Insure normal vitamin D levels in pregnant women.
6. Until prokineticin-1 becomes clinically available, measure pregnancy-associated plasma protein levels as early as first trimester of pregnancy to forecast an increased risk of preeclampsia later on in pregnancy.
7. Give antithrombin III concentrate in pregnancy-associated DIC and liver disease of preeclampsia to stop both the DIC and the bleeding.
8. Give a large dose of Lasix[®] intravenously, once blood products replacement and bleeding has stopped, to prevent pulmonary edema and save lives.

CARDIOMYOPATHY CAUSES 23% OF U.S. MATERNAL DEATHS



Normal Chest X-ray



Cardiomyopathy With Enlarged Heart

BRAIN NATRIURETIC PEPTIDE

- Brain natriuretic peptide (BNP) is a protein/hormone that is made in the heart.
- In heart failure, patients' BNP levels are higher than normal in order to compensate for the increase in pressure in the heart that these patients have.
- BNP does this by vasodilating patients' arteries and thus lowering their blood pressure by widening blood vessels and thereby lowering the venous pressure near the right side of the heart. It also acts like a diuretic by increasing urine output by promoting sodium excretion by the kidneys.
- African Americans have lower levels of plasma NTproBNP (a precursor for BNP) than Caucasians, which may be partially owing to genetic variation. Low natriuretic peptide levels in African Americans may contribute to the greater risk for HTN and its sequelae in this population.

THE BNP TEST

BNP levels may be performed on whole blood or plasma obtained either by venipuncture (available in USA) or by a finger prick test just like doing a glucose determination (not currently available in USA) with results being available in about 15 minutes with both techniques.

QUIDEL TRIAGE[®] METERPRO FOR WHOLE BLOOD OR PLASMA BNP AND D-DIMER TESTING IN PHYSICIAN'S OFFICE



Results in 15-20 minutes.

<https://www.quidel.com/immunoassays/triage-test-kits/triage-meterpro>

THE BNP TEST

- The usefulness of the rapid measurement of B-type natriuretic peptide in the diagnosis and monitoring of heart failure has been verified.
- The Quidel Triage[®]MeterPro may be purchased by obstetricians for their office for about \$5579.43 new and as low as \$100 on eBay.
- Cost of the BNP test is about \$31.56 with a GA Medicare reimbursement of \$39.26 and a GA Medicaid reimbursement of \$42.69.

BNP IN NORMAL PREGNANCY

- Using postpartum 6-12 month levels as controls, both BNP and NT-proBNP (a precursor of BNP) levels remain stable throughout a normal pregnancy including delivery.
- However, in the 48 hours post parturition both levels rise and then return to normal levels, which for BNP is <100 pg/ml.
- Left side of the heart volume also increases during this 48 hour period without indications of right side of the heart dysfunction but makes postpartum mothers vulnerable to volume overload.

B-TYPE NATRIURETIC PEPTIDE IN PREGNANT WOMEN WITH KNOWN HEART DISEASE

- During pregnancy, the median peak BNP level was higher in women with heart disease (79 pg/ml with a range of 51 to 152 pg/ml) compared to women without heart disease (36 pg/ml with a range of 21 to 43 pg/ml).
- A BNP <100 pg/ml had a value of 100% for identifying women who did not have adverse cardiac events during pregnancy.
- A BNP >100 pg/ml had a value of 100% for identifying women with clinically adverse cardiac events.

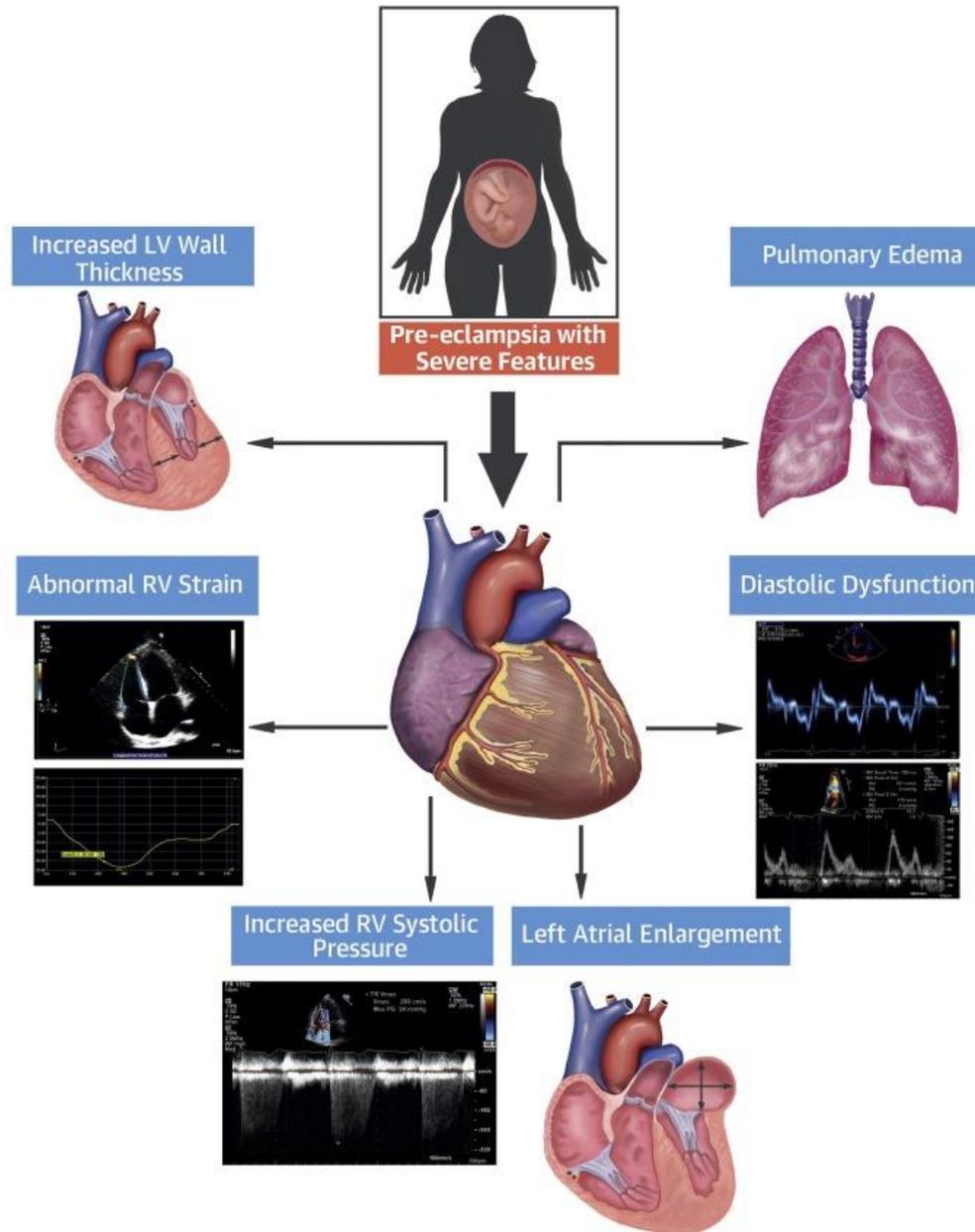
BNP LEVELS IN HYPERTENSIVE MOTHERS

- Of 52 women with hypertension as a predictor for preterm birth, 34% had an elevated BNP (>100 pg/ml), as compared to 12.5% of those with hypertension with a normal term delivery.
- Of 41 women whose newborns required NICU stay, 34.2% had an elevated BNP (>100 pg/ml), as compared to 15.4% of those whose newborns did not require NICU care.

BNP IN PREECLAMPSIA AND PERIPARTUM CARDIOMYOPATHY

- Women who remain healthy during pregnancy do not have a change in their BNP levels.
- Patients with preeclampsia have a significantly higher BNP level in the third trimester and these levels remain elevated for 3-6 months postpartum.
- Median BNP levels:
 - normal patients 17.8 pg/ml
 - mild preeclampsia 21.1 pg/ml
 - severe preeclampsia 101 pg/ml.
- 38 patients with PPCN (peripartum cardiomyopathy), compared to healthy peripartum controls, were found to have NT-proBNP levels that were approximately five times higher than the controls. Another study of 102 patients with PPCM found only four patients had a BNP under 100 pg/mL, and a mean serum BNP of 1258 pg/mL.

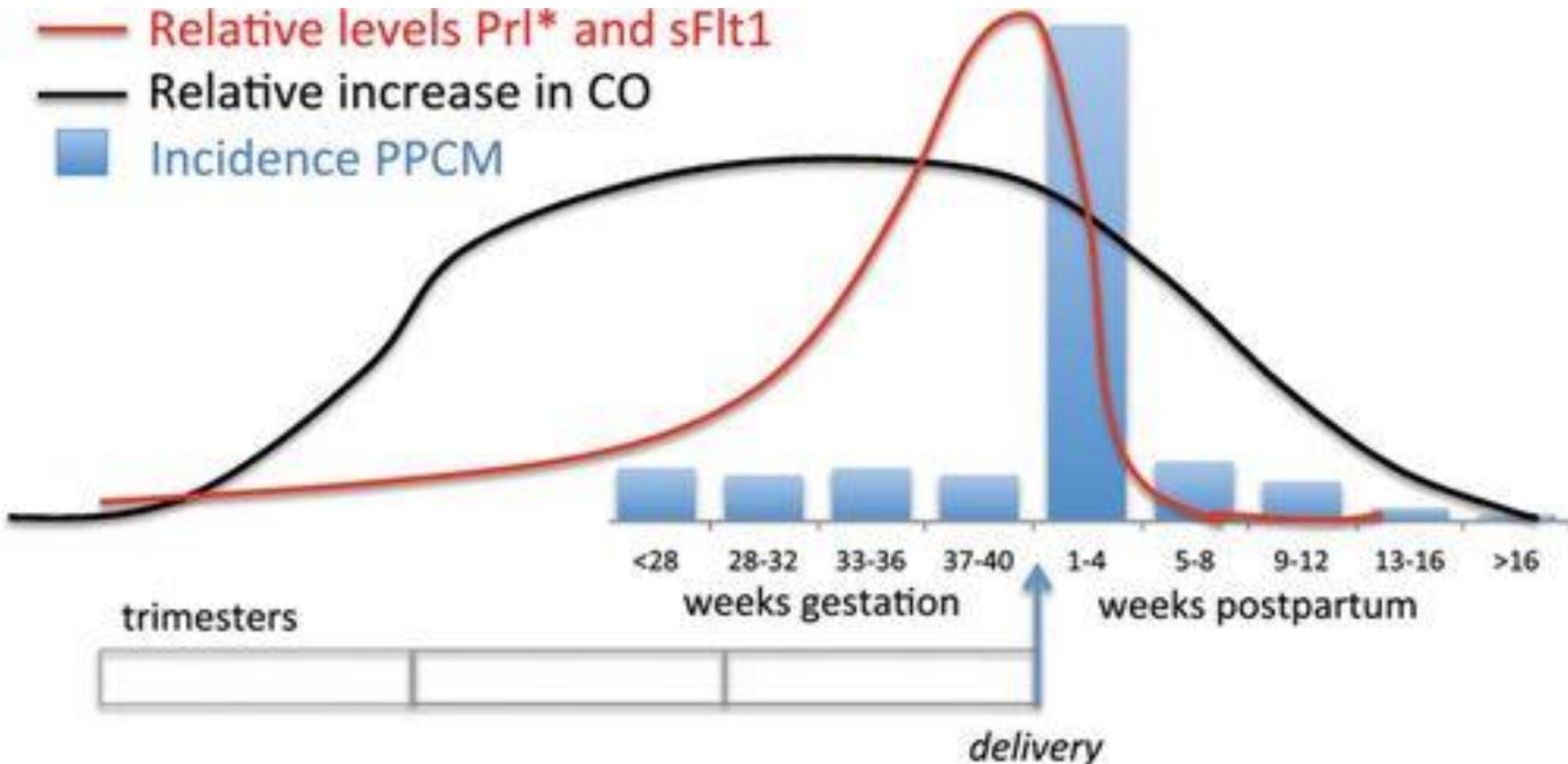
CENTRAL ILLUSTRATION: Pre-Eclampsia With Severe Features: Effects on the Heart



PREECLAMPSIA IS LINKED TO PERIPARTUM CARDIOMYOPATHY

- A recent meta-analysis of 22 studies covering 979 cases of PPCM showed an overall prevalence of preeclampsia of 22%, >4 times the 3% to 5% population prevalence.
- Any hypertensive disorder (preeclampsia, gestational hypertension, or chronic hypertension) was present in 37% (range, 29%–45%) of cases of PPCM.

CAN A RISE IN PROLACTIN AND sFlt-1 (AN ANGIOGENIC FACTOR) LEVELS PREDICT PERIPARTUM CARDIOMYOPATHY?



Comparison of timing during and after pregnancy of hemodynamic changes, exemplified as cardiac output (CO; in black), elevations in prolactin and soluble Fms-like tyrosine kinase 1 (sFlt1) hormones (red), and incidence of peripartum cardiomyopathy (PPCM; blue bars).

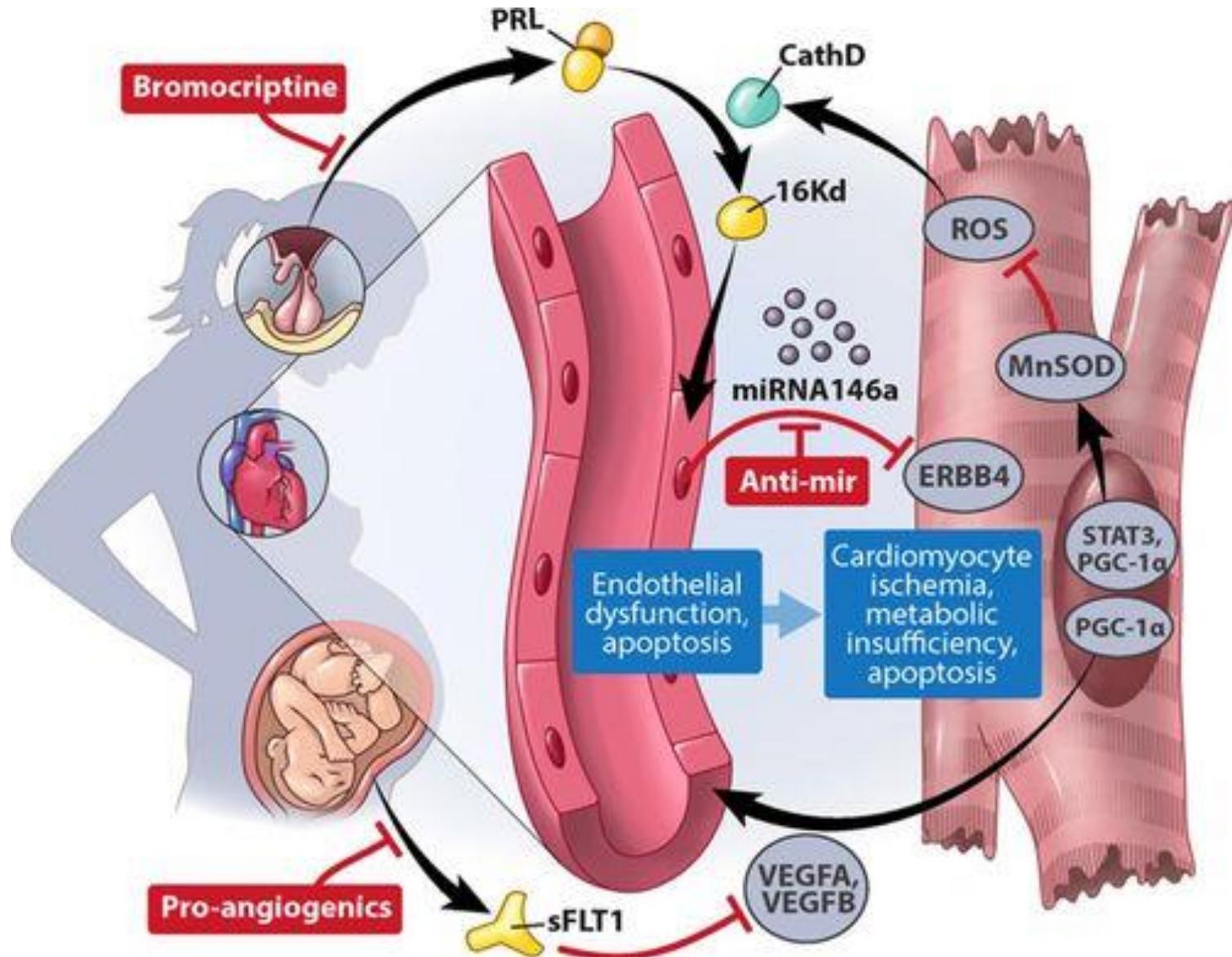
CALIFORNIA MATERNAL QUALITY CARE COLLABORATIVE: ROLE OF BNP

- “BNP is a simple, readily available, relatively inexpensive test (costs about \$40.00) that may assist clinicians in triaging patients who present with symptoms for further diagnostic testing.
- This test can be of particular value for obstetricians as most women exhibit some degree of fatigue, shortness of breath, palpitation and/or swelling during pregnancy. Adding BNP to routine evaluation of cases with symptoms out of proportion to pregnancy or to those patients presenting with symptoms suggestive of cardiac disease may reduce potential morbidity.”

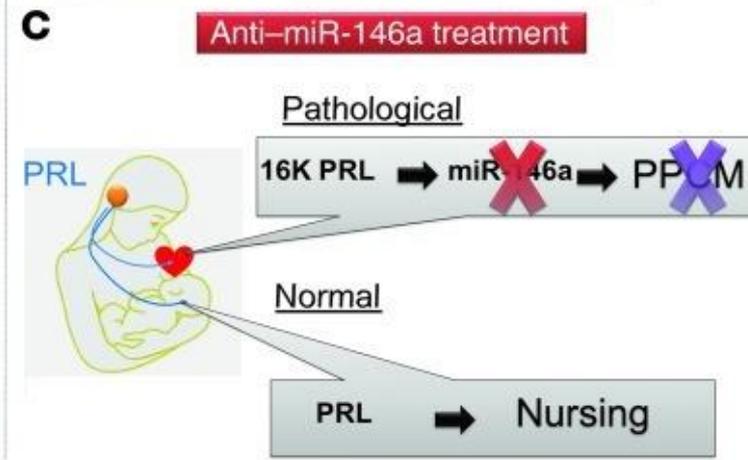
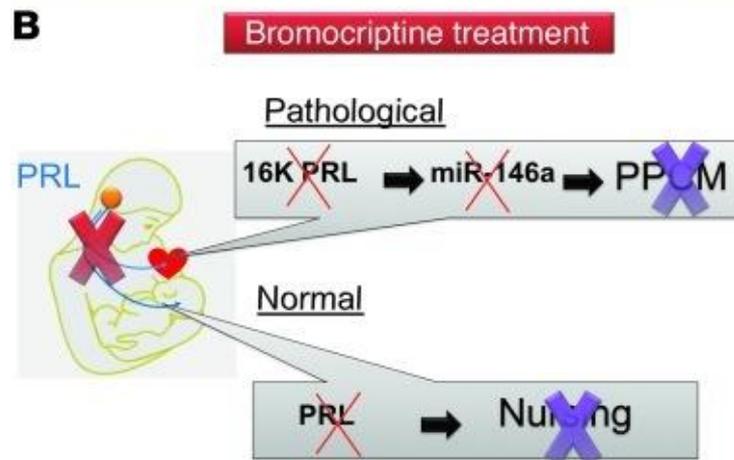
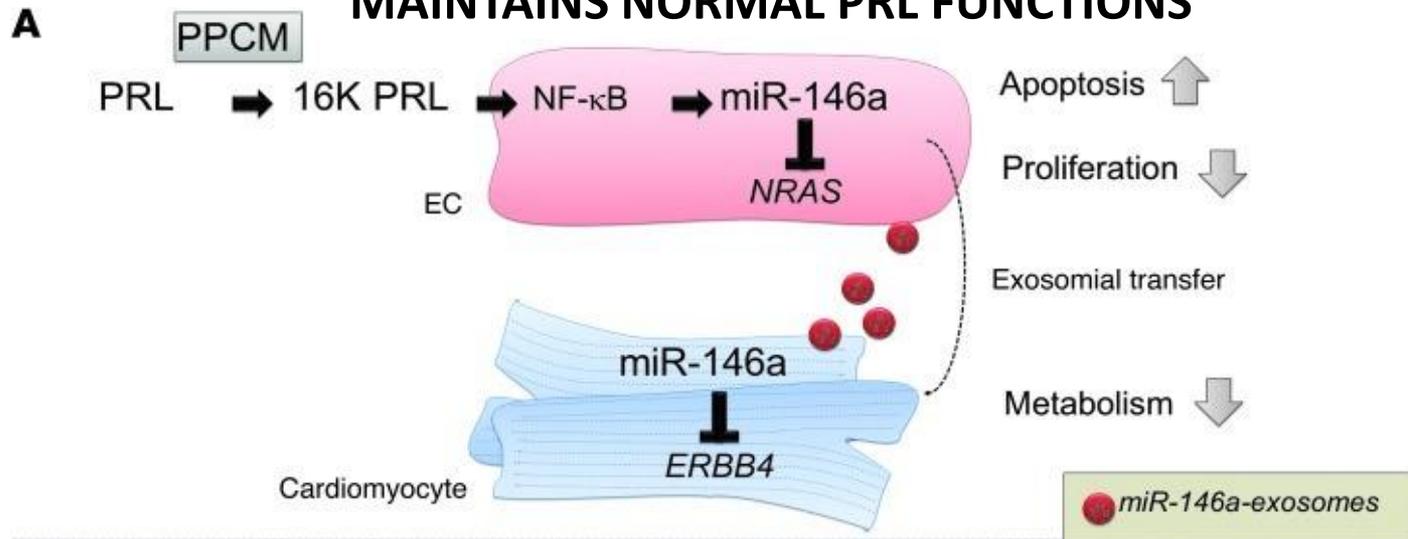
AFRICAN AMERICAN MOTHERS HAVE AN INCREASED RISK FOR CARDIOMYOPATHY

- A population-based study, utilizing United States National Hospital Discharge Survey data, found that 32.2% of PPCM cases occurred in women identified as African American, while the percentage of African American mothers in the population during the same time period was 15.7%.
- In Augusta, Georgia MCG found that African American race had an univariate odds ratio for PPCM of 15.7-fold.

VASCULO-HORMONAL HYPOTHESIS OF THE PATHOPHYSIOLOGY OF PERIPARTUM CARDIOMYOPATHY (PPCM)



ROLE OF miR-146a IN PPCM AND PROPOSED ALTERNATIVE TREATMENT THAT MAINTAINS NORMAL PRL FUNCTIONS



(A) In PPCM patients, PRL is cleaved into 16K PRL, which (via NF-κB) increases miR-146a expression in ECs. By targeting NRAS, miR-146a reduces proliferation and viability in ECs and contributes to destruction of the cardiac microvasculature. miR-146a is released from ECs protected by the exosomes that fuse with cardiomyocytes, where miR-146a targets ERBB4 and impairs metabolism. (B and C) Proposed therapeutic options for PPCM management. (B) Blocking PRL completely by use of bromocriptine eliminates pathophysiological 16K PRL, but also nursing ability. (C) Use of anti-miR-146a in less severely affected patients may improve PPCM recovery, while keeping normal nursing functions.

A THEORY ON HOW PERIPARTUM CARDIOMYOPATHY OCCURS

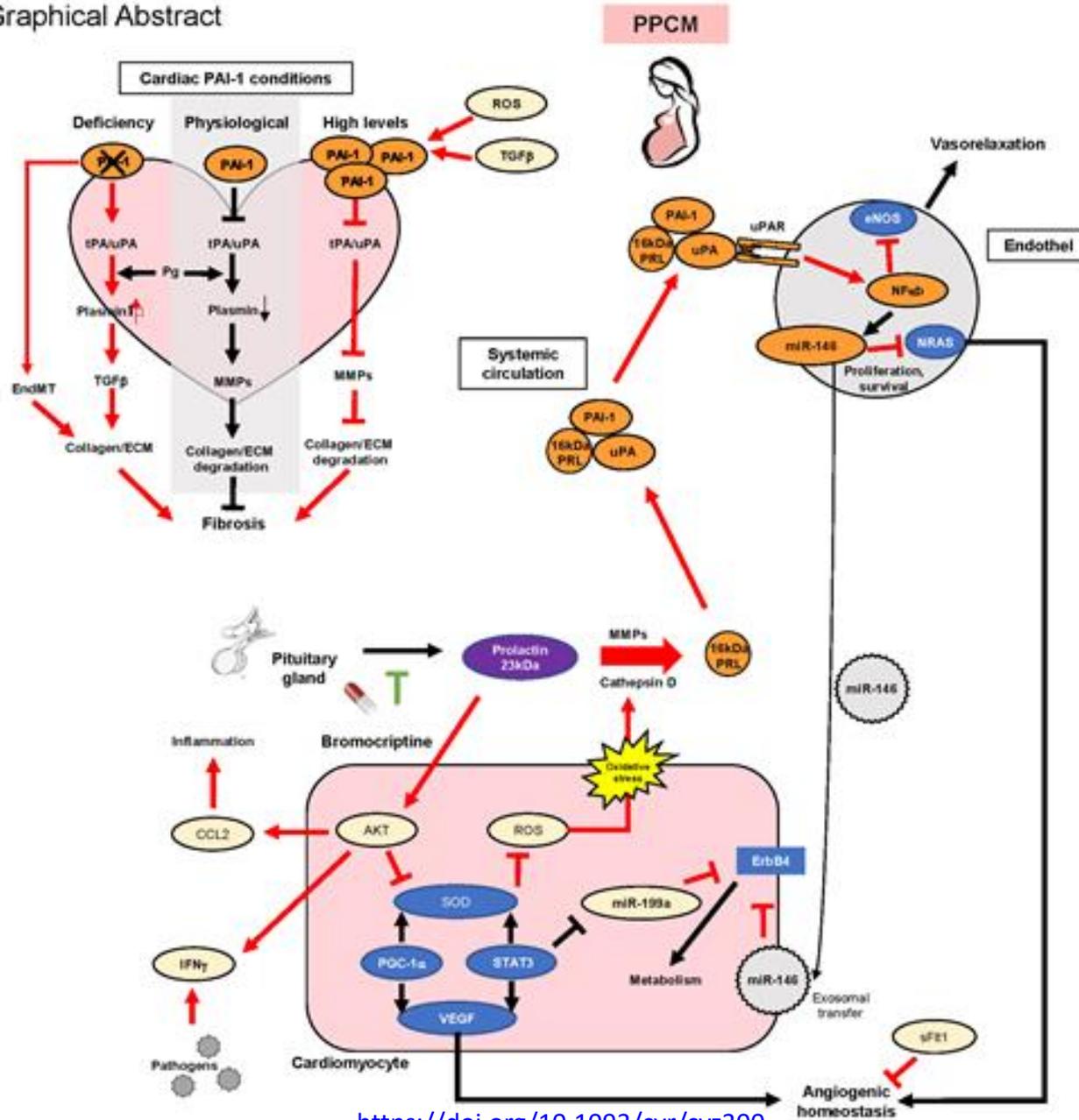
“In PPCM patients, circulating and cardiac PAI-1 expression are upregulated. While circulating PAI-1 may add 16kDa-PRL to induce vascular impairment via the uPAR/NF-κB/miR-146a pathway, experimental data suggest that cardiac PAI-1 expression seems to protect the PPCM heart from fibrosis. Thus, measuring circulating PAI-1 and miR-146a, together with an uPAR/NF-κB-activity assay could be developed into a specific diagnostic marker assay for PPCM, but unrestricted reduction of PAI-1 for therapy may not be advised.”

A THEORY ON HOW PERIPARTUM CARDIOMYOPATHY OCCURS

- “Our study suggests that PAI-1 adds 16kDa-PRL to induce the vascular damaging, non-canonical uPAR-NF- κ B signaling pathway as a central pathophysiology of PPCM.
- Circulating PAI-1 levels showed a positive correlation with miR-146a plasma levels.
- PAI-1, together with the uPAR-NF- κ B activity assay, emerged as a diagnostic marker for PPCM.
- The local cardiac upregulation of PAI-1 in PPCM hearts seems to protect from cardiac fibrosis and inflammation, and may prevent permanent cardiac damage during acute PPCM.
- Due to its controversial role in PPCM, i.e. driving vascular damage but protecting the heart from fibrosis, PAI-1 seems unsuitable as a therapeutic target to treat PPCM.”

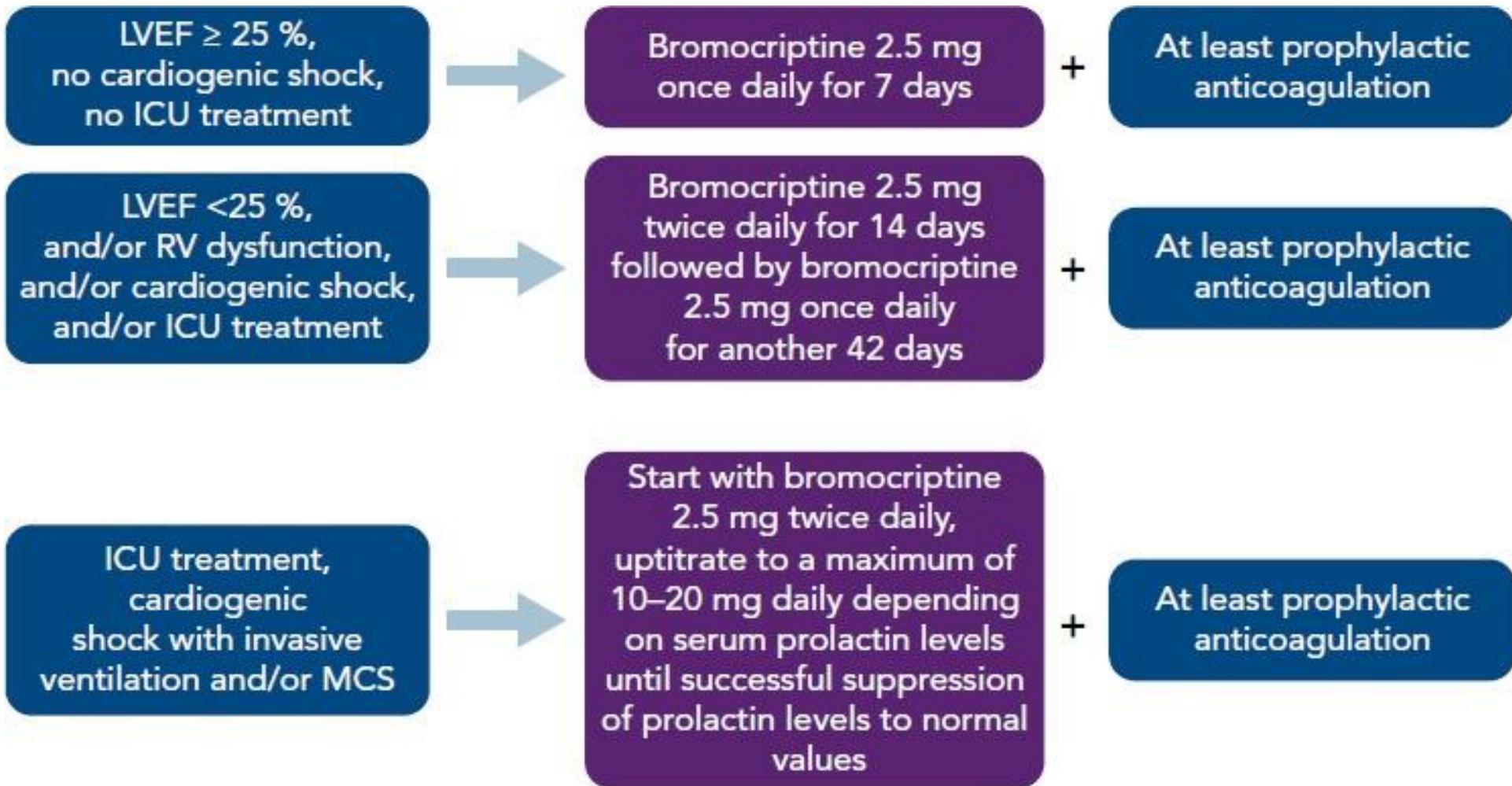
CURRENT THEORY ON HOW PERIPARTUM CARDIOMYOPATHY OCCURS

Graphical Abstract



<https://doi.org/10.1093/cvr/cvz300>

PROPOSED BROMOCRIPTINE TREATMENT OF ACUTE PERIPARTUM CARDIOMYOPATHY (FROM GERMANY)

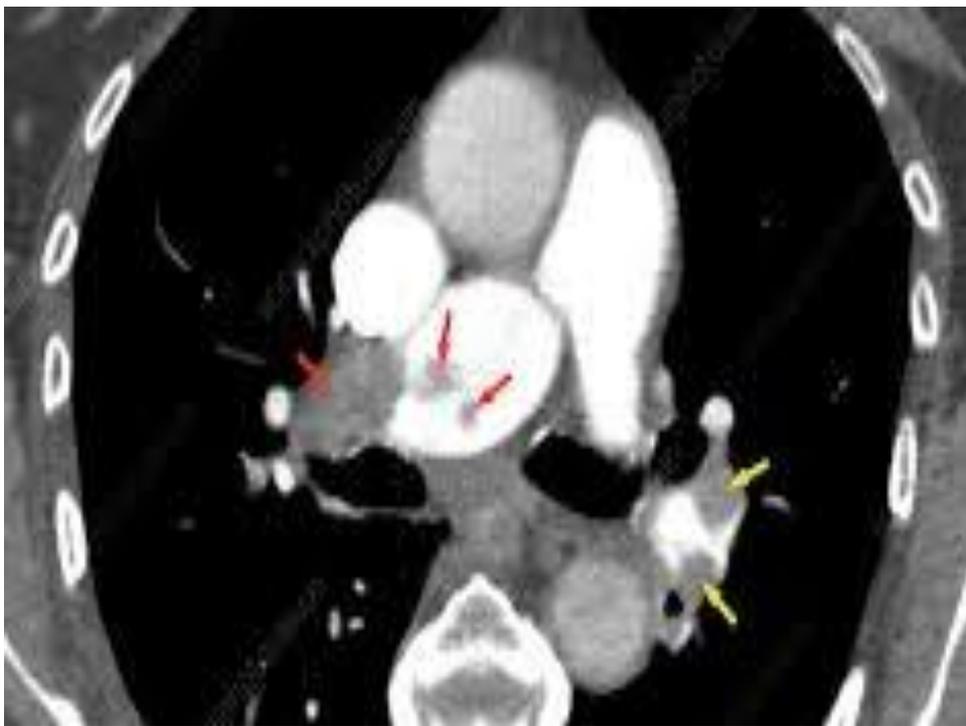


ICU = intensive care unit; LVEF = left ventricular ejection fraction; MCS, mechanical circulatory support (e.g. extracorporeal membrane oxygenation, percutaneous microaxial pump); RV = right ventricle.

MY FIRST SUGGESTION

Measure and monitor BNP levels (a readily available blood test) for heart issues and preeclampsia.

PULMONARY EMBOLISM CAUSES 20% OF U.S. MATERNAL DEATHS



CT Scan of Multiple Pulmonary Emboli

Surgical Removal of a Pulmonary Embolus

RISK STRATIFICATION AND D-DIMER FOR PULMONARY EMBOLUS EXCLUSION IN PREGNANCY

- The YEARS algorithm:

YEARS Criteria:

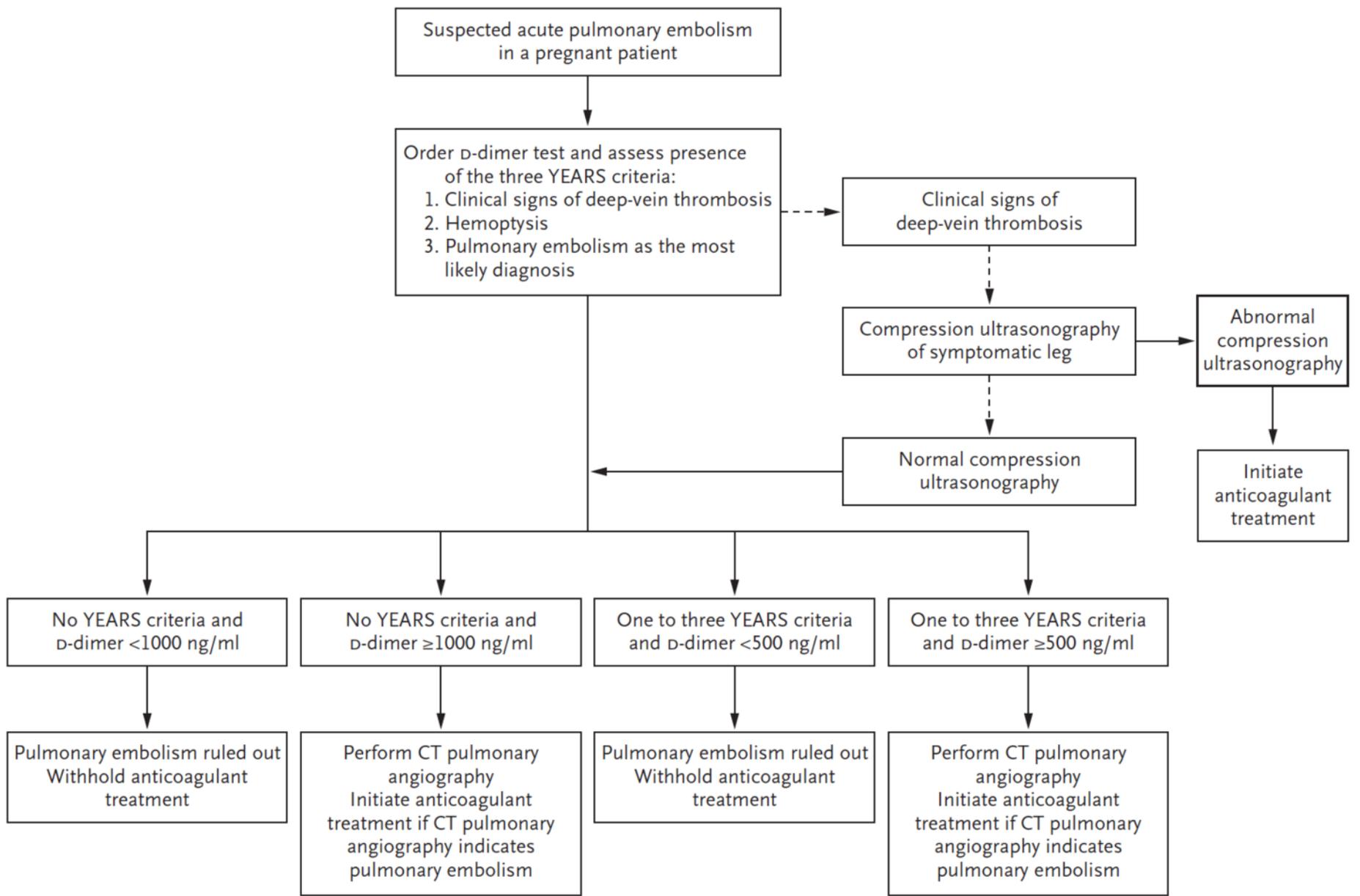
clinical signs of deep-vein thrombosis

hemoptysis (coughing up blood)

other clinical signs of pulmonary embolism

Measurement of the level of D-dimer (a small protein fragment present in the blood after a blood clot is degraded)

- Pulmonary embolism is ruled out if none of the three (YEARS algorithm) criteria are met and the D-dimer level is less than 1000 ng per milliliter or if one or more of the three criteria are met and the D-dimer level is less than 500 ng per milliliter.



RESULTS OF YEARS CRITERIA IN PREGNANCY

- When a total of 510 women were screened, CT pulmonary angiography was not indicated, and, thus was avoided, in 195 patients (39%).
- CT pulmonary angiography was avoided in 65% of patients, who began the study in the first trimester, and in 32% of patient, who began the study in the third trimester.

COST EFFECTIVENESS OF YEARS

ALGORITHM

- Price of Triage[®] MeterPro D-Dimer cartridge is about \$31.50, average Medicaid reimbursement is about \$7.50, and average Medicare reimbursement is about \$12.56.
- Average price of CT pulmonary angiogram is \$2586 with Medicare average reimbursement of \$300.14, average Medicaid reimbursement of \$160.27, and average commercial insurance reimbursement of \$1163.70.

MY SECOND SUGGESTION

Follow the YEARS algorithm with D-Dimer levels (a readily available blood test) for DVT and pulmonary emboli detection.

CEREBRAL VASCULAR ACCIDENT (STROKE) HAS A 10% MORTALITY



POSTPARTUM CEREBRAL VASCULAR EVENTS

- Pregnancy-associated stroke is a rare event with an incidence of approximately 34 per 100,000 deliveries.
- While a pregnancy-related stroke is usually not fatal, it is a cause of lifelong severe disability.
- Analysis by the Centers for Disease Control and Prevention (CDC) showed that in the US ***postpartum admissions for pregnancy-associated stroke increased 83% from 1994–1995 to 2006–2007.***

WHAT IS THE ROLE OF HYPERTENSION IN PREGNANCY-ASSOCIATED STROKE?

- High blood pressure (BP) in pregnant or postpartum patients, and in particular systolic BP of 160 mm Hg or higher, may be associated with pregnancy-associated stroke.
- The American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy **supports monitoring patients with hypertensive diseases of pregnancy for at least 72 hours postpartum and then again 7–10 days after delivery or earlier if symptoms are present.**

BUT IT IS NOT JUST HYPERTENSION!

Risk of postpartum stroke differed by specific hypertensive diseases of pregnancy:

preeclampsia superimposed on chronic hypertension (72.0/100,000 deliveries)

**severe preeclampsia
(67.9/100,000 deliveries)**

**mild preeclampsia
(46.0/100,000 deliveries)**

**gestational hypertension
(22.5/100,000 deliveries)**

BUT IT IS NOT JUST HYPERTENSION

“Our data demonstrate the challenging nature of reducing risk of postpartum stroke readmission because **more than 80% of patients readmitted with pregnancy-associated stroke did not have a diagnosis of hypertensive diseases of pregnancy or chronic hypertension during their index hospitalization.**”

CEREBRAL VASCULAR ACCIDENTS

INCIDENCE WAS UP 23% IN YOUNG ADULTS OVER 12 YEARS

- Incidence of stroke in young adults has increased exponentially with age.
- **Women were more affected than men, most prominently in the youngest patients (18–44 years).**
- The relative proportion of ischemic stroke increased with age (**for 18–24 years: 38.3% and for 44–49 years: 56.5%**).
- The relative proportion of intracerebral hemorrhage decreased with age (for 18–24 years: 34.0% and for 44–49 years: 18.3%).
- Incidence of any stroke in young adults increased in 12 years (for 1998: 14.0/100,000 person-years and for 2010: 17.2/100,000 person-years; +23%; $p < 0.001$).
- This was driven by an increase in those aged over 35 years and the ischemic stroke incidence.
- However, during the same time period the incidence of stroke decreased in those ≥ 50 years (a net decline of 11%; $p = 0.009$).
- **Therefore, the incidence of any stroke in the young increases with age (particularly in patients over 35), is higher in women than men aged 18–44 years, and has increased overall by 23% in one decade.**

LATEST DATA ON INCREASE OF WOMEN SERVING IN THE MILITARY

- From 1973 to 2010 the number of active-duty enlisted women in the military grew from about 42,000 to 167,000. By February, 2018 that number had risen to 213,851 women, about 16 percent of the total force.
- In 2010 nearly one-third (31%) of active-duty women were African American.
- Since the 1990s, changes in military policies and a decade long conflict have contributed to **an increase in combat exposure among women, from 7% among pre-1990 veterans to 24% of post-1990 veterans.**

POSTTRAUMATIC STRESS DISORDER AND CEREBRAL VASCULAR ACCIDENTS: A HAZARD FOR PREGNANT VETERANS AND OTHERS

In a study by the VA in veterans, PTSD is associated with a significant increase in risk of early incident transient ischemic attack (TIA) and ischemic stroke independent of established stroke risk factors, coexisting psychiatric disorders, and healthcare utilization. Sex moderated the relationship for adults with ischemic stroke but not TIA. These findings from the largest study to date on this issue confirms previous smaller studies' findings that psychological factors, including PTSD, may be important targets for future age-specific stroke prevention strategies for young adults.

THE VA DATA ASSOCIATING POSTTRAUMATIC STRESS DISORDER AND ISCHEMIC CEREBRAL VASCULAR ACCIDENTS

- Over a 13-year period a study of 987 855 veterans who at baseline had no history of transient ischemic attack (TIA) or ischemic stroke, TIA and ischemic stroke were diagnosed by the Veterans Health Administration in a significant number of young patients with a mean age of 30.29.
- Posttraumatic Stress Disorder (PTSD) was diagnosed in 28.6% of the patients with an ischemic cerebral vascular event during follow-up.
- Veterans with PTSD were twice as likely to have a TIA, raising this risk factor to be more significant than that of all other established risk factors such as diabetes and sleep apnea.
- In models fully adjusted for all other risk factors, the association between PTSD and incident TIA and ischemic cerebral vascular event remains a significant risk factor for them.
- **The effect of PTSD on ischemic stroke risk was stronger in men than in women, but no effect of sex was found for TIA. Therefore, pregnant veterans, as well as pregnant women without military service, with PTSD are at an increased risk for a cerebral vascular event compared to PTSD naïve pregnant veterans and pregnant civilians with no prior military service.**

IS INSOMNIA THE ISSUE?

- Do individual symptoms of insomnia (trouble falling or staying asleep, waking up too early, and daytime dysfunction due to poor sleep) have higher risks of ischemic heart disease and ischemic stroke but not hemorrhagic stroke?
- Risks for cardiovascular disease, ischemic heart disease, and ischemic stroke are, respectively, 18%, 22%, or 10% higher in adults with any of these symptoms compared with the same risks in non-symptomatic adults.
- Associations between these three symptoms and cardiovascular disease incidence are consistently stronger in younger adults or any adult without baseline hypertension.
- No association is found between these three symptoms and hemorrhagic stroke.
- **Three insomnia symptoms insomnia (trouble falling or staying asleep, waking up too early, and daytime dysfunction due to poor sleep) are associated with an increased independent risk of total cardiovascular disease and ischemic stroke but not hemorrhagic stroke.**

YES, INSOMNIA MAY BE THE COMMON LINK TO STROKES IN YOUNG ADULTS

- Insomnia is one of the most common symptoms of PTSD, and has been reported to occur in 90-100% of Vietnam era Veterans with the disorder.
- In the Millennium Cohort Study, an ongoing epidemiologic cohort study of military health, 92% of active duty personnel with PTSD, compared to 28% of those without PTSD, reported clinically significant insomnia.
- **As these studies indicate, insomnia is the norm for Veterans with PTSD.**
- Sleep disturbances are common in pregnancy. A US National Sleep Foundation's Women and Sleep Survey in 1998 found **78% of women reported disturbed sleep during pregnancy** and 15% of women developed Restless Legs Syndrome (RLS) during 3rd trimester of pregnancy. Additionally, 15% of pregnant or recently pregnant women reported one weekday nap and 60% women reported at least one weekend nap.
- The overall prevalence of insomnia in students is 34.2% in women and 22.2% in men. **There was an almost 50% increase in sleep problems from 2010 (22.6%) to 2018 (30.5%), which is more pronounced in women students.**
- Sleep problems are both prevalent and increasing among students. This warrants attention as a public health problem in this population.

INSOMNIA IS LINKED TO ALL OF THOSE ELECTRONIC DEVICES WE NOW HAVE

- **Engaging in a greater number and range of sleep-interfering activities brought on by electronic media before going to bed has also been associated with less nocturnal sleep and more daytime sleepiness in adolescents.**
- Several mechanisms have been postulated about how media disrupts sleep. One is that **the use of media directly displaces sleep**; an adolescent or young adult may simply stay up later enjoying whatever media he or she is using. In addition, electronic media allow for greater interaction between friends. After 9:00 pm, 34% of adolescents in the study sample were text messaging, 44% were talking on the phone, 55% were online, and 24% were playing computer games. In another study of Belgian teenagers, 62% of the subjects used their phones after the lights were turned off, and phone use at this time was associated with increased daytime tiredness the next day.

IT MAY ALSO BE DUE TO PHYSIOLOGICAL CHANGES DUE TO ALL OF THOSE ELECTRONIC DEVICES WE NOW HAVE

- Another possible mechanism for the detrimental effect of electronics use on sleep is **that the light produced by electronic devices may disrupt circadian rhythms by suppressing melatonin**, resulting in the inability to fall asleep at a reasonable time. Recent studies have demonstrated that exposure to relatively low-intensity light can alter circadian rhythms and suppress nocturnal melatonin secretion.
- Media use may cause increased sleep-disrupting mental, emotional, and physiologic arousal. One study found that **subjective sleepiness was lower, sleep latency was longer, and rapid eye movement (REM) sleep was shorter in subjects after playing video shooting games**, independent of the brightness of the screen used. Another study that compared playing an interactive computer game with watching a movie on television in the evening found a decline in verbal memory performance, prolonged sleep latency, and an increase in light sleep in the computer game cohort.

MY THIRD SUGGESTION

In addition to evaluating and treating hypertension to reduce the risks of CVAs, also evaluate for and treat:

- 1) angiogenic cause(s) of preeclampsia (once FDA approved),
- 2) posttraumatic stress disorder, and
- 3) insomnia.

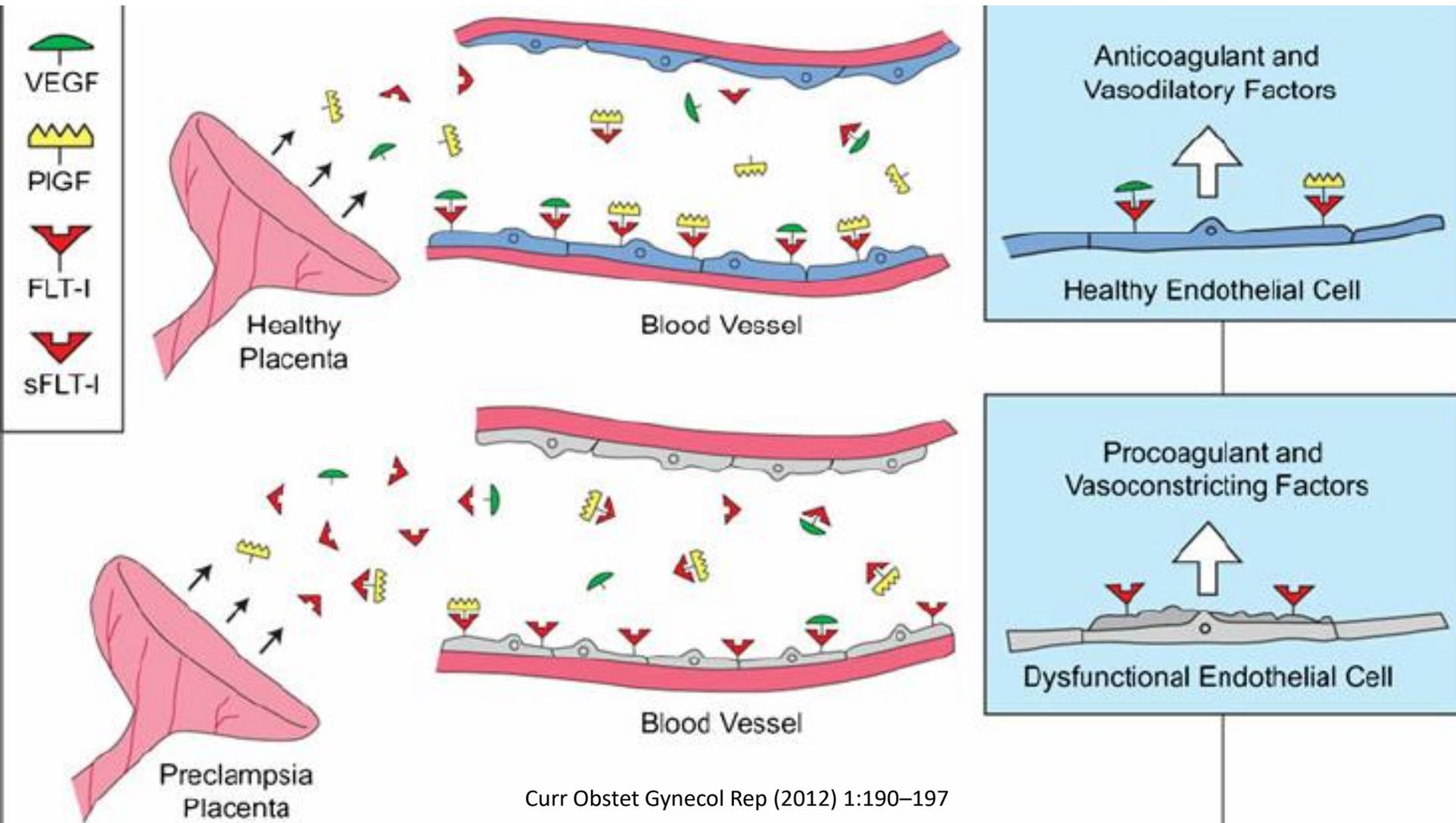
PREECLAMPSIA CAUSES 5.6% TO 11.8% OF U.S. MATERNAL DEATHS





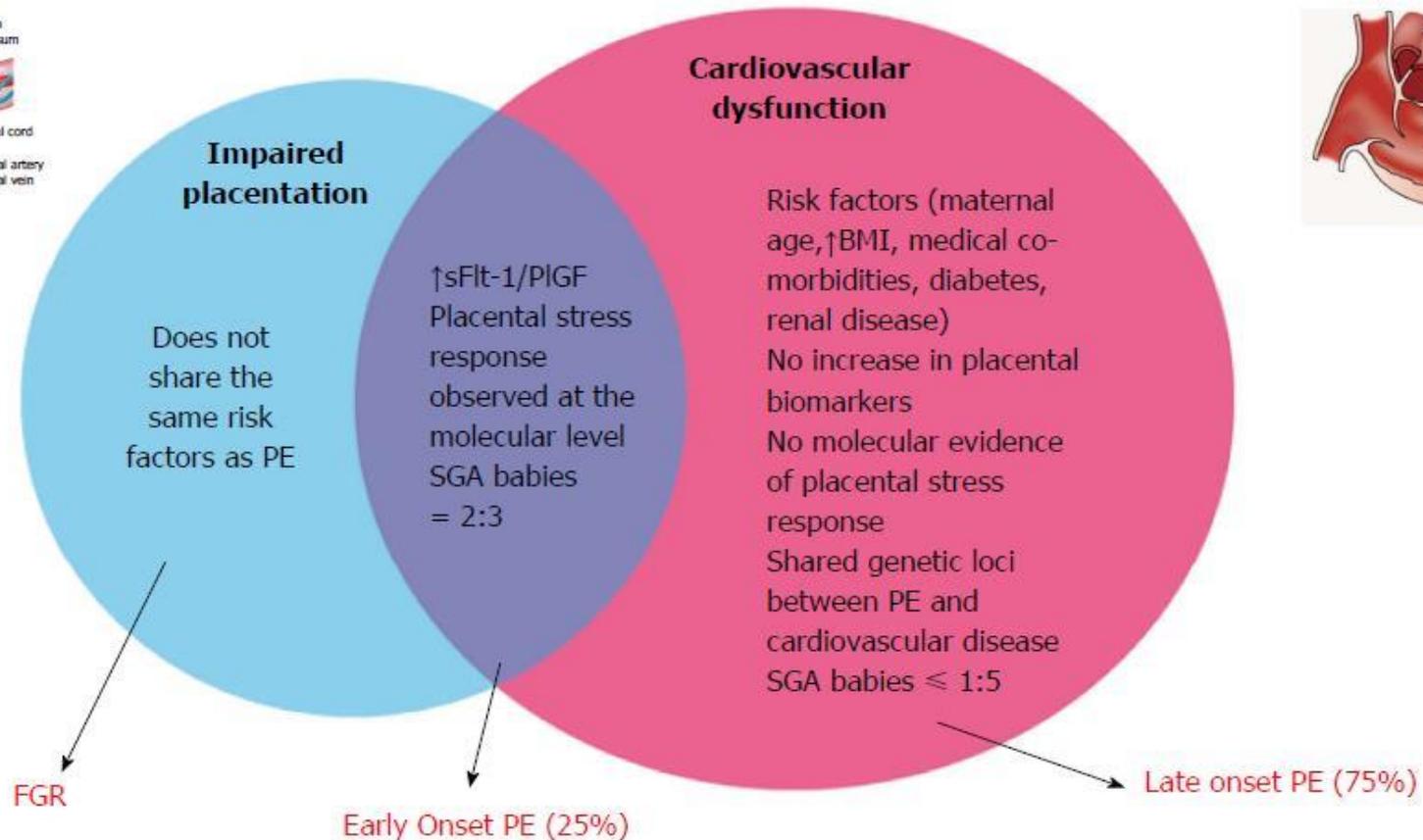
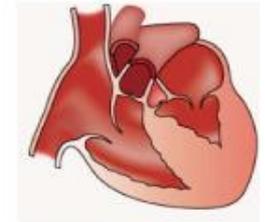
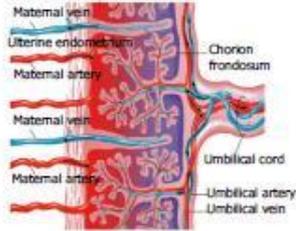
PREECLAMPSIA: A DISEASE OF THE PLACENTA?

PREECLAMPSIA: A DISEASE OF BOTH THE PLACENTA AND ANGIOGENESIS?



PREECLAMPSIA: A DISEASE OF THE PLACENTA, ANGIOGENESIS, AND THE HEART?

The dual aetiology of Preeclampsia



The key components, both specific and common to impaired placentation and cardiovascular dysfunction and their presence in fetal growth restriction, early-onset and late-onset preeclampsia. FGR: Fetal growth restriction; PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1; SGA: Small-for-gestational-age; BMI: Body mass index.

PREECLAMPSIA/ECLAMPSIA: A LETHAL COMPLICATION OF PREGNANCY

- Preeclampsia/eclampsia is one of the four most common reasons for maternal death. The perinatal mortality rate for eclampsia in the US ranges from 5.6% to 11.8%.
- African American women are two times more likely to die from eclampsia than women of other races.

PREECLAMPSIA: GOT HAVE A PLACENTA

- The development of preeclampsia does not necessarily require a uterus or indeed a fetus, as **the condition has been reported in abdominal and molar pregnancies** respectively.
- However, a placenta is essential for the disease to occur, and is therefore central in the pathogenesis.
- Furthermore, it is well documented that the cure for preeclampsia is delivery of the placenta, further supporting the crucial role played by the placenta in the development of preeclampsia.

WHAT IS A MOLAR PREGNANCY?

A molar pregnancy is a slow-growing tumor that develops from the cells that help an embryo attach to the uterus and help form the placenta after fertilization of an egg by a sperm (trophoblasts). It contains many cysts (sacs of fluid). It is usually benign (not cancer) but it may spread to nearby tissues (invasive mole). It may also become a malignant tumor called choriocarcinoma. Molar pregnancy is the most common type of what is called a gestational trophoblastic tumor. Also called hydatidiform mole.

PREECLAMPSIA: ALL IN THE FAMILY

The risk of preeclampsia is positively correlated between close relatives.

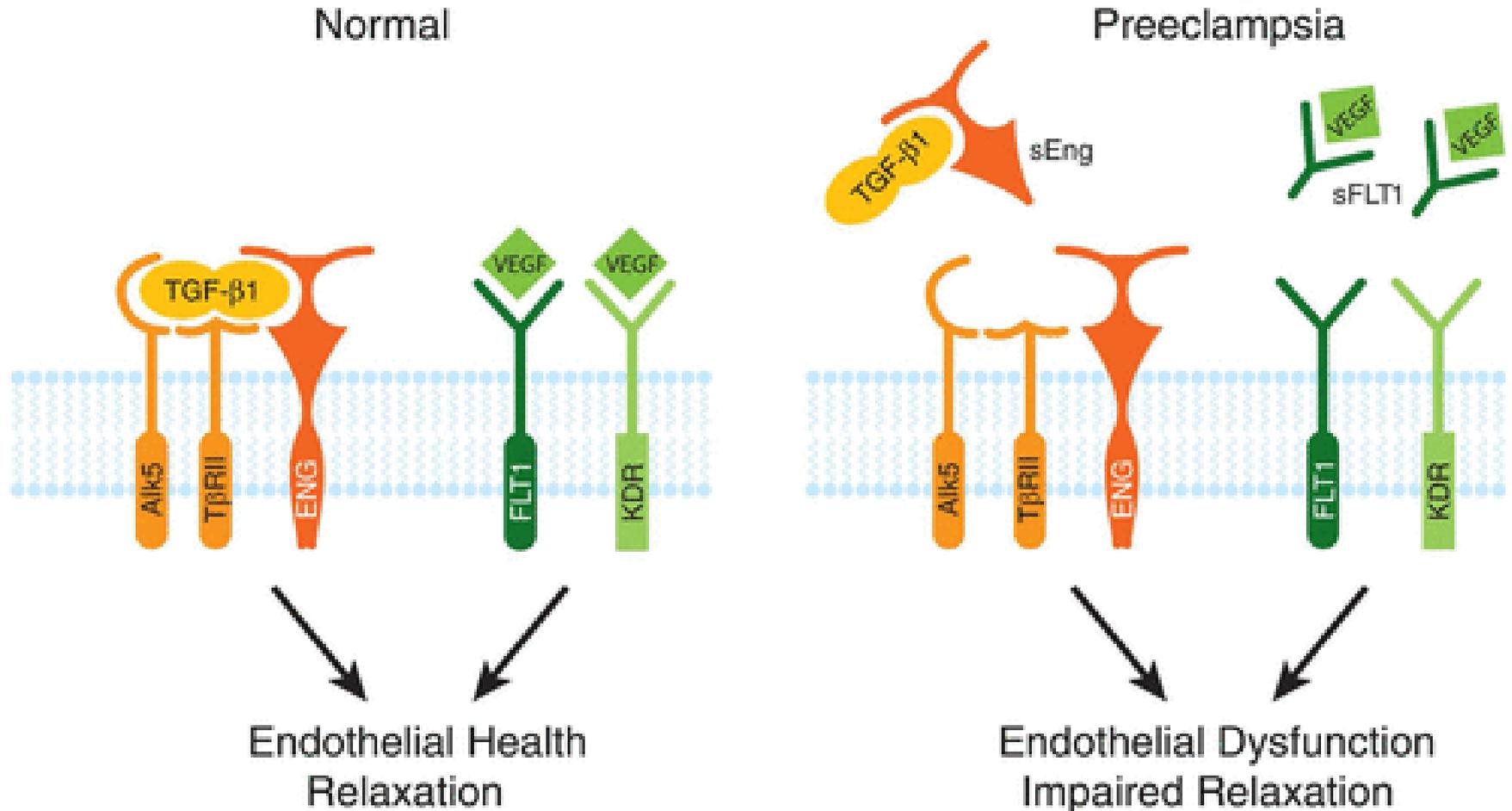
20-40% of daughters and 11-37% of sisters of women with preeclampsia also develop preeclampsia.

Twin studies have also shown a high genetic correlation approaching 40%.

PREECLAMPSIA: THE ROLE OF PLACENTAL BLOOD VESSEL GROWTH FACTORS (ANGIOGENIC FACTORS)

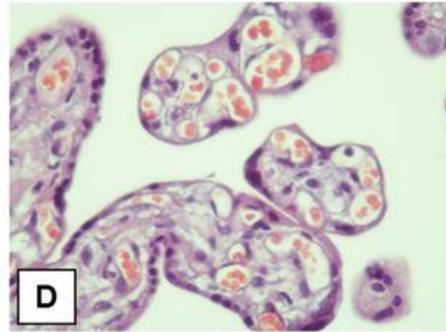
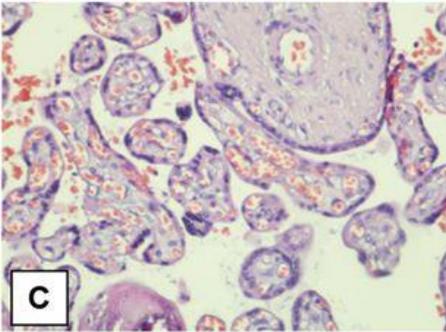
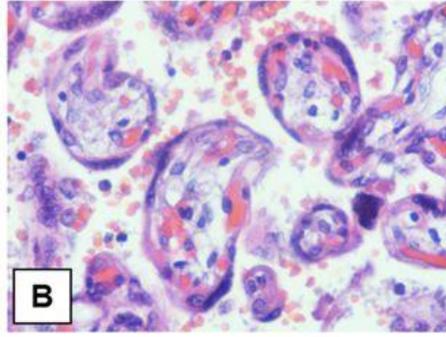
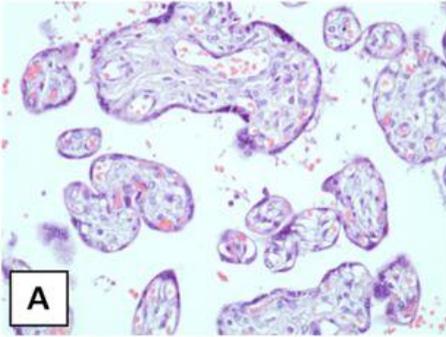
- The growth and health of blood vessels in the placenta and mother are crucial for a healthy newborn and mother.
- Blood vessel growth factors, called angiogenic factors, are critical to the normal development of blood vessels.
- Two antiangiogenic factors called sFlt-1 (soluble fms-like tyrosine kinase 1) and sENG (soluble endoglin), disrupt normal vascular growth by antagonizing two proangiogenic factors that are required to maintain normal blood vessel health: VEGF (vascular endothelial growth factor) and TGF- β 1 (transforming growth factor- β 1 signaling).

PREECLAMPSIA: THE PLACENTA



PLACENTAL VILLOUS TREES IN NORMAL (PHYSIOLOGICAL) AND PREECLAMPSIA PREGNANCIES

physiological pregnancy



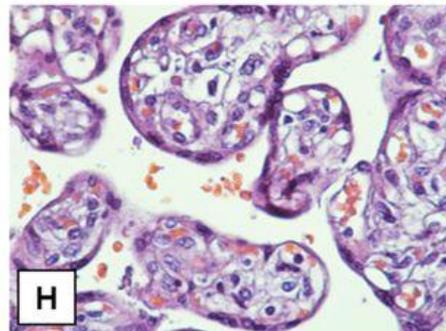
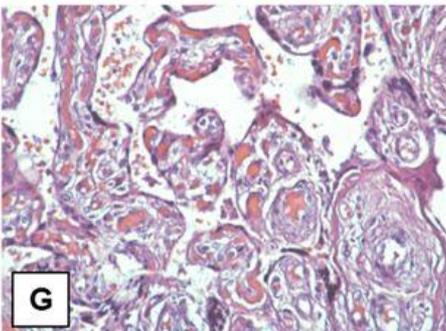
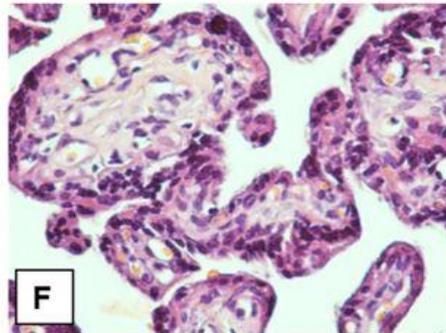
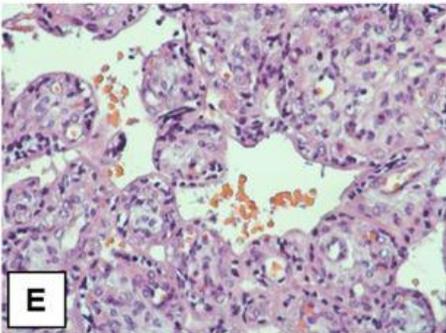
(A–D) Morphological changes in the placental villous trees during normal (physiological) pregnancy at the 27th week:

(A) x200 and (B) x400

Morphological changes in the placental villous trees during normal (physiological) pregnancy at the 38th week:

(C) x200 and (D) x400

preeclampsia



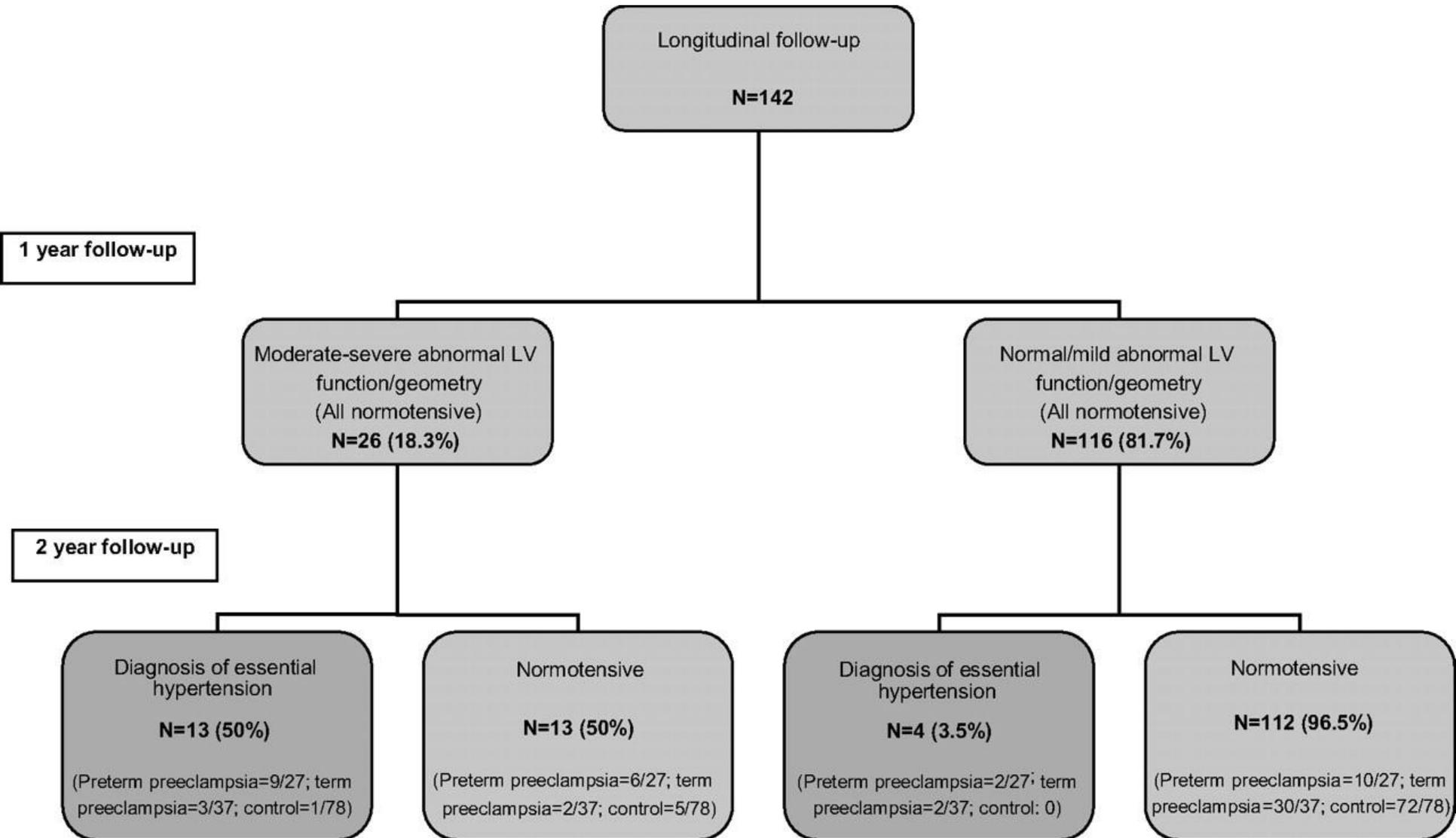
(E–F) Morphological changes in the placental villous trees in early-onset placenta in preeclampsia at the 26th week:

(E) x200 and (F) x400

(G–H) Morphological changes in the placental villous trees in late-onset preeclampsia at the 38th week:

(G) x200 and (H) x400

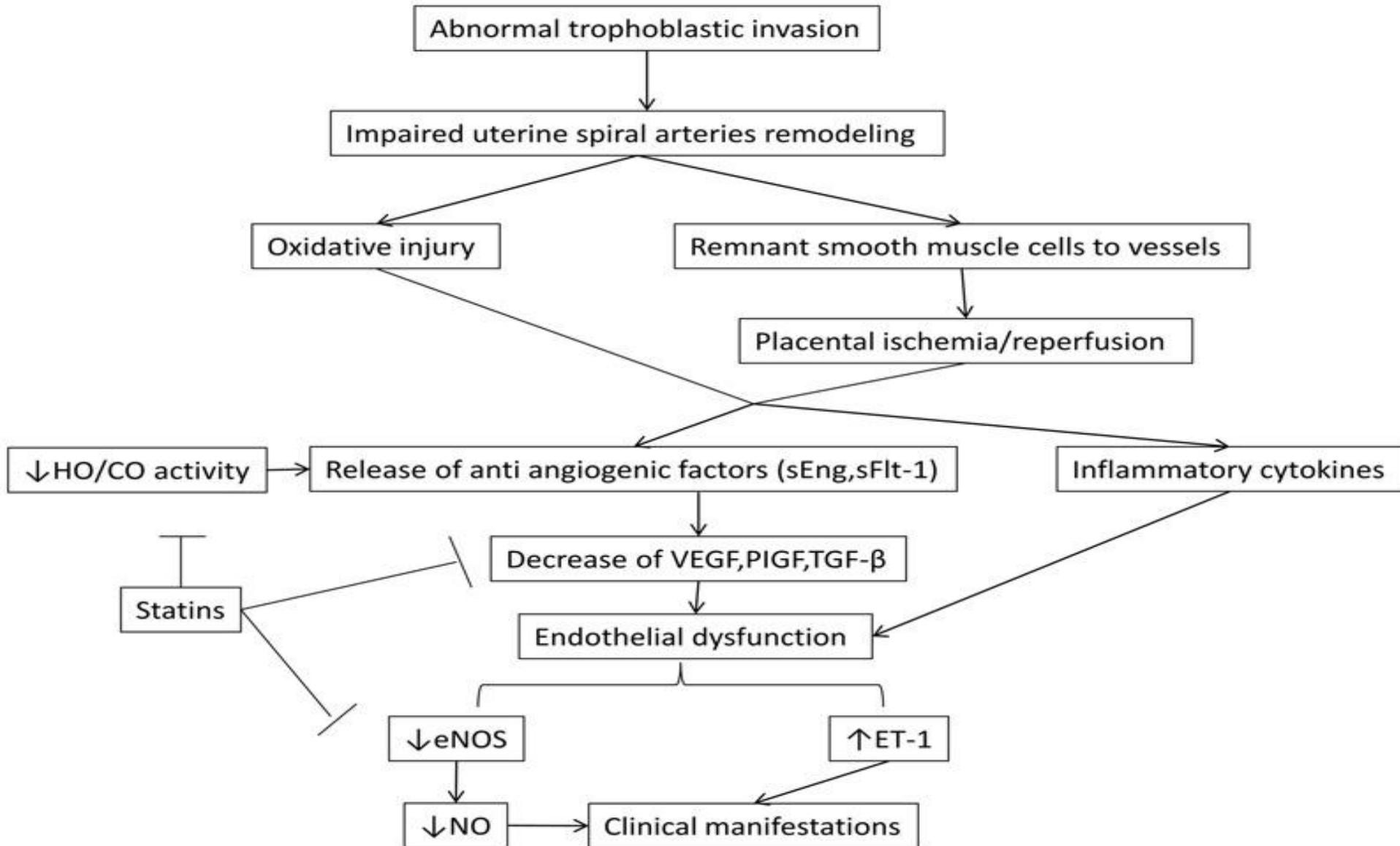
PREECLAMPSIA HAS LONGTERM CARDIAC CONSEQUENCES



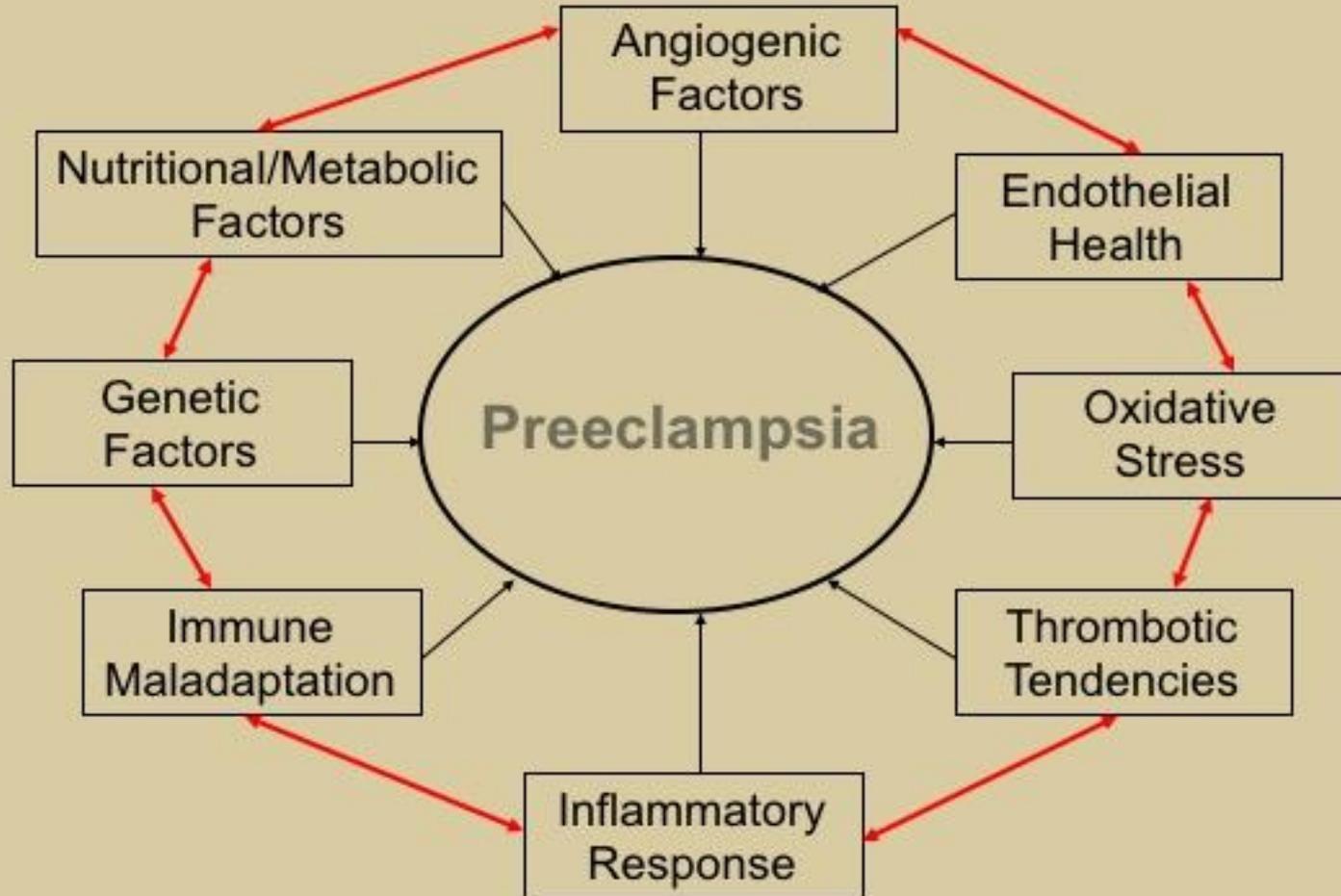
PROPOSED PATHOGENESIS OF PREECLAMPSIA

- In normal pregnancy, low sFlt-1 concentrations allow for proper VEGF and PlGF signaling. The anticoagulant and vascular tone status of the healthy blood vessels (endothelium) is maintained.
- In preeclampsia, increased production and release of the antiangiogenic factor sFlt-1 from the placenta leads to a decrease in bioavailable VEGF and PlGF (<100 pg/mL). This leads to an impairment of the VEGF/PlGF signaling axis and generalized blood vessel (endothelial) dysfunction.
- A ratio of an antiangiogenic factor (sFlt-1) and a proangiogenic factor (PlGF) has been developed to quantify the imbalance of placental angiogenic factors in preeclampsia.

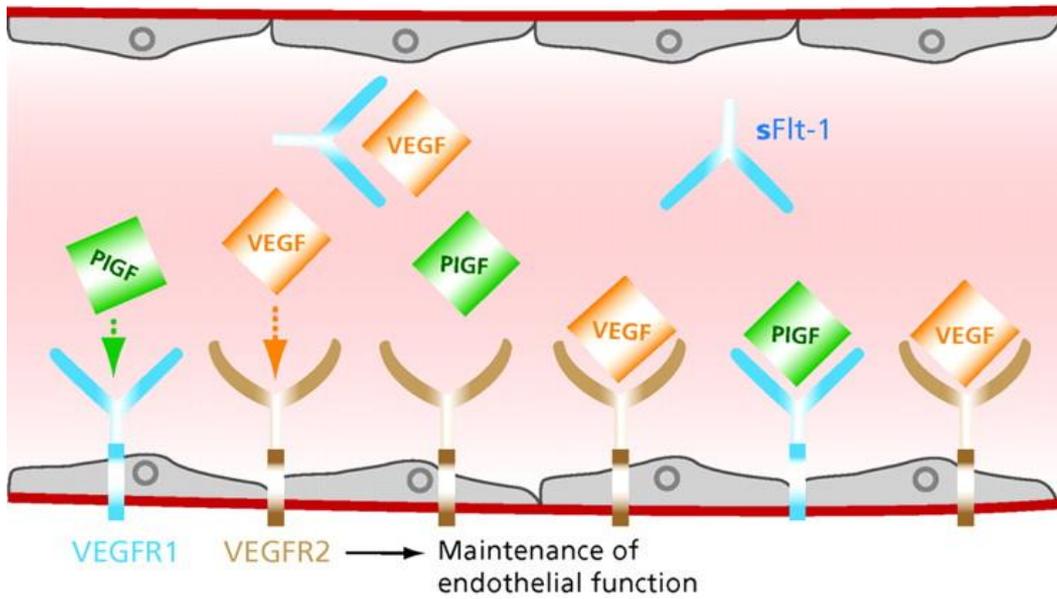
PREECLAMPSIA: IT'S COMPLICATED



ANGIOGENIC FACTORS IMBALANCE IN THE PREECLAMPSIA CIRCLE



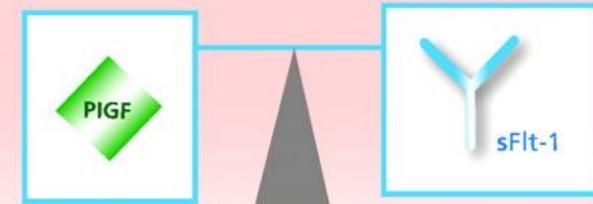
Normal Pregnancy



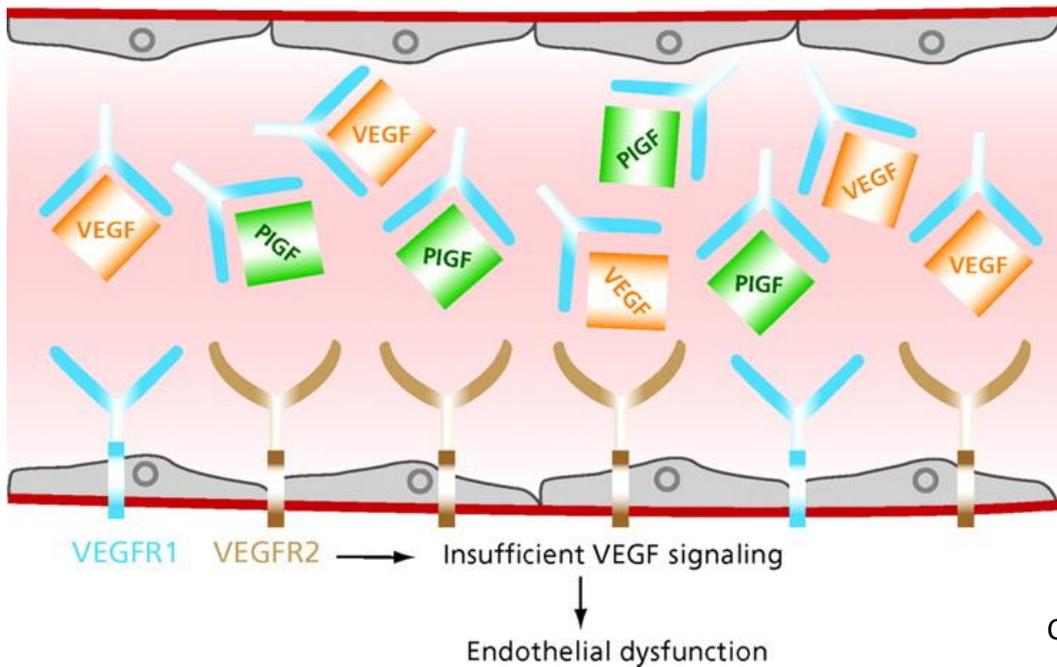
sFlt-1/PlGF ratio

Normal pregnancy

sFlt-1/PlGF: low

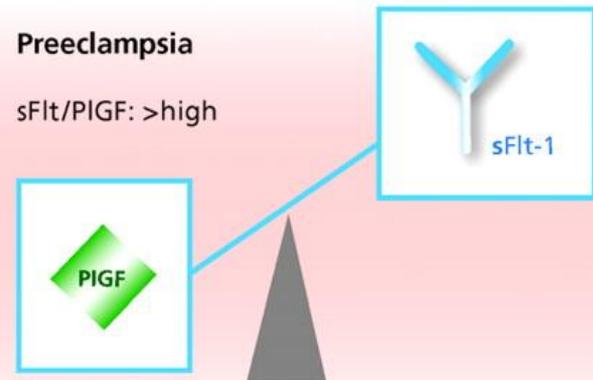


Preeclampsia



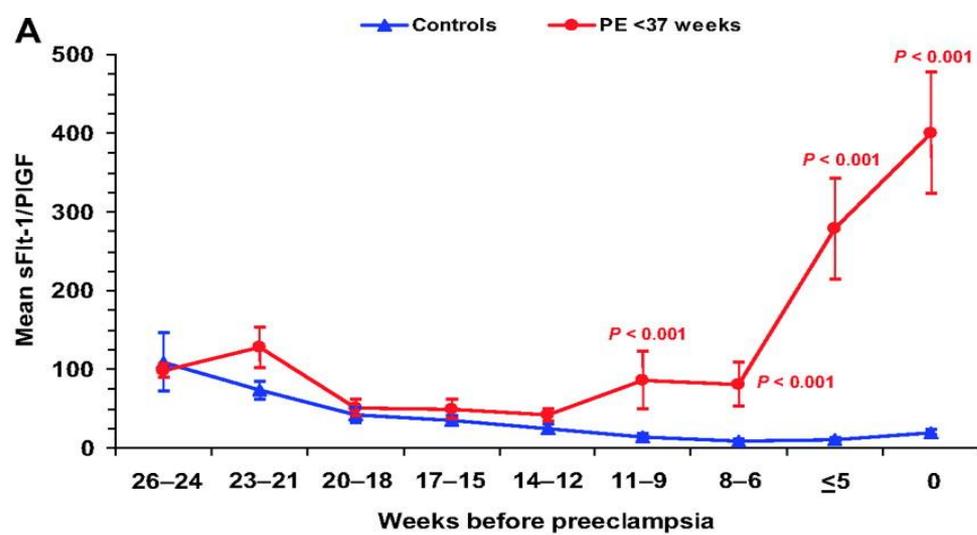
Preeclampsia

sFlt-1/PlGF: >high

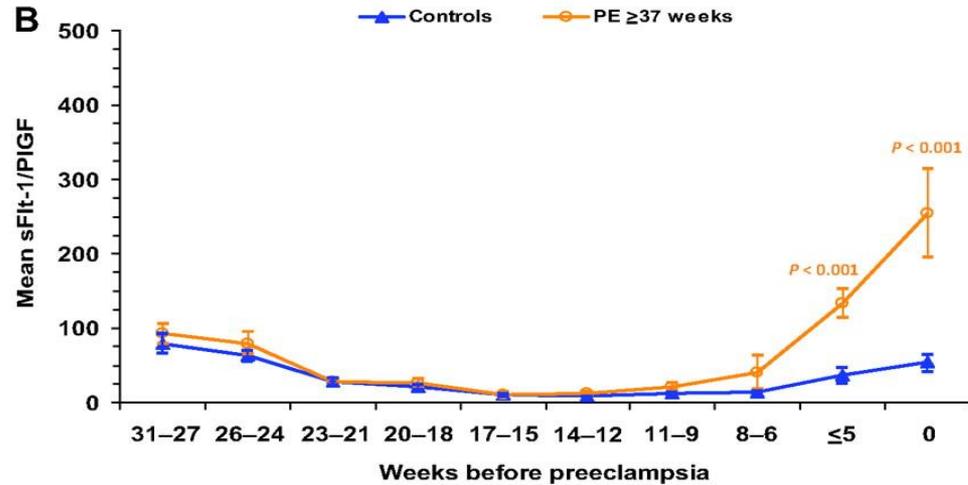


A VERIFIED BLOOD TEST TO FORECAST PREECLAMPSIA

In a study of over 600 women undergoing initial evaluation of preeclampsia, **a sFlt-1/PlGF ratio of ≥ 85 (i.e., having significantly more sFlt-1, an antiangiogenic factor, than PlGF, a proangiogenic factor,) correlated with a diagnosis of preeclampsia and predicted adverse outcomes and delivery within 2 weeks among women presenting < 34 weeks gestation (normal term delivery starts at 37 weeks).**



Specimen pairs	4	16	19	16	9	25	25	21	40
Specimen gestational age (days)									
Controls	86	98	118	123	122	171	196	198	241
PE <37 weeks	82	96	118	123	122	170	196	198	240



Specimens pairs	16	40	26	20	15	55	26	14	66	16
Specimen gestational age (days)										
Controls	93	105	125	133	177	191	200	239	256	264
PE ≥ 37 weeks	91	105	125	135	178	192	200	239	257	268

A POINT OF CARE APPROACH TO DIAGNOSIS OF PREECLAMPSIA (NOT AVAILABE IN USA)



G7 PRE-ECLAMPSIA DIAGNOSTIC DEVICE



FURTHER VERIFICATION OF THE PREDICTABILITY OF THE sFlt-1/PIGF RATIO TO FORECAST PREECLAMPSIA

- Furthermore, the sFlt-1/PIGF ratio performed better than all other currently available tests for predicting preeclampsia.
- A study of 402 patients presenting with preterm singleton pregnancies by the same group as before showed that ***a sFlt-1/PIGF ratio >85 had a positive predictive value of 59% in all patients and 74% among patients presenting <34 weeks for developing preeclampsia with severe features within 2 weeks.***
- In another multisite study of angiogenic factors, ***a sFlt-1/PIGF ratio of ≤ 38 had a negative predictive value of 99.9% for ruling out preeclampsia within 1 week.*** A follow-up study from the same cohort ***showed a negative predictive value of 95% within 4 weeks.***

VERIFICATION OF THE PREDICTABILITY OF THE sFlt-1/PIGF RATIO IN FORECASTING PREECLAMPSIA

- Patients with preeclampsia with normal angiogenic profiles have fewer adverse outcomes suggesting that the angiogenic form is the clinically more significant form of preeclampsia.
- **Overall, angiogenic factors appear to be a reliable risk-stratification method among women with suspected preeclampsia, especially for preterm preeclampsia, allowing for appropriate management.**

THE ROLE OF VITAMIN D IN PREGNANCY

- Recent cardiovascular literature has revealed the important role of vitamin D in normal blood vessel development.
- **Vitamin D deficiency has been linked with increased risk for both preeclampsia and intrauterine growth restriction in patients with early onset severe preeclampsia.**
- The role of the placenta in the genesis of preeclampsia is only now being understood.
- **Vitamin D expression was positively correlated with normal levels of placenta angiogenic factors—PGIF, sFlt-1, retinoid X receptor-A and retinoid X receptor-B--but not with achieving normal VEGF.**

WHY DO AFRICAN AMERICANS HAVE MORE PREECLAMPSIA THAN OTHER RACES?

- **Caucasian, African American, and Hispanic patients with early-onset preeclampsia defined as hypertension and proteinuria with onset prior to 32 weeks all showed alterations in the levels of angiogenic factors:** lower mean levels of PGIF, a proangiogenic factor, but higher mean levels of sENG, an antiangiogenic factor, than controls.
- **In this same patient group, Caucasian and Hispanic patients also had higher mean levels of the antiangiogenic factor VEGFR1 than controls. But this was not true for African American patients.**
- **African American patients were found to have higher levels of the PGIF when compared to Caucasian and Hispanic patients.**

WHY DO AFRICAN AMERICANS HAVE MORE PREECLAMPSIA THAN OTHER RACES?

- **Whether Vitamin D insufficiency is more prevalent among African Americans, as has been frequently stated in the medical literature, was recently called into question.**
- African Americans' placentae showed statistically significantly lower expression levels of an antiangiogenic factor sFlt-1 than Caucasians.
- VEGF expression level in placentae was lower in African Americans than in Caucasians, although it was not statistically significant.

[https://www.ajog.org/article/S0002-9378\(12\)01867-4/pdf](https://www.ajog.org/article/S0002-9378(12)01867-4/pdf).

J Nutr. 2006 Apr;136(4):1126-9.

N Engl J Med 2013; 369:1991-2000.

WHY DO AFRICAN AMERICAN MOTHERS HAVE MORE PREECLAMPSIA THAN OTHER RACES?

- The weakest association of early-onset preeclampsia with PGIF and soluble sENG was observed in African Americans.
- As for VEGFR1, the association was not significantly different among the racial-ethnic groups.
- **African American mothers appear to have genetic differences in the levels of placental angiogenic markers that may explain their two times normal increased risk for preeclampsia/eclampsia death.**

sFlt-1/PIGF RATIO IS A COST EFFECTIVE INDICATOR (NOT YET AVAILABLE IN USA)

- In 1050 German women with singleton pregnancies in whom preeclampsia was suspected, **a sFlt-1:PIGF ratio of 38 or lower had a negative predictive value of 99.3% (i.e., no preeclampsia in the subsequent week). The positive predictive value of an sFlt-1:PIGF ratio above 38 for a diagnosis of preeclampsia within 4 weeks was 36.7%.**
- Out of 192 suspected preeclamptic German mothers, **in 16.9% the hospitalization decision was changed after knowledge of the ratio.** In 13 women (11.0%), the initial decision to hospitalize was changed to no hospitalization. In seven women (5.9%) the revised decision was hospitalization.

sFlt-1/PIGF RATIO IS A COST EFFECTIVE INDICATOR (NOT YET AVAILABLE IN USA)

- **Germany:** In the model adapted to the German DRG payer system, introduction of the sFlt-1/PIGF) ratio test with a cut-off value of 38 **could reduce the proportion of women hospitalized in Germany from 44.6% to 24.0%**, resulting in an expected cost saving of €361 per patient or 404.3 US dollars (1€ = 1.12 US dollar).
- **Switzerland:** The assumed cost for sFlt-1/PIGF evaluation was €141 (1€ = 1.12 US dollar). Total average costs/pregnant woman (including birth) were €10,925 vs. €10,579 (sFlt-1/PIGF), and total costs were €66,469,362 vs. €64,363,060 (sFlt-1/PIGF). Implementation of sFlt-1/PIGF evaluation would potentially achieve **annual savings of €2,105,064** (€346/patient or 387.52 US dollars) **per annum, mainly due to reduction in unnecessary hospitalization.**

sFlt-1/PIGF RATIO IS COST EFFECTIVE (NOT YET AVAILABLE IN USA)

- **UK:** Introduction of the sFlt-1/PIGF ratio test into clinical practice is expected to result in cost savings of £344 per patient (443.76 US dollars) compared with a no-test scenario. **Savings are generated primarily through an improvement in diagnostic accuracy and subsequent reduction in unnecessary hospitalization.** (1 Pound sterling = 1.29 US dollar)
- **Brazil:** Introduction of the sFlt-1/PIGF ratio test resulted in cost savings in both settings (Hospital M'Boi Mirim (Public Hospital): Real \$185.06 and Hospital Einstein (Private Hospital): Real \$635.84 per patient) compared with a 'no-test' scenario. **Savings are generated primarily through an improvement in diagnostic accuracy and a reduction in unnecessary hospitalization.** (1 Real\$ = 0.25 US dollar)

sFlt-1/PIGF RATIO IS COST EFFECTIVE (NOT YET AVAILABLE IN USA)

Average cost in US dollars of a vaginal birth circa 2016/**average cost with sFlt-1/PIGF RATIO (cost of sFlt-1/PIGF ratio \$151 priced in) / % saving:**

\$10,808/ ? / ?	USA
\$ 2,500/\$2,096/+16%	Germany
\$ 7,751/\$7,363/+ 5%	Switzerland
\$ 2,300/\$1,856/+19%	Great Britain
\$ 2,025/\$1,866/+ 8%	Brazil

<https://liveinbrazil.org/2012/12/17/prices-for-giving-birth-in-brazil/>.

<https://www.insider.com/costs-giving-birth-around-the-world-2018-7>.

sFlt-1/PIGF RATIO AND USE OF LOW DOSE ASPIRIN IN PREECLAMPSIA

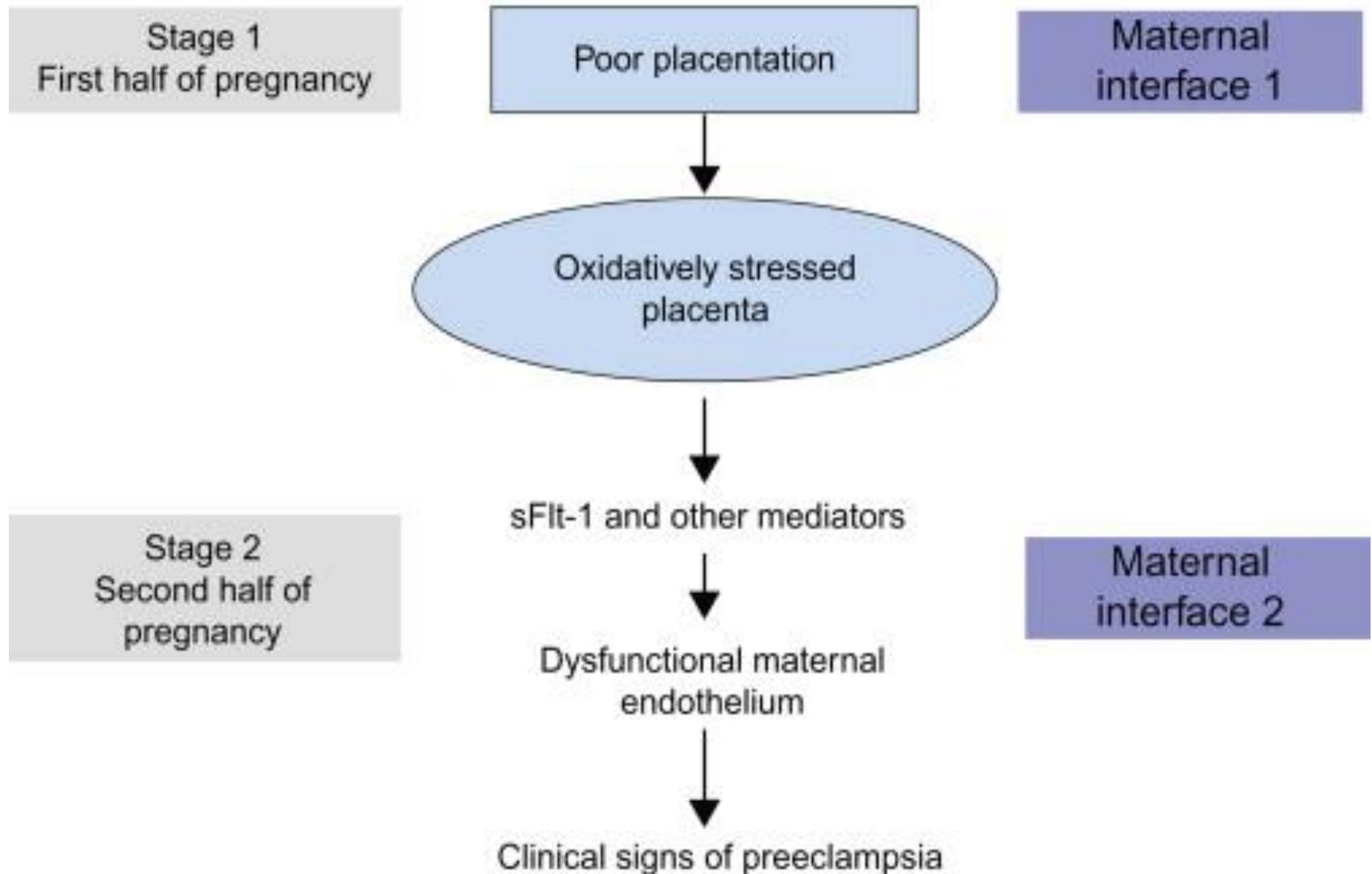
- The sFlt-1/PIGF ratio was significantly higher in women with an adverse obstetric outcome compared to women with a normal pregnancy, starting between 20 and 24 weeks of gestation.
- There was no effect of aspirin on sFlt-1/PIGF ratio in women with chronic hypertension, antiphospholipid antibody syndrome/systemic lupus, thrombophilia and controls.
- The use of **aspirin (150 mg per day)** showed a trend towards an improvement of the sFlt-1/PIGF ratio in women with preeclampsia in a previous pregnancy and **a significant effect on the sFlt-1/PIGF ratio in women with a pathologic first trimester screening for preeclampsia.**

SUMMARY OF THE RECOMMENDATIONS FOR THE USE OF THE sFlt-1/PlGF RATIO IN WOMEN WITH SIGNS AND SYMPTOMS OF PREECLAMPSIA BASED ON THE OPINIONS OF EXPERTS IN THE USE OF THIS ANGIOGENIC RATIO

sFlt-1/PlGF result (EP/LP)	Interpretation	Time to delivery (EP)	What should be done?
Low: <38	Rule out PE: 1 week: NPV ≈99% 4 weeks: NPV ≈95%	Unmodified	Reassuring the patient No further determinations are needed unless new suspicion arises
Intermediate: 38–85/38–110	Rule in PE: 4 weeks: PPV ≈40%	20% remain pregnant after 1 month	Follow-up visit and retest in 1–2 weeks Maternal education about signs and symptoms of PE
High: >85/>110	Diagnosis of PE (or PD-related disorder) is highly likely	15% remain pregnant after 2 weeks	Follow-up visit and retest in 2–4 days EP: consider referral to higher-level center LP: consider lowering the threshold for labor induction
Very high: >655/>201	Short-term complications and need to deliver are highly likely	30% remain pregnant after 2 days	Close surveillance EP: corticoids to the mother for fetal maturation

NPV, negative predictive value; PD, placental dysfunction; PE, preeclampsia; PlGF, placental growth factor; PPV, positive predictive value; sFlt-1, soluble fms-like tyrosine kinase-1; EP, early phase (<34 weeks of gestation); LP, late phase (≥34⁺⁰ weeks of gestation).

Two stages of preeclampsia and
two maternal-fetal immune interfaces



PROKINETICIN 1 LINKED TO STAGE 1 FIRST HALF OF PREGNANCY PREECLAMPSIA

- PROK1 (Prokineticin 1) also called EG-VEGF (endocrine gland-derived vascular endothelial growth factor), a newly discovered (2001) **hypoxia-regulated angiogenic factor**, has emerged as a crucial regulator of embryo implantation and placentation.
- PROK1 is a critical factor that facilitates trophoblast invasion into the placenta. This process of vascular remodeling rises to a peak by the end of the first trimester and declines rapidly thereafter. Poor invasion can lead to the development of pathological condition such as preeclampsia and intrauterine growth restriction.
- **Abnormal levels of PROK1 has been linked to recurrent pregnancy loss, preeclampsia, fetal growth restriction and preterm birth.**

J. Cell. Mol. Med. Vol 22, No 1, 2018 pp. 163-172.

J Physiol. 2019 Jun;597(12):3069-3083.

<https://clinicaltrials.gov/ct2/show/NCT01490489>

PROKINETICIN-1 PREDICTS STAGE 2 SECOND HALF OF PREGNANCY PREECLAMPSIA

- Screening by a combination of maternal risk factors, uterine artery Doppler, mean arterial pressure, PAPP-A (maternal serum pregnancy-associated plasma protein A), and PGIF can identify about 95% of cases of early onset preeclampsia for a false-positive rate of 10%.
- Prokineticin-1 (PROK1) predicted preeclampsia with 83.3% sensitivity, 85.7% specificity at a value of >293.4 pg/mL in the first trimester.
- Elevated PROK1, which is currently not FDA approved, in the first trimester is a more effective marker than PAPP-A, which is FDA approved, in the prediction of preeclampsia.

PREGNANCY-ASSOCIATED PLASMA PROTEIN A AND GESTATIONAL DIABETES , HYPERTENSION, AND ABNORMAL PLACENTATION

- There are positive associations between low circulating PAPP-A, an insulin-like growth factor, concentrations in week 15 of pregnancy and the future development of gestational diabetes and high blood pressure.
- **Recent studies suggest that low PAPP-A levels are associated with abnormal placentation, leading to the development of preeclampsia during late gestation.**

Canadian Family Physician October 2014, 60 (10) 899-903.

Singapore Med J 2018; 59(1): 55-59.

Petry CJ, et al. J Clin Endocrinol Metab. 2017.

CURRENT SCREENING FOR PREECLAMPSIA IN THE FIRST TRIMESTER

- **The prevalence of preeclampsia (8.4% vs. 2.6%) and early-onset preeclampsia (i.e. before 34 weeks of gestation) (1.1% vs. 0.1%) was significantly higher in women with lower than 10 percentile levels of PAPP-A drawn in the first trimester than in those with higher percentile levels.**
- Low first trimester PAPP-A levels (less than 10th percentile or <0.4 multiples of the normal median (MoM) values.) suggests increased future risk of preeclampsia and correlate with significantly higher levels of sFlt-1 levels at 34-35 weeks than control pregnancies.
- Furthermore, low first trimester PAPP-A status significantly predicted decreased odds of normal pregnancy.
- Some studies have demonstrated **an even more pronounced decrease of PAPP-A in the early second trimester of pregnancy in women who subsequently develop preeclampsia** compared with women who do not develop preeclampsia.

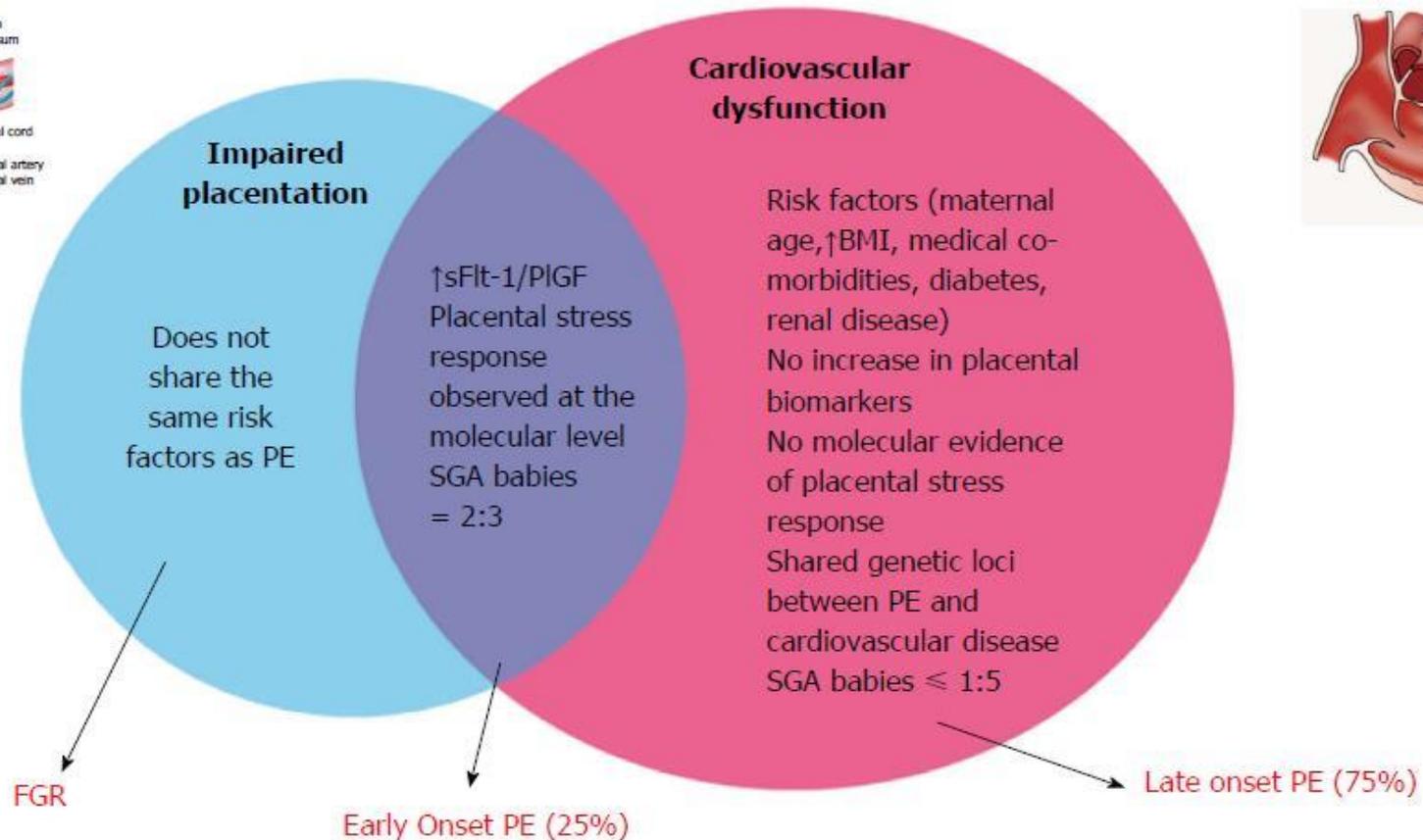
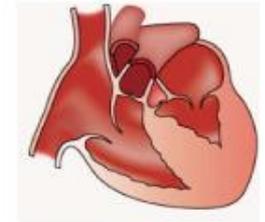
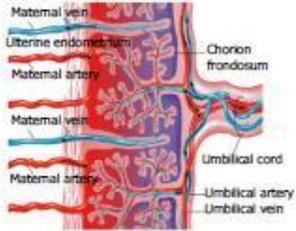
Saxena,A.R., Seely, E.W., Rich-Edwards, J.W. et al. BMC Pregnancy Childbirth (2013) 13: 85.

Adv Clin Chem. 2014;63:169-209.

Singapore Med J 2018; 59(1): 55-59.

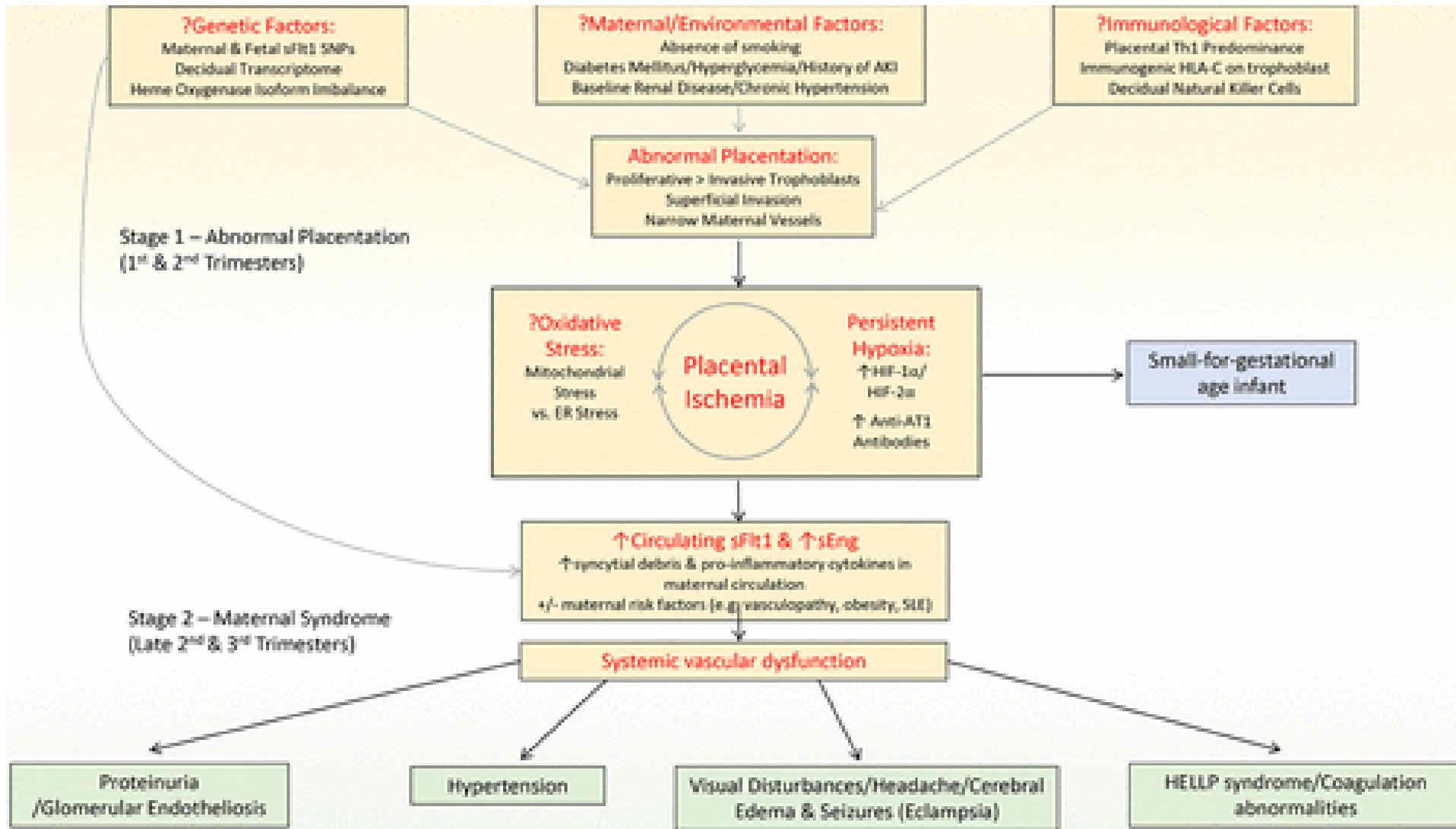
PREECLAMPSIA: WHICH COME FIRST: ANGIOGENESIS ISSUES OR THE HEART ISSUES?

The dual aetiology of Preeclampsia



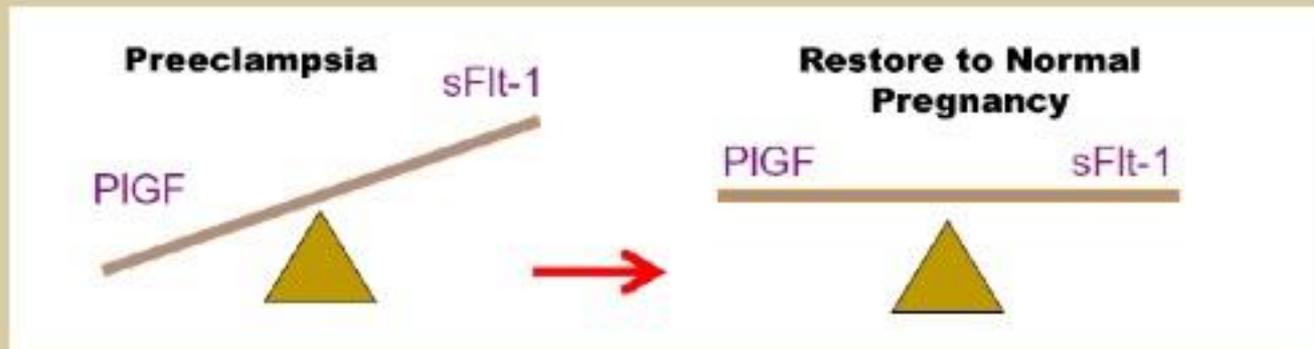
The key components, both specific and common to impaired placentation and cardiovascular dysfunction and their presence in fetal growth restriction, early-onset and late-onset preeclampsia. FGR: Fetal growth restriction; PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1; SGA: Small-for-gestational-age; BMI: Body mass index.

PUTTING IT ALL TOGETHER FOR PREECLAMPSIA



EXPENSIVE FUTURE THERAPIES FOR PREECLAMPSIA/ECLAMPSIA: RESTORING THE BALANCE IN ANGIOGENIC FACTORS

Angiogenic factor balance in preeclampsia

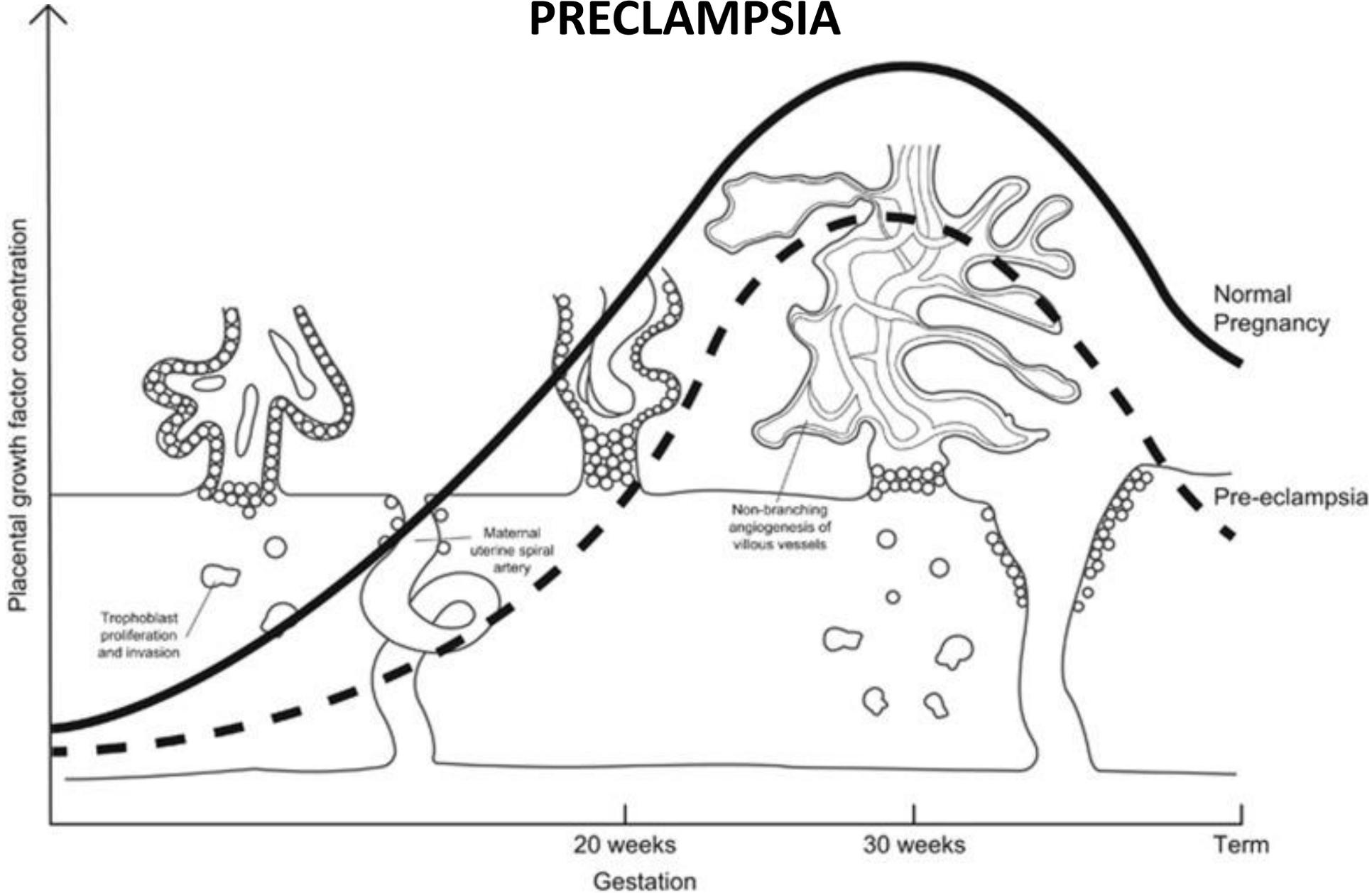


- \uparrow s-Flt-1 and \downarrow PlGF even weeks prior to clinical preeclampsia
- Biomarkers
- Therapeutics – apheresis, VEGF therapy

EXPENSIVE FUTURE THERAPIES FOR THE CAUSE OF PREECLAMPSIA/ECLAMPSIA: PIGF INFUSION

- Treatment with either VEGF or PlGF has been effective in attenuating hypertension and proteinuria in multiple animal models of preeclampsia.
- VEGF, however, may have overdose toxicity risks that have not been observed in PlGF treatment, suggesting that human recombinant PlGF is a potentially safer therapeutic option for human clinical trials.

CIRCULATING PIGF LEVELS DURING NORMAL AND PRECLAMPSIA



REMOVING PLASMA: APHARESIS



<https://www.youtube.com/watch?v=8lzdniwYAR4>

EXPENSIVE FUTURE THERAPIES FOR THE CAUSE OF PREECLAMPSIA/ECLAMPSIA: REMOVAL OF sFlt-1

- Eleven women with preeclampsia underwent apheresis therapy (removal of plasma similar to dialysis) to remove sFlt-1 from their circulation.
- There was a mean reduction of plasma sFlt-1 of 18% (range 7% to 28%), which was observed along with a 44% reduction in total protein/creatinine ratio (improvement in kidney function).
- Women with preeclampsia who did not receive treatment delivered an average of only 3 days after the time of admission, while women who received one treatment had their pregnancies extended an average of 8 days (range 2-11) after time of admission, and women receiving multiple treatments had their pregnancies extended 15 days after admission (range 11-21).
- Except for a transient lowering of blood pressure, no adverse effects from the apheresis were reported upon examination of mother and fetus.

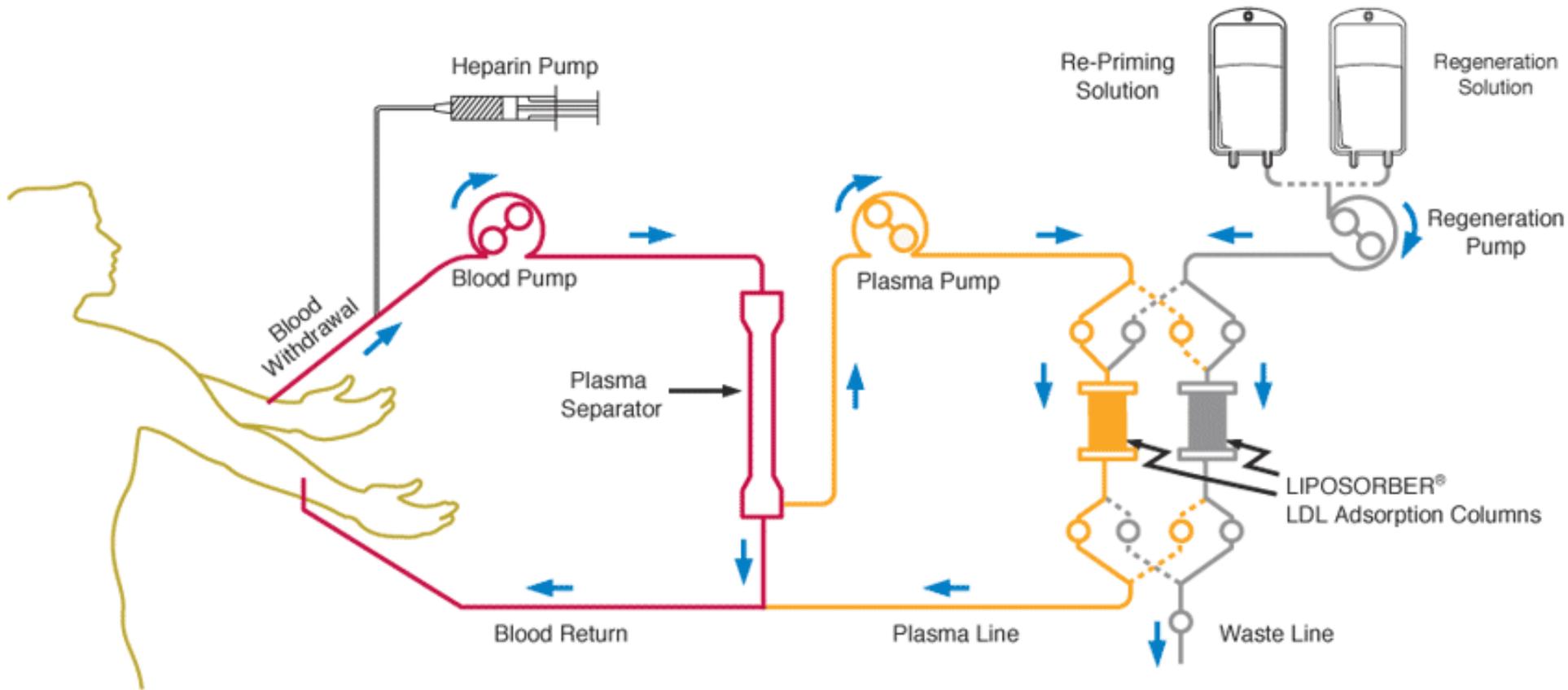
EVERY THING OLD IS NEW AGAIN

- The Liposorber LA-15 Device is a dextran sulfate cellulose column, one of several currently approved in Europe and United States (1996) for pheresis of lipoproteins in the treatment of familial hypercholesterolemia.
- Such devices have been in use for over 30 years. Published experience in pregnant women with familial hypercholesterolemia suggests that lipoprotein pheresis can be safely used in pregnancy after appropriate individual benefit/risk assessment for both mother and fetus is considered.
- The Liposorber LA-15 system selected for this trial has been evaluated for its ability to efficiently and selectively remove sFlt-1 in vitro.

LIPOSORBER LA-15 SYSTEM



HOW THE LIPOSORBER LA-15 SYSTEM WORKS



THE OLD NEW KID ON THE BLOCK

Proof-of-concept trial on selective removal of sFlt-1 in pregnant women with preeclampsia via apheresis utilizing the TheraSorb® Flt-1 adsorption column estimated completion date January 2020.



<https://www.miltenyibiotec.com/CH-en/lp/2018/therasorb-save-trial.html>

<https://clinicaltrials.gov/ct2/show/NCT02923206>

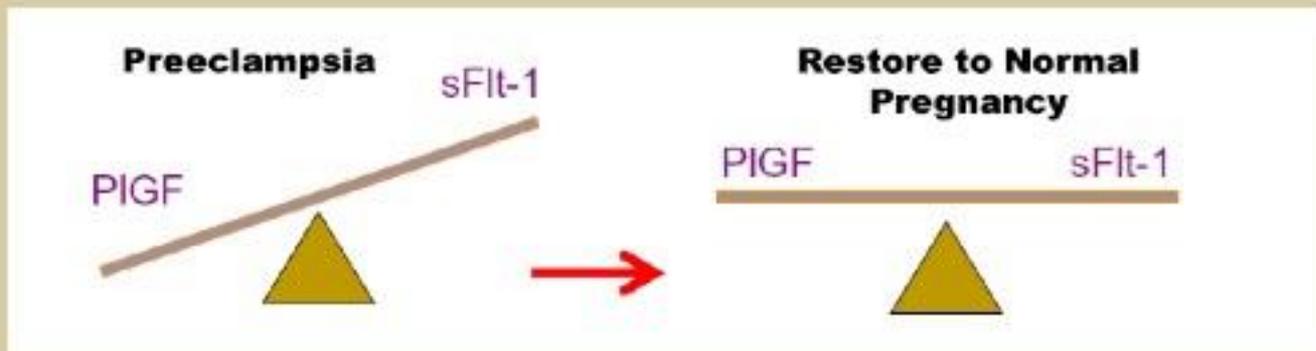
THE NEW NEW KID ON THE BLOCK

The Targeted Apheresis Column for Preeclampsia (TAC-PE) is an apheresis column that selectively removes sFlt-1 from the mother's blood. On April 17, 2019, the FDA granted a Breakthrough Device Designation for TAC-PE.



A CHEAP FUTURE POSSIBLE THERAPY FOR PREECLAMPSIA/ECLAMPSIA: RESTORING THE BALANCE IN ANGIOGENIC FACTORS

Angiogenic factor balance in preeclampsia



- \uparrow s-Flt-1 and \downarrow PlGF even weeks prior to clinical preeclampsia
- Biomarkers
- Therapeutics – apheresis, VEGF therapy

WHAT WILL BE THE ROLE OF PARVASTATIN IN PREECLAMPSIA?

- A few case reports in humans have been recently published with regard to using pravastatin in preeclampsia.
- A case of a 30-year-old woman with known antiphospholipid syndrome, thrombosis and preeclampsia at the 23rd week of gestation has been described. The patient was treated with combined medication including pravastatin (20 mg), enoxaparin (0.4 BD) and aspirin (100 mg OD). Blood pressure and proteinuria improved and normalization of previous pathological Doppler findings of the uterine arteries were noticed.
- In another study of four patients, presented with hypertension, proteinuria, preeclampsia, and growth restricted fetuses before the 30th week of gestation, the daily administration of pravastatin (40 mg), resulted in reduced levels of sFlt-1 and stabilization of impaired glomerular function and hypertension.
- A double blind, randomized placebo-controlled, multicenter trial of pravastatin to ameliorate early onset pre-eclampsia (StAmP) is currently recruiting and investigators focus on the impact of pravastatin in the reduction of anti-angiogenic markers in women with early preeclampsia. Additionally, in July 2019 the Pravastatin for Prevention of Preeclampsia trial started a randomized placebo-controlled multi-center clinical trial of 1,550 women with a prior history of preeclampsia that required delivery at less than 34 weeks, randomized to either 20mg pravastatin or an identical appearing placebo daily until delivery.

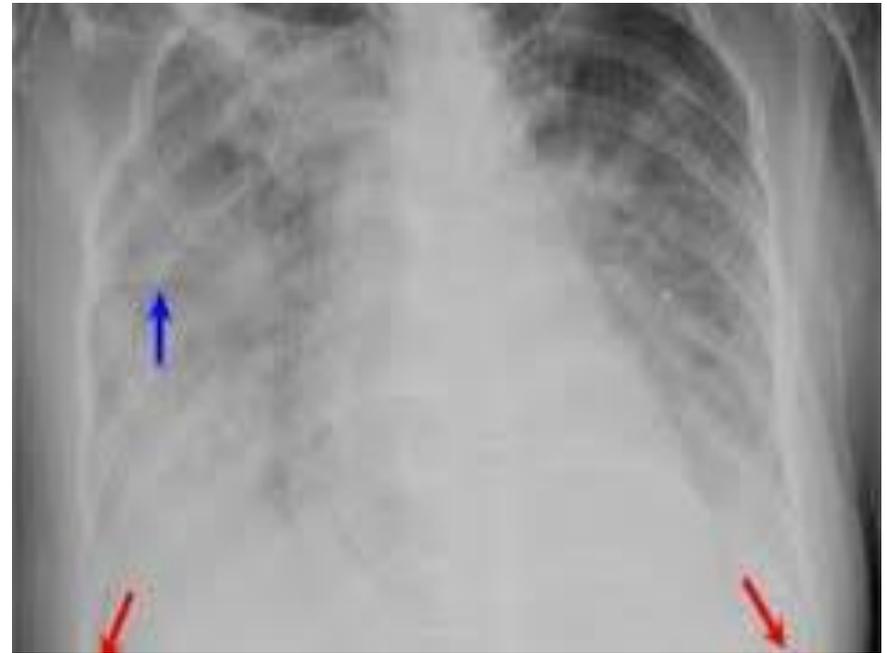
MY FOURTH, FIFTH, AND SIXTH SUGGESTIONS

- Pending FDA approval, perform two blood tests--sFlt-1 and PlGF levels and the sFlt-1/PlGF ratio--to predict who will be having preeclampsia and, thus, who are also at highest risk of cerebral vascular event.
- Insure normal vitamin D levels in pregnant women.
- Until the blood test for prokineticin-1 (PROK1) becomes clinically available, perform the PAPP-A blood test as early as first trimester of pregnancy to forecast an increased risk of preeclampsia later on in pregnancy.

HEMORRHAGE AND PULMONARY EDEMA (THE LEADING CAUSE OF DEATH AT TIME OF DELIVERY)



Normal Chest X-ray



Pulmonary Edema

PHYSIOLOGY OF NORMAL PREGNANCY

During pregnancy, the pregnant mother undergoes significant anatomical and physiological changes in order to nurture and accommodate the developing fetus. These changes begin after conception and affect every organ system in the body. For most women experiencing an uncomplicated pregnancy, these changes resolve after pregnancy with minimal residual effects.

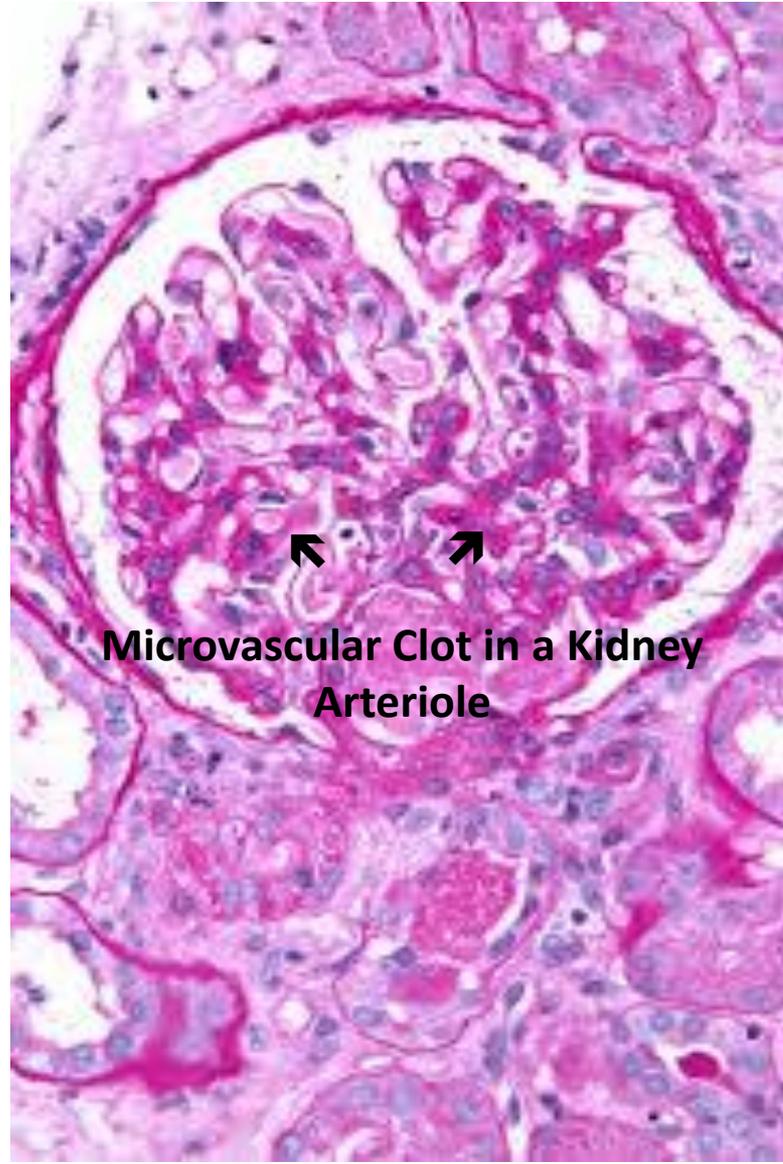
PHYSIOLOGY OF NORMAL PREGNANCY

Plasma volume increases progressively throughout normal pregnancy. Most of this 50% increase occurs by 34 weeks' gestation and is proportional to the birth weight of the baby.

WHAT CAUSES EXCESSIVE CLOTTING IN PREGNANCY

- Pregnancy normally alters the balance within the coagulation system in favor of clotting to avoid hemorrhage at time of delivery and thereby predisposes the pregnant and postpartum woman to venous thrombosis, pulmonary embolus, disseminated intravascular coagulation (DIC), and cerebral vascular accidents. Why?
- **Concentrations of endogenous anticoagulant factors antithrombin III and protein S (both made in the liver) normally decrease while the concentrations of several procoagulant factors normally increase.**
- **Antithrombin III inactivates most of the clotting factors that are elevated in late pregnancy.** The reduction in antithrombin III levels in pregnancy limits the pregnant mother's ability to avoid excessive clot formation. Protein S acts in a similar fashion but only with two clotting factors.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC) UNDER THE MICROSCOPE



**Microvascular Clot in a Kidney
Arteriole**

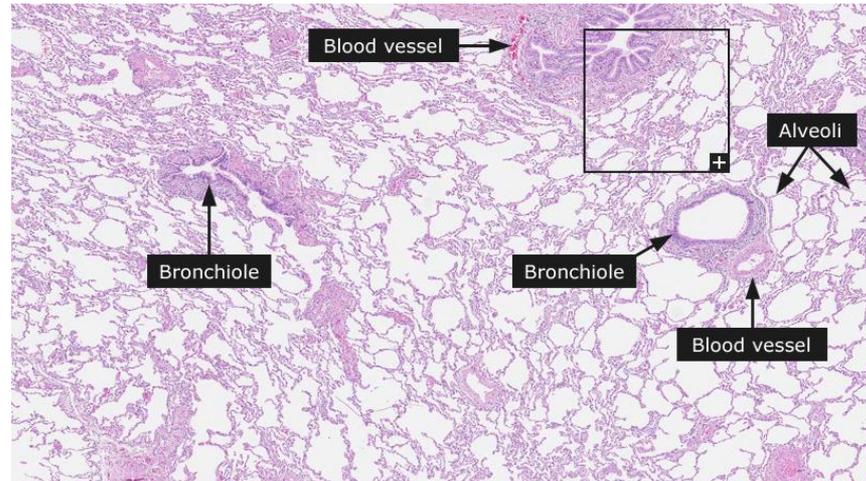
AVOIDING DIC DEATHS IN DELIVERY

- **The imbalance of procoagulants and anticoagulants is present from the first trimester and for at least 12 weeks following delivery.** Routine in vitro tests of coagulation [activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT)] remain normal in the absence of anticoagulants or a coagulopathy. ***Antithrombin III levels though drop 30% at time of normal delivery and then return to baseline level.***
- **Because of this acute reduction in Antithrombin III levels at time of delivery, anything** (such as an amniotic fluid embolism or infection) **that causes a further drop in Antithrombin III levels will predispose the mother to having disseminated intravascular coagulation (DIC), which is associated with 25% of maternal deaths.**
- ***In my experience in treating all of the obstetrical cases of DIC for 22 years at Northside Hospital Atlanta, giving Antithrombin III concentrate based on plasma volume reversed the DIC and prevented death in all of the cases.***

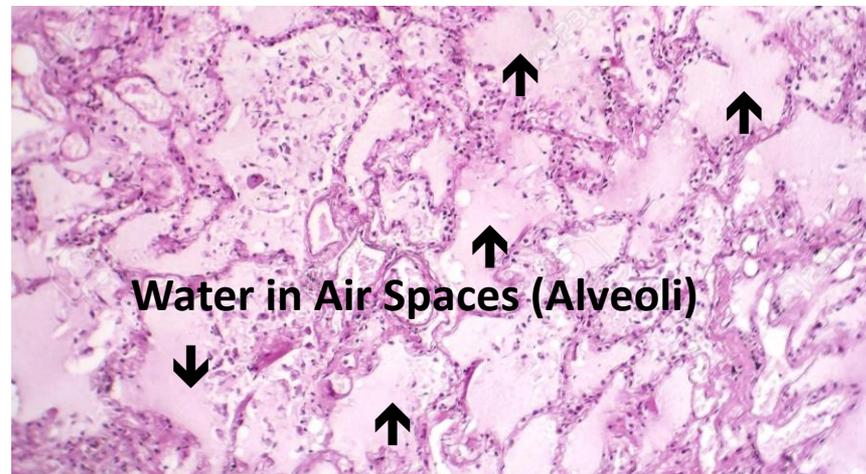
AVOIDING HEMORRHAGE DEATHS WITH DELIVERY

- Because of the need to give large volumes of red cells, plasma, cryoprecipitate and platelet concentrates to women who bleed excessively with delivery, their total body volume overload situation only gets worse once the hemorrhage stops.
- This results in the patients going into pulmonary edema and requiring ventilator support, which leads to a downward spiral with pneumonia and renal failure with death as a frequent result.
- *In my experience, giving Lasix® 100 mg intravenously, once the bleeding stops, prevented these complications from happening in all of my cases and saved their lives, as well as (except for a few exceptions) allowing their being discharged within 5 days.*

PULMONARY EDEMA UNDER THE MICROSCOPE



Normal Lung



Pulmonary Edema in Lung Tissue

https://www.123rf.com/photo_104372503_histopathology-of-acute-pulmonary-edema-light-micrograph-showing-accumulation-of-fluid-inside-alveol.html

<https://www.proteinatlas.org/learn/dictionary/normal/lung>

MY SEVENTH AND EIGHTH SUGGESTIONS

- Give antithrombin III concentrate in pregnancy-associated DIC and liver disease of preeclampsia to stop both the DIC and the bleeding.
- Give a large dose of Lasix[®] intravenously, once blood products replacement and bleeding has stopped, to prevent pulmonary edema.

SAVING AFRICAN AMERICAN MOTHERS WITH PREECLAMPSIA WHO BLEED WITH DELIVERY

- The rate of preeclampsia and eclampsia for African American women is 61% higher than it is for Caucasian women and 50% higher than for women overall. Therefore, **African American mothers are at an increased risk to have higher levels of sFlt-1 due to a greater incidence of preeclampsia and eclampsia than other races.**
- **Higher sFlt-1 values, as seen in all races with preeclampsia and eclampsia, are associated with increased heart wall stiffness, worse right heart dysfunction, and higher arterial load, all of which result in pulmonary edema requiring diuresis.**
- Therefore, African American women have an increased incidence of needing to receive high doses of intravenous Lasix® once the bleeding has stopped to avert death since they have an increased incidence of preeclampsia and eclampsia.

EIGHT SUGGESTED MEASURES TO LOWER MORBIDITY AND MORTALITY IN 2020

1. Measure and monitor BNP levels for heart issues and preeclampsia.
2. Follow the YEARS algorithm with D-Dimer level for DVT and pulmonary emboli detection.
3. Evaluate and treat for the angiogenic cause(s) of preeclampsia (once FDA approved), evidence of posttraumatic stress syndrome, and the presence of insomnia to lower cerebral vascular events.
4. Pending FDA approval, measure sFlt-1 and PlGF levels and the sFlt-1/PlGF ratio to predict who will be having preeclampsia and, thus, who are also at highest risk of cerebral vascular event.
5. Insure normal vitamin D levels in pregnant women.
6. Until prokineticin-1 becomes clinically available, measure pregnancy-associated plasma protein levels as early as first trimester of pregnancy to forecast an increased risk of preeclampsia later on in pregnancy.
7. Give antithrombin III concentrate in pregnancy-associated DIC and liver disease of preeclampsia to stop both the DIC and the bleeding.
8. Give a large dose of Lasix[®] intravenously, once blood products replacement and bleeding has stopped, to prevent pulmonary edema and save lives.

