PREGNANCY INDUCED HYPERTENSION
1. **Definition of Hypertension in Pregnancy:** a blood pressure in excess of 125/75 prior to the 32nd week of gestation and 125/85 thereafter (association with increased fetal mortality).

May be secondary to one of four clinical syndromes:

A. **Chronic essential hypertension** (are at increased risk for developing preeclampsia)

B. **Gestational hypertension:** appearance of hypertension late in pregnancy usually not associated with signs of toxemia. Usually overweight, positive family hx of essential HTN, may have prior hx of intermittent HTN, may develop HTN later in life.

C. **Preeclampsia (Toxemia):** a systemic disease occurring late in pregnancy (third trimester) with clinical manifestations of sudden appearance of edema, hypertension, with evidence of renal, hepatic, hematologic or neurologic involvement.

D. **Preeclampsia superimposed upon chronic hypertension or renal disease** (as these women are at increased risk).

2. **Physiologic changes in normal Pregnancy:**

   - increased cardiac output of about 30 to 40%
   - increase in blood volume about 50%
   - decrease in peripheral vascular resistance
   - decrease in blood pressure
   - increase in renal blood flow about 70%
   - increase in CFR about 50%

   These changes are associated with changes in serum chemistries:

   - decrease in BUN to < 10 mg/dl
   - decrease in creatinine to < 0.7 mg/dl
   - decrease in uric acid to < 4.0 mg/dl
   - decrease in serum albumin, hematocrit (due to hemodilution)
   - decrease in plasma osm and sodium (increased thirst and reduction in tonicity at which ADH released)
   - decrease pCO₂ (progesterone induced hyperventilation)

**Hormonal changes:**

marked increase in renin secretion (some of uteroplacental origin and some from a paradoxical increase in renal renin secretion despite hypervolemia, perhaps secondary to increased prostaglandins)
- increased angiotensin II and aldosterone:

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\text{Angiotensinogen} \quad \downarrow \quad \text{Renin} \quad \leftarrow \quad \text{Angiotensin I} \quad \downarrow \quad \text{angiotensin converting enzyme (primarily in lung)} \quad \downarrow \quad \text{Angiotensin II I}
\]

Stimulation of Adrenal Aldosterone secretion

of note, despite the increase in All levels, there is a decreased sensitivity to this vasoconstrictor, perhaps related to the marked increase in vasodilatory PGs in pregnancy. All may increase in response to the vasodilation to "maintain" BP. Also, no significant sodium retaining effects of aldosterone due to antagonism by progesterone.

Increased production of vasodilatory prostaglandins (PGE$_2$ and PGI$_2$):

probably of placental as well as other vascular endothelial origin; and decreased production of the vasoconstrictor PG, thromboxane: PGs are 20 carbon fatty acids with a cyclopentane ring derived from the precursor arachadonic acid. PGI$_2$ (prostacyclin) is a vasodilator and inhibitor of platelet aggregation. Thromboxane causes platelet aggregation and vasoconstriction.

3. **Clinical features of Preeclampsia:**

Sudden appearance during the third trimester of:

- edema, particularly of the face and hands (secondary to sodium retention and a shift of fluid from the intravascular to interstitial spaces)
- hypertension (increased sensitivity to angiotensin II may be an early feature)
- elevated plasma urate (due to decreased urate clearance)
- Proteinuria (due to glomerular endothelial cell injury)
- decrease in GFR with resulting increase in BUN and creatinine
- consumptive coagulopathy with decrease in platelets, increase in prothrombin and partial thromboplastin times, and microangiopathic hemolytic anemia, an4 if severe, decreased fibrinogen and increased fibrin degradation products.

- neurologic irritability with headache, hyper-reflexia
- hepatic involvement with increase liver enzymes
- intrauterine growth retardation

**Eclampsia:** the occurrence of seizures associated with severe toxemia

**HEELP syndrome:** Hemolysis, Elevated Liver enzymes, Low Platelets

All of the above features may not be present in any one individual at any one time. Although elevation in blood pressure is often a heralding feature, it is not always present nor does it necessarily correlate with the severity of the disease. The degrees of elevation of plasma urate and decrease in platelet counts correlate more closely with poor fetal outcome (probably better markers of the pathologic process).

4. **Predisposing conditions:** Supply vs Demand

Medical conditions: hypertension, collagen vascular disease, diabetes mellitus (all share the common feature of microvascular abnormalities)

Obstetrical conditions: primigravidas, twin pregnancies, hydatidiform mole (all may have relative decrease in the ability to adequately vascularize the placental).

5. **Etiology of Preeclampsia:** Still a MYSTERY.

A. Major pathophysiology features:

Preeclampsia is characterized by increased vasoconstriction (with prominent decreases in uterine and renal blood flow) and diffuse endothelial cell injury with platelet aggregation.

B. Role of reduced Placental perfusion:

Preeclampsia is a disorder specific to pregnancy. The important pregnancy product necessary for development of the disorder is the trophoblast (can occur in pregnancies without a fetus, i.e. may occur in hydatidiform mole even more frequently than normal pregnancies; can also

Pregnancy Induced Hypertension
occur in abdominal pregnancies indicating that distention of the uterus is not the important factor).
The important factor leading to the disorder is reduced trophoblast perfusion. Preeclampsia can be induced in animal models only by reducing uterine perfusion. Placental biopsies demonstrate that the spiral arteries are not normally dilated, and are frequently occluded with fibrinoid material (termed atherosis). These abnormalities probably long antedate clinical manifestations of the disorder.

How then does reduced placental perfusion become a multi-system maternal disease?

C. The earliest maternal changes (antedating clinical disease by months) are:
- increased sensitivity to pressors such as All;
- activation of platelets and the coagulation cascade
- endothelial cell activation

D. Role of altered prostaglandin synthesis:

Evidence has accumulated suggesting an abnormality in synthesis of prostaglandins (with a decrease in vasodilatory prostaglandins coupled with a possible increase in vasoconstrictor prostaglandins). Endothelial cell injury and activation may underlie these changes as prostaglandins are endothelial cell products. Reduced vascular PGI2/PGE2 synthesis with "unbalanced" thromboxane production occurs in preeclampsia ---- leads to vasoconstriction and platelet aggregation --- leading to fibrin deposition and end organ damage.

E. Role of Endothelial cell injury / activation: a central feature of preeclampsia.

Biochemical markers of endothelial cell activation have been found in preeclamptic women: increased Factor VIII antigen; increased fibronectin; increased endothelin (a 21 amino acid peptide produced and secreted by endothelial cells that is the most potent endogenous vasoconstrictor substance yet identified; bears striking homology to the snake venom, sarafotoxin).

There may be some as yet unidentified "substance" in the circulation from decreased placental perfusion that injures endothelial cells. This results in release of vasoconstrictor substances such as endothelin and thromboxane (and a decrease production of vasodilatory PGI2). This further results in a positive feedback system where endothelial cell injury leads to more endothelial cell injury.

The most consistent pathologic change in preeclampsia is "glomeruloendotheliosis": cytoplasmic swelling of endothelial cells that results in occlusion of the capillary lumen, may be accompanied by deposition of platelets and fibrin. Suggests that abnormalities in the endothelium may initiate the process. Similar pathologic findings may be found in other diseases characterized by endothelial cell injury and intravascular coagulation such as the "hemolytic uremic syndrome"
F. Role of activation of platelets: also seem to play a central role in the development of preeclampsia.

Platelet aggregation leads to "plugging" of microvasculature, fibrin deposition, endothelial cell injury leading to more platelet aggregation.

Diffuse endothelial cell injury, platelet aggregation and fibrin deposition accounts for the end-organ renal, hepatic, hematologic and CNS damage. Still unknown is what initiates the decrease in trophoblast perfusion and if there is a specific substance released into the circulation that initiates endothelial cell injury.

6. Therapeutic Options: Finding some way to interrupt the "positive feedback" loop and prevent further decrease in uteroplacental blood flow.

a. Low dose aspirin (81 mg/day or less) has been shown to be effective (Beaufils 1985, Wallenberg 1986, Schiff 1989, Benigni 1989). This dose interferes with platelet aggregation without significantly decreasing vasodilatory PG production. The above studies have shown:
- decreased incidence in the development of preeclampsia in high risk women treated with ASA as compared to placebo
- a reversal of the increased pressor sensitivity
- decrease thromboxane production (without much change in PG12)

b. Role for Ca++ supplementation: Calcium supplementation (2 gm elemental Ca++/day) vs placebo has been shown to reduce incidence of HTN disorders in 1194 primigravida (9.8% vs 14.8%, p < 0.01; Belizan NEJM 1991). Ca++ has also been shown to decrease the vascular sensitivity to Angiotensin II (Kawasaki; Am J Obstet Gyn 1985); and low urinary Ca++ excretion (< 195 mg/24h) may be predictive of preeclampsia (SanchezRamos, Obstet Gyn, 1991).

Mechanism of action - unknown; may induce smooth muscle relaxation; may act by PTH or other "hypertensive parathyroid factor" or I production of vasodilatory PG's.

Current Status - Possible Prevention

Although the name may change over the years, the unique pregnancy condition of elevated blood pressure, proteinuria, excessive edema, and hyper-reflexia is well known to all obstetricians. It is now known as pregnancy induced hypertension, but is also known as preeclampsia eclampsia syndrome, or toxemia.

Despite a dramatic decrease in maternal mortality due to eclamptic seizures, this remains a frightening endpoint for the progression of preeclampsia to eclampsia. The rate has reached a plateau over the last five to seven years. The residual maternal mortality due to PIH in related
directly to intracerebral hemorrhage.

The HELLP Syndrome (hemolysis, elevated liver enzymes and low platelets) has received significant attention as a separate entity over the past decade. It should be considered a complication of severe pregnancy-induced hypertension, and the diagnosis should be considered and sought in any woman with severe preeclampsia. Physical symptoms and signs are those of severe preeclampsia, vis. pouding headaches, blurred vision, and scotomata, right upper-quadrant or epigastric pain related to hepatic capsular pressure and significant swelling or weight gain in relation to a drop in urine output. The laboratory data are necessary to make the diagnosis. There should be little hesitation in ordering a platelet count, a coagulation profile, a CBC, and liver enzyme chemistries, so that a woman who at times can be suprisingly normal-appearing will not catch us unaware.

It seems that the older woman with pregnancy-induced hypertension, particularly if it is superimposed upon a chronic medical condition, has a fulminant preeclamptic course. Hospitalization is advised early in the course of the disease for this reason, and particularly alert and compulsive care is advised for such a woman. Chronic hypertension, even if only seen during pregnancy as documented by lack of second trimester decrease in mean arterial pressure, collagen vascular disorders, or chronic renal and hepatic conditions, all predisposed to superimposed preeclampsia.

Recent evidence favors the use of low-dose aspirin to prevent the onset of preeclampsia in high-risk patients. Prospective trials of low-dose aspirin, varying in amount from 60 mg. to 100 mg. a day, have been performed. To understand the mechanism of action, a working knowledge of the prostaglandin synthesis cascade must be achieved. It seems that aspirin, at a dose less that 80 mg. per day, inhibit the enzymatic pathways leading to the vasoconstrictor thromboxane, which is one end product of the prostaglandin cascade. This favors prostacyclin production, which adds vasodilatory effects, especially important in the retroplacental vascular bed.

Vigilance through properly timed prenatal visits for patients at particular risk is the best means of diagnosing this serious complication of pregnancy. As the pregnant population includes more and more women who have delayed childbearing, we must ever-conscious of the possibility of severe pregnancy-induced hypertension and its malignant sequelae.