Thrombocytopenia in Pregnancy

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• No conflicts of interest to disclose.
OUTLINE

• Normal Physiologic Changes of Pregnancy
• Diagnosis & Definitions
• Differential Diagnosis
• Management
• Treatment
• Mode of Delivery
• Mode of Anesthesia
• Transfusion
• NAIT
Platelet function

Circulating platelets; endothelial damage → Platelet adhesion → Platelet aggregation → Platelet-Fibrin plug → Clot retraction

http://www.med-ed.virginia.edu/courses/path/innes/nh/function.cfm
Platelet function

• Symptoms - bleeding into mucous membranes
  – Petechiae, ecchymoses, epistaxis, gingival bleeding, and menometrorrhagia.
  – Bleeding into joints (hemarthrosis) is uncommon (vs hemophiliacs)
  – Life-threatening bleeding is less common but can occur, resulting in hematuria, gastrointestinal bleeding, and, although rare, intracranial hemorrhage
Physiologic Changes in Pregnancy
Platelet count

- Mean platelet counts in pregnancy slightly decrease, but typically stay in the normal nonpregnant range
- Lower limit of normal (106k – 120k)
- Platelet width and volume increase
  - Increased platelet consumption leads to increased proportion of younger and larger platelets
  - Equated with low grade intravascular coagulation
  - Increased level of thrombocytopoiesis is a consequence of both dilutional and consumptive stimuli or normal pregnancy
Definition

• Mild – 100,000 – 150,000
• Moderate - 50,000 – 100,000
• Severe - <50,000

• Spontaneous bleeding at <20k
• Serious bleeding complications are rare, even in those with severe thrombocytopenia
• Bleeding with trauma/surgery if <50k

ACOG Bulletin
Epidemiology

• 7-8% of all pregnancies
• 3/1000 will have clumping of platelets in EDTA and are NOT at risk for bleeding and do not require further evaluation/surveillance unless indicated for other conditions such as hypertension, etc
• ITP occurs in 3/1000 pregnancies
Platelet clumping
Etiologies and Differential Diagnosis

• Major
  – Gestational thrombocytopenia
  – Severe preeclampsia
  – HELLP syndrome
  – Disseminated intravascular coagulation
  – Platelet clumping
  – Medications – Heparin/enoxaparin, quinine derivatives
Etiologies and Differential Diagnosis

• Uncommon
  – Immune thrombocytopenia purpura
  – Human immunodeficiency virus
  – Lupus
  – APLS
Etiologies and Differential Diagnosis

• Rare causes
  – Thrombotic thrombocytopenic purpura
  – Hemolytic Uremic syndrome
  – Type IIB von Willebrand’s disease
  – Hematologic malignancies
  – Folate deficiency
  – Congenital disorders – May-Hegglin Anomaly and Gray Platelet syndrome
Major Causes of Thrombocytopenia During Pregnancy

- Spurious, due to EDTA-induced platelet aggregation
- Gestational thrombocytopenia
- Preeclampsia-eclampsia, including HELLP syndrome
- Autoimmune thrombocytopenia (idiopathic or related to drugs, systemic lupus erythematosus, antiphospholipid antibodies, or HIV)
Major Causes of Thrombocytopenia During Pregnancy

- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome
- Congenital platelet disorders
  - Gray platelet syndrome
  - May-Hegglin syndrome
- Bone marrow disease
- Hypersplenism
Diagnosis

- H&P
- CBC
- Manual platelet count
- Peripheral smear
- Citrate treated tube – removes EDTA clumping effect
- Labs to exclude other conditions
- +/- Platelet antibodies
Gestational thrombocytopenia

- No history of bleeding diathesis
- Platelets >50-70k
- Poses no risk to mother or fetus
- Serial platelet counts
- No need for treatment
- No indication to alter mode of anesthesia or delivery
Immune Thrombocytopenic Purpura (ITP)

- Autoimmune disease
- Increased platelet destruction by reticuloendothelial system
- 3 per 1000 pregnancies
Immune Thrombocytopenic Purpura (ITP)

- **Childhood**
  - Adolescents, follows infection
  - Rapid remission, rare relapses

- **Adult**
  - Chronic, frequent exacerbations, remissions
  - Usually requires long-term steroids or immune globulin therapy
ITP

• Diagnosis
  – H&P and degree of thrombocytopenia
  – Platelet antibody testing
    • Sensitivity/specificity varies with lab
    • Traditional antibody testing cannot distinguish ITP from gestational thrombocytopenia
    • Direct – platelet bound
    • Indirect – Free, indirect, serum
      – Have been associated with neonatal thrombocytopenia in women with ITP
        » 13-24% of women with true ITP will give birth to neonates with platelets <50k
      – Antiplatelet antibodies lack high PPV, but the NPV is high, again will vary among labs
ITP – Management issues

• Corticosteroids
  – To maintain platelets >30k during pregnancy
  – To maintain platelets >50k at delivery
  – Most panels (ACOG, Am Society of Hematology, Creasy) recommend starting steroids when platelets <50k

• Creasy suggests ‘More aggressive treatment is often pursued close to the estimated due date, in anticipation of potential bleeding, surgery, or need for regional anesthesia. Some anesthesiologists may require a platelet count greater than 80,000/μL before deeming the woman's condition safe for placement of an epidural catheter.’
ITP - Management

• Refractory cases
  – IVIG
  – Platelet transfusion
  – Splenectomy
  – Immunosuppressive medications – azathioprine, vincristine
  – Rh immune globulin has been reported
FIG. 4-3  Management of the pregnant woman with immune thrombocytopenic purpura.
ITP – Mode of delivery

- Hemorrhagic complications appear to be unrelated to mode of delivery
- Most hemorrhagic complications occur in neonatal period
- Maternal treatment (steroids, IVIG) does not affect rate of hemorrhagic complications

Burrows 1988; Cook 1991; Burrows 1993; Payne 1997; Laros 1994; Burrows 1993; Silver 1998
ITP – Mode of delivery

• Series of 474 neonates (born to mothers with ITP) – 29% (vaginal) vs 30% (cesarean) suffered clinical bleeding (Cook 1993)

• Per Creasy - A careful analysis of the literature also suggests that no case of ICH has been directly attributable to intrapartum events

• ICH infrequency – No cases of ICH in series of 16,000 ITP pregnancies (Burrows 1993)
  – 3 infants had ICH but were due to alloimmune, not autoimmune thrombocytopenia
  – The proportion of infants with platelet counts lower than 50,000/μL is about 15%, and this may be an overestimate of the risk because of publication bias.
ITP – Mode of delivery

• Reserve cesarean for obstetrical indications
Thrombotic Thrombocytopenic Purpura

- Rare, life threatening, medical emergency
- Platelets aggregate, producing platelet thrombi, occluding arterioles and capillaries, leads to ischemia, infarction
  - Can affect any organ system
  - Esp brain, kidneys
Microangiopathic Hemolytic Anemia

A schistocyte count greater than 1% appears to be diagnostic of TTP in the appropriate clinical setting (Burns 2004)
TTP – Clinical Diagnosis

- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Neurologic abnormalities
  - Confusion, HA, paresis, visual hallucinations, seizures
- Fever
- Renal dysfunction
- *Top 3 in 75% of TTP patients, pentad seen in 40%
- Differentiation from other microangiopathic hemolytic anemias of pregnancy (severe preeclampsia/HELLP)
TTP – Management

• Medical

• Plasmapheresis/plasma exchange
  – FFP to temporize and transfer to facility capable of plasmapheresis

• IV steroids

• Dialysis if renal failure is present

• Refractory cases
  – Vincristine
  – Cryoprecipitate
  – Splenectomy
  – Azathioprine
Management of the gravida with TTP. Before adopting this approach, the treating physician must be certain of the diagnosis. TTP is a clinical diagnosis and can mimic severe preeclampsia. The criteria for diagnosing TTP are listed in Table 4-6.
HELLP syndrome

- Delivery
- Seizure prophylaxis
- Hypertensive control
- +/- Steroids
Neonatal thrombocytopenia

• Differential Diagnosis
  - Infection/sepsis
    • TORCH – Toxoplasma gondii, hepatitis B, syphilis, Varicella-Zoster, HIV, parvovirus B19, Rubella, CMV, HSV
    • Perinatal infection with E. coli, H. influenza, Group B streptococcus
  - Disseminated intravascular coagulation
  - Neonatal alloimmune thrombocytopenia
Neonatal thrombocytopenia

• Differential Diagnosis
  – Maternal autoimmune thrombocytopenia with transplacental passage of antibodies
    • Immune thrombocytopenic purpura – ITP
    • Lupus
  – Maternal exposure to antiplatelet medications
    • Heparin, Enoxaparin
  – Bone marrow disorders (aplastic anemia), inherited thrombocytopenias
Neonatal Alloimmune Thrombocytopenia (NAIT)

• Definition -

• Maternal alloimmunization against platelet antigens inherited from the father
  – Or against platelet antigens that are seen as foreign to the mother
NAIT - Epidemiology

• Epidemiology
  – Most common cause of severe thrombocytopenia (\(<50,000/\mu L\)) in the newborn in the first few days of life
  – 1 in 1-5,000 births
  – Can occur as early as 18-20 weeks gestation
  – No gender preference
  – 50% of cases occur during a first pregnancy

• Risk factors
  – Previous child with NAIT or family history of NAIT
  – Recurrence risk \(\sim100\%\), if homozygous FOB
NAIT - Pathophysiology

- Pathophysiology
  - Maternal alloimmunization against fetal platelet antigens inherited from the father - severity depends on antigen
  - Most commonly occurs in women lacking human platelet antigen (HPA) -1a - mother is HPA 1b/1b, with anti HPA 1a and a father that is HPA 1a/1a or HPA 1a/1b
    - 80-90% of cases occur in HPA-1a negative mothers
    - 98% of the US population is HPA-1a (+)
      - 2% of US population is HPA -1a negative or HPA 1b homozygotes
    - HPA-1a incompatibility causes the most severe form of the disease
      - HPA -3a causes the next most severe form
    - HPA-1a and -5b are the most commonly involved HPAs
    - Asian population – HPA -4 system is the most frequent cause of NAIT
  - HLA antigens not commonly involved or thought to result in alloimmunization
<table>
<thead>
<tr>
<th>HPA system name</th>
<th>Antigen</th>
<th>Familiar name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphisms of glycoprotein IIIa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPA-1</td>
<td>HPA-1a</td>
<td>$P_1^{A^1}$, Zw^a</td>
</tr>
<tr>
<td></td>
<td>HPA-1b</td>
<td>$P_1^{A^2}$, Zw^b</td>
</tr>
<tr>
<td>HPA-4</td>
<td>HPA-4a</td>
<td>Pen^a, Yuk^b</td>
</tr>
<tr>
<td></td>
<td>HPA-4b</td>
<td>Pen^b, Yuk^a</td>
</tr>
<tr>
<td>HPA-6</td>
<td>HPA-6bw</td>
<td>Ca, Tu</td>
</tr>
<tr>
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<td>HPA-7bw</td>
<td>Mo</td>
</tr>
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<td>HPA-8bw</td>
<td>Sr-a</td>
</tr>
<tr>
<td>HPA-10</td>
<td>HPA-10bw</td>
<td>La(a)</td>
</tr>
<tr>
<td>HPA-11</td>
<td>HPA-11bw</td>
<td>Gro(a)</td>
</tr>
<tr>
<td>HPA-14</td>
<td>HPA-14bw</td>
<td>Oe(a)</td>
</tr>
<tr>
<td>HPA-16</td>
<td>HPA-16bw</td>
<td>Duv(a)</td>
</tr>
<tr>
<td>Polymorphisms of glycoprotein IIb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPA-3</td>
<td>HPA-3a</td>
<td>Bak^a, Lek</td>
</tr>
<tr>
<td></td>
<td>HPA-3b</td>
<td>Bak^b</td>
</tr>
<tr>
<td>HPA-9</td>
<td>HPA-9bw</td>
<td>Max^a</td>
</tr>
</tbody>
</table>

Polymorphisms of glycoprotein Ia
- HPA-5
- HPA-5a
- Br^b, Zavb
- HPA-5b
- Br^a, Zava
- HPA-13
- HPA-13bw
- Sit(a)

Polymorphisms of glycoprotein Ib
- HPA-2
- HPA-2b
- Ko^a, Sib-a
- HPA-12
- HPA-12bw
- Ly(a)

Other probable platelet alloantigen specificities
- HPA-15
- HPA-15a
- Gov a
- HPA-15b
- Gov-b

NAIT - Clinical presentation

- Clinical presentation
  - Health newborn with widespread petechiae or purpura
  - Visceral hemorrhage – GI or bladder
  - Intracranial hemorrhage – may occur in utero or intrapartum or in the neonatal period
    - Occurs in 7-20% of cases of NAIT – 75% of these cases occur in the antenatal period – as early as mid 2nd trimester
  - Fatal in 1/3 of patients
  - 20-30% have neurologic impairment
- High recurrence rate in subsequent pregnancies
  - Usually more severe
NAIT - Diagnosis

• Diagnosis
  – Diagnosis is made in thrombocytopenic infants when maternal and paternal platelet typing reveals the father has a platelet antigen that the mother lacks and the mother has detectable antibodies to this antigen.
  – A combination of test results are used to determine the likelihood of NAIT
Pregnancies at risk for NAIT - History

• Previous pregnancy affected by NATP or previous baby affected – severity, ICH present or not

• Fetal death due to intracranial hemorrhage

• Neonatal thrombocytopenia of undetermined etiology
  – All cases of neonatal thrombocytopenia <50k, regardless of etiology

• Family history (esp in sisters of the patient)
Pregnancies at risk for NAIT

- After an index case, over 85% of the couple's subsequent fetuses will carry the offending platelet antigen and be at risk for NATP
  - Ex – affected proband – likely HPA 1b/1b
- Father
  - 25% HPA 1a/1b – 50% of progeny will be 1a/1b and at risk
  - 75% are HPA 1a/1a – 100% of progeny will be 1a/1b and at risk
NAIT - lab

- Universal screening not cost effective
- Personal or family history suggestive of NAIT
  - Maternal HPA antibodies
  - Maternal and paternal platelet antigen testing usually performed simultaneously looking for incompatibility for the HPA – 1a/1b antigen system
  - Maternal serum antibody screening is for HLA antibodies and RBC antigens (HLA not thought to be a significant cause of NATP, but if it is, then it’s probably class I)
  - If initial antibody screen is negative, then testing each trimester if there is HPA incompatibility since the HPA antibodies can occur later in the pregnancy
NAIT - lab

• Fetal platelet typing
  – Fetal DNA from amniocytes
    • Amniocentesis is preferred as CVS potential risk for sensitization is greater
    • If FOB is heterozygous, fetal antigen typing is recommended to avoid unnecessary treatment in fetuses not at risk
  – Uses PCR to determine fetal HPA status by typing fetal DNA for platelet antigens
NAIT - Management

• Management
  – Expectant
  – In-utero platelet transfusions
  – Medical
    • IVIG
    • Corticosteroids
  – Neonatal platelet transfusion (antigen negative)
Natural history
• Bussel 1997 – review of 3 trials – N=107
  – Pre-treatment
    • 53 pt with plt <20k (50%), only 4 had normal platelet counts (>100k)
    • Majority HPA 1a incompatibility
    • 41/107 infants sampled at 25 weeks had platelet counts lower than previous affected siblings
    • If >50,000 and did not get treated – platelet count decreased by 10,000/mL³ per week
  – Most significant predictor for more severe disease in subsequent pregnancy was antenatal hemorrhage in the affected sibling
• Starting with IVIG, avoid initial FBS
NAIT - Management

- Management
  - Expectant – in absence of intervention, thrombocytopenia in the second affected child is always as or more severe than in the previous affected infant
  - Intracranial hemorrhage is the reason for the majority of morbidity and mortality and prevention of this is the goal of treatment
    - Up to 75% of ICH occurs antenatally
Fetal blood sampling

• Management
  – In-utero platelet transfusions
  – Invasive
    • Any fetal blood sampling procedure – 1% risk of fetal loss
    • Risk is higher in an affected NAIT pregnancy – up to 8% due to exsanguination at puncture site of cord
  – In utero transfusion of platelets concentrated (maternal) should be performed at the time of FBS if platelet count is determined to be <50k before the needle is removed to avoid exsanguination
NAIT

- Management – medical
  - IVIG
  - Corticosteroids
NAIT - IVIG

• *Has been shown to reduce the risk of intracranial hemorrhage when compared to prior untreated pregnancies (bussel 1998, lynch 1992)

• Most common to start IVIG –
  – 1gm/kg/week in pregnancies at 20 weeks of gestation
  – High risk pregnancy –
    • Hx of antenatal ICH,
    • Hx of peripartum ICH
    • Platelet count <20k obtained via cordocentesis
    • If above is present – may need to do 2gm/kg/week or add 1mg/kg/day of prednisone
When to add steroids

- Bussel 1996 – 54 patients
  - All got IVIG +/- dexamethasone
  - Rescue therapy for nonresponders – prednisone 60mg /day increased the platelet counts
  - Dexamethasone did not help improve platelet counts
Antenatal therapy – a protocol

• **Standard risk** – previous affected child with thrombocytopenia without ICH
  - IVIG 1gm/kg/week or prednisone 0.5mg/kg/day starting at 20 weeks

• **High risk** – previous affected child with thrombocytopenia and ICH in peripartum period
  - IVIG 1gm/kg/week + prednisone 1mg/kg/day starting at 20 weeks
Antenatal therapy – a protocol

- Very high risk – previously affected child with antenatal ICH
  - IVIG – 2gm/kg/week started at 12 weeks
  - FBS at 20 weeks, if plt <50k, prednisone 1mg/kg/day is started
  - Weekly in utero platelet transfusions or delivery are the remaining options when medical therapy is not adequate

- Cesarean delivery – (vaginal delivery possible option if fetal platelets >50k prior to delivery)
When to add steroids

• Bussel 1996 – 54 patients
  – All got IVIG +/- dexamethasone
  – Rescue therapy for nonresponders – prednisone 60mg /day increased the platelet counts
  – Dexamethasone did not help improve platelet counts
NAIT

- In-utero intracranial hemorrhage
Conclusions

• Thrombocytopenia
  – Exclude clumping first
  – Remember differential diagnosis

• For ITP adding steroids at platelet counts of 50-70k is controversial, most recommend starting steroids when <50k

• Differentiate maternal from neonatal thrombocytopenia
References

- Email darren.farley@awhogyn.com for references other than those listed
References


References - Creasy

- See notes
Article Review

• What do thrombocytopenia and latency antibiotics have in common?
Absolutely nothing.
Antibiotic Therapy for Reduction of Infant Morbidity After Preterm Premature Rupture of the Membranes

A Randomized Controlled Trial

Brian M. Mercer, MD; Menachem Miodovnik, MD; Gary R. Thurnau, MD; Robert L. Goldenberg, MD; Anita F. Das, MS; Risa D. Ramsey, BSN; Yolanda A. Rabello, MSEd; Paul J. Meis, MD; Atef H. Moawad, MD; Jay D. Iams, MD; J. Peter Van Dorsten, MD; Richard H. Paul, MD; Sidney F. Bottoms, MD†; Gerald Merenstein, MD; Elizabeth A. Thom, PhD; James M. Roberts, MD; Donald McNellis, MD; for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network

JAMA. 1997;278:989-995
Context.—Intrauterine infection is thought to be one cause of preterm premature rupture of the membranes (PPROM). Antibiotic therapy has been shown to prolong pregnancy, but the effect on infant morbidity has been inconsistent.

Objective.—To determine if antibiotic treatment during expectant management of PPROM will reduce infant morbidity.

Design.—Randomized, double-blind, placebo-controlled trial.

Setting.—University hospitals of the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.

Patients.—A total of 614 of 804 eligible gravidas with PPROM between 24 weeks’ and 0 days’ and 32 weeks’ and 0 days’ gestation who were considered candidates for pregnancy prolongation and had not received corticosteroids for fetal maturation or antibiotic treatment within 1 week of randomization.
**Interventions.**—Intravenous ampicillin (2-g dose every 6 hours) and erythromycin (250-mg dose every 6 hours) for 48 hours followed by oral amoxicillin (250-mg dose every 8 hours) and erythromycin base (333-mg dose every 8 hours) for 5 days vs a matching placebo regimen. Group B streptococcus (GBS) carriers were identified and treated. Tocolysis and corticosteroids were prohibited after randomization.

**Main Outcome Measures.**—The composite primary outcome included pregnancies complicated by at least one of the following: fetal or infant death, respiratory distress, severe intraventricular hemorrhage, stage 2 or 3 necrotizing enterocolitis, or sepsis within 72 hours of birth. These perinatal morbidities were also evaluated individually and pregnancy prolongation was assessed.
Results.—In the total study population, the primary outcome (44.1% vs 52.9%; \(P=0.04\)), respiratory distress (40.5% vs 48.7%; \(P=0.04\)), and necrotizing enterocolitis (2.3% vs 5.8%; \(P=0.03\)) were less frequent with antibiotics. In the GBS-negative cohort, the antibiotic group had less frequent primary outcome (44.5% vs 54.5%; \(P=0.03\)), respiratory distress (40.8% vs 50.6%; \(P=0.03\)), overall sepsis (8.4% vs 15.6%; \(P=0.01\)), pneumonia (2.9% vs 7.0%; \(P=0.04\)), and other morbidities. Among GBS-negative women, significant pregnancy prolongation was seen with antibiotics (\(P<0.001\)).
Figure 2.—Interval from randomization to delivery after expectant management of preterm premature rupture of the membranes at 24 weeks' and 0 days' gestation to 32 weeks' and 0 days' gestation according to antibiotic-group or placebo-group assignment. The $P$ values reflect analysis of percentage of women whose neonates remained undelivered. For the survival analysis, $P<.001$. 
Conclusions.—We recommend that women with expectantly managed PPROM remote from term receive antibiotics to reduce infant morbidity.
Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial

S L Kenyon, D J Taylor, W Tarnow-Mordi, for the ORACLE Collaborative Group*

Methods 4826 women with pPROM were randomly assigned 250 mg erythromycin (n=1197), 325 mg co-amoxiclav (250 mg amoxicillin plus 125 mg clavulanic acid; n=1212), both (n=1192), or placebo (n=1225) four times daily for 10 days or until delivery. The primary outcome measure was a composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital. Analysis was by intention to treat.

Findings Two women were lost to follow-up, and there were 15 protocol violations. Among all 2415 infants born to women allocated erythromycin only or placebo, fewer had the primary composite outcome in the erythromycin group (151 of 1190 [12·7%] vs 186 of 1225 [15·2%], p=0·08) than in the placebo group. Among the 2260 singletons in this comparison, significantly fewer had the composite primary outcome in the erythromycin group (125 of 1111 [11·2%] vs 166 of 1149 [14·4%], p=0·02). Co-amoxiclav only and co-amoxiclav plus erythromycin had no benefit over placebo with regard to this outcome in all infants or in singletons only. Use of erythromycin was also associated with prolongation of pregnancy, reductions in neonatal treatment with surfactant, decreases in oxygen dependence at 28 days of age and older, fewer major cerebral abnormalities on ultrasonography before discharge, and fewer positive blood cultures. Although co-amoxiclav only and co-amoxiclav plus erythromycin were associated with prolongation of pregnancy, they were also associated with a significantly higher rate of neonatal necrotising enterocolitis.

Interpretation Erythromycin for women with pPROM is associated with a range of health benefits for the neonate, and thus a probable reduction in childhood disability. However, co-amoxiclav cannot be routinely recommended for pPROM because of its association with neonatal necrotising enterocolitis. A follow-up study of childhood development and disability after pPROM is planned.
<table>
<thead>
<tr>
<th>Birthweight (g)</th>
<th>Co-amoxiclav only (n=1205)</th>
<th>Placebo only (n=1225)</th>
<th>p</th>
<th>Any co-amoxiclav (n=2394)</th>
<th>No co-amoxiclav (n=2415)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>2083 (755)</td>
<td>2072 (769)</td>
<td>0.69</td>
<td>2103 (763)</td>
<td>2087 (769)</td>
<td>0.47</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2060 (180–4710)</td>
<td>2055 (240–4366)</td>
<td>.</td>
<td>2080 (180–4710)</td>
<td>2060 (240–4420)</td>
<td>.</td>
</tr>
<tr>
<td>&lt;2500</td>
<td>877 (72-8%)</td>
<td>880 (71-8%)</td>
<td>0.60</td>
<td>1718 (71-8%)</td>
<td>1743 (72-2%)</td>
<td>0.75</td>
</tr>
<tr>
<td>&lt;1500</td>
<td>271 (22-5%)</td>
<td>284 (23-2%)</td>
<td>0.68</td>
<td>521 (21-8%)</td>
<td>539 (22-3%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Admission to NICU/SCBU</td>
<td>848 (70-4%)</td>
<td>880 (71-8%)</td>
<td>0.42</td>
<td>1666 (69-6%)</td>
<td>1716 (71-1%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Total babies ventilated</td>
<td>254 (21-1%)</td>
<td>283 (23-1%)</td>
<td>0.23</td>
<td>498 (20-8%)</td>
<td>534 (22-1%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Total babies in &gt;21% O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>383 (30-1%)</td>
<td>436 (35-6%)</td>
<td>0.05</td>
<td>755 (31-5%)</td>
<td>806 (33-4%)</td>
<td>0.17</td>
</tr>
<tr>
<td>At 48 h</td>
<td>316 (26-2%)</td>
<td>358 (29-2%)</td>
<td>0.1</td>
<td>621 (25-9%)</td>
<td>660 (27-3%)</td>
<td>0.27</td>
</tr>
<tr>
<td>At 7 days</td>
<td>168 (13-9%)</td>
<td>181 (14-8%)</td>
<td>0.56</td>
<td>326 (13-6%)</td>
<td>334 (13-8%)</td>
<td>0.83</td>
</tr>
<tr>
<td>At 14 days</td>
<td>135 (11-2%)</td>
<td>140 (11-4%)</td>
<td>0.80</td>
<td>249 (10-4%)</td>
<td>259 (10-7%)</td>
<td>0.71</td>
</tr>
<tr>
<td>At 28 days</td>
<td>112 (9-3%)</td>
<td>116 (9-5%)</td>
<td>0.88</td>
<td>209 (8-7%)</td>
<td>211 (8-7%)</td>
<td>0.99</td>
</tr>
<tr>
<td>RDS confirmed by radiography</td>
<td>241 (20-0%)</td>
<td>266 (21-7%)</td>
<td>0.3</td>
<td>483 (20-2%)</td>
<td>502 (20-8%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Treatment with exogenous surfactant</td>
<td>182 (15-1%)</td>
<td>217 (17-7%)</td>
<td>0.08</td>
<td>350 (14-6%)</td>
<td>393 (16-3%)</td>
<td>0.11</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt; dependence &gt;28 days</td>
<td>111 (9-2%)</td>
<td>114 (9-3%)</td>
<td>0.94</td>
<td>205 (8-6%)</td>
<td>208 (8-6%)</td>
<td>0.95</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt; at 36 weeks post conception</td>
<td>69 (5-7%)</td>
<td>76 (6-2%)</td>
<td>0.62</td>
<td>136 (5-7%)</td>
<td>142 (5-9%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>Overall</td>
<td>82 (6-8%)</td>
<td>100 (8-2%)</td>
<td>0.20</td>
<td>165 (6-9%)</td>
<td>168 (7-0%)</td>
</tr>
<tr>
<td></td>
<td>If born within 14 days</td>
<td>63 (5-2%)</td>
<td>85 (6-9%)</td>
<td>0.08</td>
<td>121 (5-1%)</td>
<td>146 (6-0%)</td>
</tr>
<tr>
<td>Necrotising enterocolitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected or proven</td>
<td>50 (4-1%)</td>
<td>33 (2-7%)</td>
<td>0.08</td>
<td>92 (3-8%)</td>
<td>58 (2-4%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Proven</td>
<td>24 (1-9%)</td>
<td>6 (0-5%)</td>
<td>0.001</td>
<td>44 (1-8%)</td>
<td>17 (0-7%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Abnormal cerebral ultrasonography</td>
<td>46 (3-8%)</td>
<td>61 (5-0%)</td>
<td>0.16</td>
<td>92 (3-8%)</td>
<td>111 (4-6%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Deaths</td>
<td>79 (6-6%)</td>
<td>82 (6-7%)</td>
<td>0.89</td>
<td>156 (6-5%)</td>
<td>152 (6-3%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Composite primary outcome</td>
<td>163 (13-5%)</td>
<td>186 (15-2%)</td>
<td>0.25</td>
<td>330 (13-8%)</td>
<td>337 (14-0%)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

NICU=neonatal intensive-care unit; SCBU=special-care baby unit; RDS=respiratory distress syndrome.

Table 5: Neonatal outcomes of babies born to women with pPROM randomly assigned co-amoxiclav
Methods 6295 women in spontaneous preterm labour with intact membranes and without evidence of clinical infection were randomly assigned 250 mg erythromycin (n=1611), 325 mg co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid; n=1550), both (n=1565), or placebo (n=1569) four times daily for 10 days or until delivery, whichever occurred earlier. The primary outcome measure was a composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital. Analysis was by intention to treat.

Findings None of the trial antibiotics was associated with a lower rate of the composite primary outcome than placebo (erythromycin 90 [5.6%], co-amoxiclav 76 [5.0%], both antibiotics 91 [5.9%], vs placebo 78 [5.0%]). However, antibiotic prescription was associated with a lower occurrence of maternal infection.

Interpretation This trial provides evidence that antibiotics should not be routinely prescribed for women in spontaneous preterm labour without evidence of clinical infection.
Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial

Lancet 2008; 372: 1319-27

S Kenyon, K Pike, D R Jones, P Brocklehurst, N Marlow, A Sait, D J Taylor

Summary

Background The ORACLE II trial compared the use of erythromycin and/or amoxicillin–clavulanate (co-amoxiclav) with that of placebo for women in spontaneous preterm labour and intact membranes, without overt signs of clinical infection, by use of a factorial randomised design. The aim of the present study—the ORACLE Children Study II—was to determine the long-term effects on children after exposure to antibiotics in this clinical situation.

Methods We assessed children at age 7 years born to the 4221 women who had completed the ORACLE II study and who were eligible for follow-up with a structured parental questionnaire to assess the child’s health status. Functional impairment was defined as the presence of any level of functional impairment (severe, moderate, or mild) derived from the mark III Multi-Attribute Health Status classification system. Educational outcomes were assessed with national curriculum test results for children resident in England.

Findings Outcome was determined for 3196 (71%) eligible children. Overall, a greater proportion of children whose mothers had been prescribed erythromycin, with or without co-amoxiclav, had any functional impairment than did those whose mothers had received no erythromycin (658 [42.3%] of 1554 children vs 574 [38.3%] of 1498; odds ratio 1.18, 95% CI 1.02–1.37). Co-amoxiclav (with or without erythromycin) had no effect on the proportion of children with any functional impairment, compared with receipt of no co-amoxiclav (624 [40.7%] of 1523 vs 608 [40.0%] of 1520; 1.03, 0.89–1.19). No effects were seen with either antibiotic on the number of deaths, other medical conditions, behavioural patterns, or educational attainment. However, more children whose mothers had received erythromycin or co-amoxiclav developed cerebral palsy than did those born to mothers who received no erythromycin or no co-amoxiclav, respectively (erythromycin: 53 [3.3%] of 1611 vs 27 [1.7%] of 1562, 1.93, 1.21–3.09; co-amoxiclav: 50 [3.2%] of 1587 vs 30 [1.9%] of 1586, 1.69, 1.07–2.67). The number needed to harm with erythromycin was 64 (95% CI 37–209) and with co-amoxiclav 79 (42–593).

Interpretation The prescription of erythromycin for women in spontaneous preterm labour with intact membranes was associated with an increase in functional impairment among their children at 7 years of age. The risk of cerebral palsy was increased by either antibiotic, although the overall risk of this condition was low.

Funding UK Medical Research Council.
Review article notes
Icu care manual notes

- Figures of algorithms
Causes of Thrombocytopenia in Pregnancy

- Gestational thrombocytopenia
- Pregnancy-induced hypertension
- HELLP syndrome
- Pseudothrombocytopenia (laboratory artifact)
- Human immunodeficiency virus (HIV) infection
- Immune thrombocytopenic purpura
- Systemic lupus erythematosus
- Antiphospholipid syndrome
- Hypersplenism
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Congenital thrombocytopenias
- Medications (heparin, quinine, quinidine, zidovudine, sulfonamides)
Platelet count

- mean platelet counts in pregnancy slightly decrease, but typically stay in the normal nonpregnant range

- lower limit of normal (106k – 120k)

- platelet width and volume increase
  - increased platelet consumption leads to increased proportion of younger and larger platelets
  - equated with low grade intravascular coagulation
  - increased level of thrombocytopoiesis is a consequence of both dilutional and
creasy
Acog slides
• DIEDPMTO; if poss implement any question bank questions
• Definition
• Incidence
• Etiology
• Diagnosis
• Differential diagnosis
• Pathophysiology
• Maternal complications
• Treatment/Management
• Outcome/Recurrence risk
• Extra slides after this
• Misc slides
• Cardiac, pulmonary physiology
• Resp failure tx
Cardiovascular Changes of Pregnancy

- Blood Volume Expands by 50%
- Mild Myocardial Hypertrophy
- Looks Like Chronic Strain on the Heart
- Increased Capacitance of Systemic and Pulmonary Veins
- Decreased Systemic Vascular Resistance and Pulmonary Vascular Resistance
Heart Rate Across Gestation

![Graph showing heart rate across gestation weeks with error bars](image-url)
Stroke Volume Across Gestation
Cardiovascular Changes of Pregnancy

• Cardiac Output Increased by 30-50%
• Twin Pregnancy: Add another 15%
• Starts Early and Peaks at 20 Weeks
• Increase in Stroke Volume
• Increase in Heart Rate
Cardiac Output Across Gestation
Cardiovascular Changes of Pregnancy

- Systemic Vascular Resistance: Drops

Figure 3–6. Change in systemic vascular resistance (S.V.R.) during normal pregnancy and the first year postpartum in nulliparous and parous women. Open circles, 15 nulliparous women; open squares, 15 parous women. Data are presented as mean ± SEM. 52PP, 52 weeks postpartum; NP, nonpregnant. (From Clapp J, Capeless E: Cardiovascular function before, during and after the first and subsequent pregnancies. Am J Cardiol 80:1469, 1997, with permission.)
Cardiovascular Changes of Pregnancy

• Cardiac Output to Uterus and Placenta
  – 2-3% Non-Pregnant
  – 17% by Term (up to 1000 ml/min)

• CO to Kidneys (20%), Skin (10%), Brain (10%), and Coronary Arteries (5%) Unchanged, but Overall Increases by 50%
Effect of Labor on Cardiac Output

Figure 3-9. Changes in cardiac output and stroke volume during normal labor. (From Hunter S, Robson S: Adaptation of the maternal heart in pregnancy. Br Heart J 68:540, 1992, with permission.)
Cardiac Output Depends on Maternal Positioning

FIGURE 5-11 Sequential changes (±SEM) in blood pressure throughout pregnancy in 69 women in supine (blue lines) and left lateral recumbent positions (red lines). PP = postpartum. (Adapted from Wilson and colleagues, 1980.)
Central Hemodynamic Changes

Table 1-4  Central Hemodynamic Changes Associated with Late Pregnancy ($n = 10$)

<table>
<thead>
<tr>
<th></th>
<th>Nongravid</th>
<th>Gravid</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>86 ± 8</td>
<td>90 ± 6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>6 ± 2</td>
<td>8 ± 2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>4 ± 3</td>
<td>4 ± 3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 ± 10</td>
<td>83 ± 10</td>
<td>+17%</td>
</tr>
<tr>
<td>Cardiac output (L./min)</td>
<td>4.3 ± 0.9</td>
<td>6.2 ± 1.0</td>
<td>+43%</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne/sec/cm$^2$)</td>
<td>1530 ± 520</td>
<td>1210 ± 266</td>
<td>−21%</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne/sec/cm$^2$)</td>
<td>119 ± 47</td>
<td>78 ± 22</td>
<td>−34%</td>
</tr>
<tr>
<td>Serum colloid osmotic pressure (COP: mm Hg)</td>
<td>20.8 ± 1.0</td>
<td>18.0 ± 1.5</td>
<td>−14%</td>
</tr>
<tr>
<td>COP–PCWP gradient (mm Hg)</td>
<td>14.5 ± 2.5</td>
<td>10.5 ± 2.7</td>
<td>−28%</td>
</tr>
<tr>
<td>Left ventricular stroke work index (LVSWI: gm/m/m$^2$)</td>
<td>41 ± 8</td>
<td>48 ± 6</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
Pregnancy as Heart Disease

- Dyspnea is Common (75%)  
- Decreased Exercise Tolerance, Fatigue, Orthopnea, Syncope, Chest Discomfort are all Common  
- Peripheral Edema, Tachycardia, JVD are all Common  
- Heart Sounds are Louder  
- Murmurs are Common
Pulmonary Changes of Pregnancy

• Lung Volume and Pulmonary Function

Figure 3-10. Lung volumes in nonpregnant and pregnant women. TLC, total lung capacity; VC, vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; IRV, inspiratory reserve volume; TV, tidal volume; ERV, expiratory reserve volume; RV, residual volume. (From Cruickshank DP, Wigton TR, Hays PM: Maternal physiology in pregnancy. In Gabbe SG, Niebyl JR, Simpson JL [eds] Obstetrics: Normal and Problem Pregnancies, 3rd ed. New York, Churchill Livingstone, 1996, p 94, with permission.)
# Normal Arterial Blood Gas Values During Pregnancy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.40–7.46</td>
</tr>
<tr>
<td>$P_{CO_2}$</td>
<td>26–32 mm Hg</td>
</tr>
<tr>
<td>$P_{O_2}$</td>
<td>87–106 mm Hg</td>
</tr>
<tr>
<td>$HCO_3^-$</td>
<td>18–21 mEq/liter</td>
</tr>
</tbody>
</table>

Normative data should be established for individual populations residing at high altitude.
Pulmonary Insults are More Likely During Pregnancy and Pregnant Women are More Prone to Respiratory Problems and Failure
Maternal Mortality
Maternal Mortality Rates, by Race/Ethnicity, 2008

Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System
Maternal Mortality Rates, by Age, 2006

Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System.

- Under 20 Years: 5.2
- 20-24 Years: 11.9
- 25-29 Years: 11.7
- 30-34 Years: 12.1
- 35 Years and Older: 28.3
Maternal Mortality

- Maternal Mortality = death occurring within 42 days after delivery and are directly related to pregnancy or childbirth. Ratio is per 100,000 live births.
- Etiologies –
  - Venous-thromboembolic disease
  - Hemorrhage (0.9/100,000)
  - Hypertension (1.3/100,000)
- 2006 – 13.3/100,000 (vs. 7/100,000 in 1996) – goal was 3.3
  - California – 16.9/100,000 in 2006 (vs. 5.6/100,000 in 1996)
- Reasons for increase –
  - Increase in cesarean rate
  - Pregnancies in women > 30 years old
  - Obesity and associated hypertension and diabetes
- Black women – 3-4x more likely to die from pregnancy complications than white women.
- US women higher risk of dying during pregnancy than 40 other countries
  - 3-5x > Greece, Germany, Spain
- For every maternal death, about 50 additional women experience serious complications during pregnancy or delivery

WHO, 2010; MMWR 2006
Normal pregnancy is characterized by increases in cardiac output and blood volume, generalized vasodilatation, a decrease in blood pressure, and resistance to pressor agents such as norepinephrine and angiotensin II. Blood pressure achieves a nadir by midpregnancy, then returns to prepregnancy levels at term. Systolic blood pressure (SBP) is less affected than diastolic blood pressure (DBP) because of the increased cardiac output that offsets the vasodilatation. Further decline is noted during sleep, which follows the pattern of normal circadian rhythms observed in nonpregnant women.

DEFINITION AND CLASSIFICATION
Hypertension in pregnancy is defined as a blood pressure of 140/90 mm Hg or higher. Korotkoff phase V (disappearance) rather than Korotkoff phase IV (muffling of sounds) is used for the determination of DBP. In the outpatient setting, blood pressure should be measured in the sitting position, after a period of rest in a quiet environment. For hospitalized patients, the lateral recumbent position eliminates the effect of compression of the inferior vena cava by the enlarged uterus that impairs venous return and causes a decline in blood pressure. Regardless of posture, special care should be taken to ensure that the patient’s arms are kept at the heart level; positioning the arms above the heart can spuriously reduce the blood pressure readings. In pregnancy, the lowest blood pressures are obtained by using the right arm while the patient is resting in the left lateral position. These blood pressure readings might merely reflect the changes in hydrostatic pressure caused by keeping the right arm above the heart. Therefore, the increases in blood pressure with a change from a lateral to a supine position may simply represent a postural phenomenon rather than positive results on a rollover test, once considered a predictor of preeclampsia.

The Working Group of the National High Blood Pressure Education Program (NHBPEP) recently published a second report revising the classification of hypertensive disorders in pregnancy. The term transient hypertension was replaced by gestational hypertension, which is used only during pregnancy for a group of women who develop high blood pressure for the first time after 20 weeks’ gestation in the absence of proteinuria. The rest of the classification remains unchanged (Table 1).

Preeclampsia
Preeclampsia is a multisystemic disease characterized by hypertension and proteinuria, a protein level of 300 mg or greater in a 24-hour urine specimen that roughly correlates with a qualitative measurement of 1+ (30 mg/dL) on dipstick urinalysis in the absence of urinary tract infection. Because of disagreement between random and 24-hour urinary protein determinations, the latter is recommended.
### TABLE 34-1. Diagnosis of Hypertensive Disorders Complicating Pregnancy

#### Gestational Hypertension:
- Systolic BP $\geq 140$ or diastolic BP $\geq 90$ mm Hg for first time during pregnancy
- No proteinuria
- BP returns to normal before 12 weeks postpartum
- Final diagnosis made only postpartum
- May have other signs or symptoms of preeclampsia, for example, epigastric discomfort or thrombocytopenia

#### Preeclampsia:

**Minimum criteria:**
- BP $\geq 140/90$ mm Hg after 20 weeks’ gestation
- Proteinuria $\geq 300$ mg/24 hours or $\geq 1+$ dipstick

**Increased certainty of preeclampsia:**
- BP $\geq 160/110$ mm Hg
- Proteinuria 2.0 g/24 hours or $\geq 2+$ dipstick
- Serum creatinine $>1.2$ mg/dL unless known to be previously elevated
- Platelets $<100,000/\mu$L
- Microangiopathic hemolysis—increased LDH
- Elevated serum transaminase levels—ALT or AST
- Persistent headache or other cerebral or visual disturbance
- Persistent epigastric pain

#### Eclampsia:
- Seizures that cannot be attributed to other causes in a woman with preeclampsia

**Superimposed Preeclampsia On Chronic Hypertension:**
- New-onset proteinuria $\geq 300$ mg/24 hours in hypertensive women but no proteinuria before 20 weeks’ gestation
- A sudden increase in proteinuria or blood pressure or platelet count $<100,000/\mu$L in women with hypertension and proteinuria before 20 weeks’ gestation

#### Chronic Hypertension:
- BP $\geq 140/90$ mm Hg before pregnancy or diagnosed before 20 weeks’ gestation not attributable to gestational trophoblastic disease
- Hypertension first diagnosed after 20 weeks’ gestation and persistent after 12 weeks postpartum

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; LDH = lactate dehydrogenase.

Pulmonary Changes of Pregnancy

- **Lung Volumes and Capacities**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Definition</th>
<th>Change in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (RR)</td>
<td>Number of breaths per minute</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Vital capacity (VC)</td>
<td>Maximum amount of air that can be forcibly expired after maximum inspiration (IC + ERV)</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Inspiratory capacity (IC)</td>
<td>Maximum amount of air that can be inspired from resting expiratory level (TV + IRV)</td>
<td>Increased 5 to 10%</td>
</tr>
<tr>
<td>Tidal volume (TV)</td>
<td>Amount of air inspired and expired with normal breath</td>
<td>Increased 30 to 40%</td>
</tr>
<tr>
<td>Inspiratory reserve volume (IRV)</td>
<td>Maximum amount of air that can be inspired at end of normal inspiration</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Functional residual capacity (FRC)</td>
<td>Amount of air in lungs at resting expiratory level (ERV + RV)</td>
<td>Decreased 20%</td>
</tr>
<tr>
<td>Expiratory reserve volume (ERV)</td>
<td>Maximum amount of air that can be expired from resting expiratory level</td>
<td>Decreased 15 to 20%</td>
</tr>
<tr>
<td>Residual volume (RV)</td>
<td>Amount of air in lungs after maximum expiration</td>
<td>Decreased 20 to 25%</td>
</tr>
<tr>
<td>Total lung capacity (TLC)</td>
<td>Total amount of air in lungs at maximal inspiration (VC + RV)</td>
<td>Decreased 5%</td>
</tr>
</tbody>
</table>

Cardiovascular Changes of Pregnancy

- Heart is Displaced Left and Upward
- Heart is Rotated to Move the Apex Laterally
- On X-ray:
  - Heart Appears Enlarged
  - Increased Prominence of Pulmonary Vasculature
  - Looks Like Cardiomegaly
Supine Hypotension

- Supine position
- I.V.C. occlusion
- Reduced atrial filling pressure
- Reduced cardiac output
  - 95% of women
    - Increased vascular resistance
      - Maintained arterial pressure
  - 5% of women
    - ? Parasympathetic response
      - Supine hypotensive syndrome
Cardiovascular Changes of Pregnancy

• Decreased Gradient between COP and PCWP: when PCWP is 4 mm Hg above the COP the risk of pulmonary edema increases

• Pregnant Women are More Prone to Pulmonary Edema
  – Changes in Capillary Permeability
  – Elevations in Cardiac Preload

• Pulmonary Edema Occurs with PCWP of 18-20
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregnant(^a) (35-38 wks)</th>
<th>Postpartum (11-13 wks)</th>
<th>Change(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>(90 \pm 6)</td>
<td>(86 \pm 8)</td>
<td>NSC</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>(8 \pm 2)</td>
<td>(6 \pm 2)</td>
<td>NSC</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>(4 \pm 3)</td>
<td>(4 \pm 3)</td>
<td>NSC</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>(83 \pm 10)</td>
<td>(71 \pm 10)</td>
<td>+17%</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>(6.2 \pm 1.0)</td>
<td>(4.3 \pm 0.9)</td>
<td>+43%</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne/sec/cm(^{-5}))</td>
<td>(1210 \pm 266)</td>
<td>(1530 \pm 520)</td>
<td>-21%</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne/sec/cm(^{-5}))</td>
<td>(78 \pm 22)</td>
<td>(119 \pm 47)</td>
<td>-34%</td>
</tr>
<tr>
<td>Serum colloid osmotic pressure (mm Hg)</td>
<td>(18.0 \pm 1.5)</td>
<td>(20.8 \pm 1.0)</td>
<td>-14%</td>
</tr>
<tr>
<td>COP-PCWP gradient (mm Hg)</td>
<td>(10.5 \pm 2.7)</td>
<td>(14.5 \pm 2.5)</td>
<td>-28%</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g/m/m(^2))</td>
<td>(48 \pm 6)</td>
<td>(41 \pm 8)</td>
<td>NSC</td>
</tr>
</tbody>
</table>

\(^a\) Measured in lateral recumbent position.

\(^b\) Changes significant unless NSC = no significant change.

COP = colloid osmotic pressure; PCWP = pulmonary capillary wedge pressure.

Adapted from Clark and colleagues (1989), with permission.
**FIGURE 34-7** Bar graph comparing nonpregnant mean blood volumes with those obtained at the time of delivery in a group of women with normal pregnancy, eclampsia in their first pregnancy, and subsequent normal pregnancy in some of the women who had eclampsia. Extensions above bars represent one standard deviation. Comparison between values with identical lowercase letters, that is, a-a, b-b, c-c, d-d, are significant *p* < .001. (Data from Zeeman and Cunningham, 2009, with permission.)
Wedge Pressures in Preeclampsia

Figure 2-9  (A) Starling curves of eclamptic and severe PIH patients treated with maintenance intravenous fluids prior to delivery. (B) Starling curves of severe PIH patients treated with aggressive crystalloid and colloid therapy prior to delivery. (From Hankins GD, Wendel GD, Cunningham FG, Leveno KJ: Am J Obstet Gynecol 1984; 150:506. Reproduced with permission.)
Wedge Pressures in Preeclampsia

**FIGURE 34-6** Ventricular function in women with severe preeclampsia–eclampsia plotted on the Braunwald ventricular function curve. The pulmonary capillary wedge pressures (PCWP) are lower in those managed with restricted fluid administration (striped area in A) compared with women managed with aggressive fluid therapy (striped area in B). In those managed with aggressive fluid infusions, eight developed pulmonary edema despite normal to hyperdynamic ventricular function in all but one. Data for A are from Benedetti (1980) and Hankins (1984) and colleagues and for B from Rafferty and Berkowitz (1980) and Phelan and Yurth (1982).
FIGURE 5-10 Relationship between left ventricular stroke work index (LVSWI) (cardiac output) and pulmonary capillary wedge pressure (PCWP) in 10 normal pregnant women in the third trimester. (Figure from Hauth and Cunningham, 1999; data from Clark and colleagues, 1989.)
Pulmonary Changes of Pregnancy

• Upper Respiratory Tract
  – Mucosa becomes Edematous and Hyperemic
  – Nasal Stuffiness and Nosebleeds

• Mechanical Changes
  – Relaxation of Ligaments in Thoracic Cage
  – Subcostal Angle Increases from 68 to 103°
  – Transverse Diameter Expands 2 cm
  – Chest Circumference Expands by 5-7 cm
  – Diaphragm Level Rises 4 cm
Pulmonary Changes of Pregnancy

• Spirometry During Pregnancy
  – FEV1 is Unchanged
  – Ratio of FEV1 to FVC is Unchanged
  – Peak Expiratory Flow is Unchanged

• Chronic Hyperventilation due to P4
  – 30-40% Increase in Tidal Volume and Minute Ventilation (occurs by 8-11 Weeks of Gestation)
Pulmonary Changes of Pregnancy

- **Gas Exchange**
  - Increased PaO$_2$ (106-108 mm Hg)
  - Decreased PaCO$_2$ (27-32 mm Hg)
  - Facilitates Transfer of CO$_2$ from Fetus to Mother and then Exhaled Out
  - Chronic Respiratory Alkalosis
  - pH Maintained by a Lower Bicarbonate Level (18-21 mEq/L)
  - A-A Gradient Increases from 14 to 20 mm Hg
  - Increased O$_2$ Uptake and Consumption (20-40% Above Non-Pregnant Levels)
## TABLE 34-2. Indicators of Severity of Gestational Hypertensive Disorders

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Nonsevere</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic blood pressure</td>
<td>≤110 mm Hg</td>
<td>≥110 mm Hg</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>&lt;160 mm Hg</td>
<td>≥160 mm Hg</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>≤2+</td>
<td>≥3+</td>
</tr>
<tr>
<td>Headache</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Convulsion (eclampsia)</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Serum transaminase elevation</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Fetal-growth restriction</td>
<td>Minimal</td>
<td>Marked</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Absent</td>
<td>Obvious</td>
</tr>
</tbody>
</table>

*aCompare with criteria in Table 34-1.*
ABG changes in pregnancy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nonpreg</th>
<th>Pregnancy 1st Trimester</th>
<th>Pregnancy 3rd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35-7.43</td>
<td>7.40-7.47</td>
<td></td>
</tr>
<tr>
<td>PCO2 mmHg</td>
<td>37-40</td>
<td>27-34</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>compensatory increase in renal bicarb excretion</td>
</tr>
<tr>
<td>PO2 mmHg</td>
<td>103</td>
<td>101-104</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>decreased in supine position and 3\textsuperscript{rd} trim</td>
</tr>
<tr>
<td>P(A-a)O2 mmHg</td>
<td>14</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>increased by 6 in supine position and 3\textsuperscript{rd} trim</td>
</tr>
<tr>
<td>bicarb (meq/L)</td>
<td>22-26</td>
<td>18-22</td>
<td></td>
</tr>
<tr>
<td>base deficit (meq/L)</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
CXR changes in pregnancy

- apparent cardiomegaly (enlarged transverse diameter)
- enlarged left atrium (lateral views)
- increased vascular markings
- straightening of left heart border
- postpartum pleural effusion (right sided)
Indications for intubation

- Respiratory rate > 40/min
- PaCO2 >40mmHg (60 nonpregnant)
- Evidence of maternal exhaustion (increased work of breathing, use of accessory muscles, retractions)
- PaCO2 >35-40mmHg with pH <7.35 and falling PaO2 <60mmHg with ≤ 90% oxygen saturation despite supplemental oxygen = respiratory failure in pregnant asthmatic (CCO, Clark p 384)
Criteria for diagnosis of respiratory failure (MOVE)

• **Mechanical**
  – vital capacity <15mL/kg
  – max inspiratory force < -25cmH20
  – respiratory rate >35/min

• **Oxygenation**
  – PaO2 <70mmHg with FIO2 .4
  – P(A-a)O2 >350mmHg with FIO2 1.0

• **Ventilation**
  – PaCO2 >55mmHg (acute) - 40 in preg, worry above 35!
  – dead space /tidal volume (Vd/Vt) >.6

• **End-inspiratory lung inflation inadequate for adequate gas exchange**
Mechanical ventilation (complications)

- Barotrauma
- Infection
Mechanical ventilation in pregnancy (Clark, CCO, p 384)

- Guidelines to avoid complications
  - Use largest possible endotracheal tube to reduce expiratory resistance
  - Use of volume cycled ventilator
  - Increased humidity to facilitate clearance of mucus
  - Allowance of adequate expiratory time
  - Sedation and possibly paralysis to minimize barotrauma
Guidelines for Initiation of Mechanical Ventilation (Foley p176)

• Primary goals of ventilatory support
  – Adequate oxygenation/ventilation
  – Reduced work of breathing
  – Synchrony between patient and ventilator
  – Avoidance of high-end inspiration alveolar pressures
Guidelines for Initiation of Mechanical Ventilation (Foley p176)

- Patient with normal lung mechanics and gas exchange (drug overdose)
  - ACV/PSV
  - FIO2 .5-1.0;
  - TV 8-15mL/kg
  - RR 8-12/min
  - Inspiratory flow rate 40-60L/min
  - Add sighs 6/h at 1.5 times Vt or PEEP of 5-7.5cm H20 to prevent atelectasis
Guidelines for Initiation of Mechanical Ventilation (Foley p176)

- Patient with severe airflow obstruction (drug overdose)
  - ACV/SIMV
  - FIO2 0.5-1
  - TV 5-7mL/kg
  - RR 12-15/min
  - Inspiratory flow rate 40-60L/min
  - Add PEEP if patient is triggering
  - Goals are to minimize alveolar dynamic hyperinflation auto PEEP below 10cmH20 or end-expiratory lung volumes <20mL/kg
Guidelines for Initiation of Mechanical Ventilation (Foley p176)

- Patient with acute or chronic respiratory failure (status asthmaticus)
  - SIMV/ACV
  - FIO2 0.4-0.6
  - TV 5-7mL/kg
  - RR 24-28/min
  - Inspiratory flow rate 40-60 L/min
Guidelines for Initiation of Mechanical Ventilation (Foley p176)

- Patient with acute hypoxemic respiratory failure (ARDS)
- ACV/PCV
- FIO₂ 1.0
- TV 5-7mL/kg
- RR 24-28/min
- Minimal PEEP to keep SaO₂ of 90%
- If volume is held constant, PEEP increases peak inspiratory airway pressure, a potentially undesirable effect in ARDS
- PEEP levels >15 cm H₂O are rarely necessary
Guidelines for Initiation of Mechanical Ventilation (Foley p176)

- Patient with restrictive lung or chest wall disease (sarcoidosis)
- FIO2 0.5-1
- TV 5-7mL/kg
- RR 18-24/min
Guidelines for Initiation of Mechanical Ventilation (Foley p176)

- Avoid high inspiratory peak pressures (>30 cm H2)
- Target pH and not pCO2 to make changes in RR and minute ventilation
- Use PEEP in diffuse lung injury to support oxygenation and reduce the FIO2
- Set trigger sensitivity to allow a minimal patient effort to initiate the inspiration
- In patients at risk, avoid choosing ventilator settings that limit expiratory time and cause or worsen auto-PEEP
- When poor oxygenation, inadequate ventilation, or excessively high peak inspiratory pressures are thought to be related to patient intolerance of ventilator settings and are not corrected by ventilator adjustment, consider sedation, analgesia, and/or neuromuscular blockade
ER care

• Initial eval
  – H&P
  – PEFR
  – oximetry
  – fetal monitoring

• Initial tx
  – inh beta2 agonist x3 doses over 60-90 min
  – O2 to maintain saturation >95%
  – if no wheezing and PEFR or FEV1 >70% baseline, discharge with follow up

• If oximetry <90%, FEV1<1.0L, or PEFR <100 L/min on presentation
  – continuous nebulized albuterol
  – IV corticosteroids
  – consider IV aminophylline
  – ABG
  – ICU
  – intubation

• if PEFR or FEV1 >40% but <70% baseline after beta2 agonist
  – ABG
  – IV corticosteroids
  – Admission to hospital
Means to provide noninvasive oxygen therapy

- **Nasal cannula**
  - FIO2 24-60%
  - flow rate up to 6 L/min
  - flow rate of ≤4L/min need not be humidified

- **Simple oxygen masks**
  - FIO2 35-50%
  - flow rate 5-10L/min
  - flow rates need to be maintained at 5L/min or higher to avoid rebreathing exhaled Co2 that can be retained in the mask

- **Partial rebreathing mask** (simple mask with reservoir bag)
  - O2 flow should be supplied to maintain the reservoir bag at least 1/3 to ½ full in inspiration
  - flow rate 6-10L/min provides FIO2 40-70% oxygen

- **Nonrebreathing mask** (similar to partial rebreather except has a series of one-way valves; one valve is b/n mask and the bag to prevent exhaled air from returning to bag)
  - delivered FIO2 60-80%
  - min flow rate of 10L/min
Indications for endotracheal intubation (GARDD)

- Gastro-pulmonary reflux and aspiration
- Airway obstruction (present or suspected)
- Respiratory arrest (actual or impending)
- Depressed mental status
- Difficulty managing secretions
Indications for Mechanical Ventilation (Invasive or Noninvasive)

- Severe respiratory or combined respiratory and metabolic acidosis
- Sustained respiratory rate of $\geq 40$/minute
- Abnormal breathing pattern suggestive of increased respiratory workload and/or respiratory muscle fatigue
- Depressed mental status
- Severe hypoxemia
Criteria for determining readiness for extubation

- PaO2 > 80mmHg on FIO2 0.6
- PaCO2 < 45mmHg
- RR < 35 breaths/min
- TV > 5mL/kg
- VC > 10mL/kg
- minute ventilation < 10L/min
- negative inspiratory force <-20 cmH2O
- shallow breathing index (resp frequency/tidal vol < 80)
Differential diagnoses for respiratory failure
Acute severe asthma (CCO, Clark, p387)

• **Goals**
  - Correct hypoxia
  - Reverse bronchospasm, optimize airflow
  - Avoid maternal exhaustion, progression to respiratory failure

• **Management protocol**
  - Admit to ICU
  - Supplemental oxygen
  - Bronchodilator therapy
    - **Albuterol** (0.5mL (0.5% solution) in 2.5mL of NS for nebulization)
    - **Epinephrine** (0.3mL of 1:1000 solution SQ q 20 min)
Lung injury, respiratory failure (CCO, Clark p364)

• Goals
  – Identify and eliminate causal agent
    • Gastric aspiration – secure airway
    • Sepsis eradicate by abx or surgical drainage
    • Failure to stop the pulmonary insults results in progressive pulmonary failure and death
  – Achieve PaO2 >60mmHg with 90% hgb saturation; PvO2 >30mmHg; PaCO2 35-40mmHg
• Assess lung injury, treat
ARDS – diagnostic criteria

• I - acute onset
• II - history compatible with certain risk factors
  – trauma
  – severe shock
  – sepsis (septic Ab included)
  – aspiration
  – venous fluid, fat or amniotic fluid embolism
  – pneumonia
  – pancreatitis
  – blood transfusion
  – seizures
  – overdose
  – drug induced
  – eclampsia
  – abruptio placentae
  – dead fetus syndrome or retained POC
  – DKA
• III – clinical exclusion of cardiogenic pulmonary edema (or PCWP < 18mmHg
• IV – respiratory distress
• V – diffuse bilateral patchy opacities in CXR
• VI- PaO2/FIO2 of <200 (less severe form with this between 201-300mmHg
ARDS – principles of treatment

• Therapeutic goals
  – adequate oxygenation
  – avoid barotrauma with treatment
  – avoid cardiovascular compromise

• Management
  – semi-fowler position – elevate head and chest to improve ventilation
  – oxygen – 10L/min with nonrebreather face mask or CPAP; consider intubation
  – continuous pulse oxymetry and cardiac monitoring
  – IV access; consider arterial line or central line
  – ID risk factors, modify if possible
ARDS – principles of treatment

- Pharmacologic therapy
  - no specific tx
  - NO, pulmonary vasodilators, surfactant, prone ventilation, ECMO
Pulmonary edema

• **Diagnosis**
  – progressive not sudden dyspnea
  – desaturation
  – tachypnea
  – ? HTN
  – bilateral crackles
  – S3/Gallop (not always)

• **RF**
  – fluid overload
  – preeclampsia
  – tocolytic treatment
  – uncontrolled hypertension
Pulmonary edema

• Management
  – semi-fowler position – elevate head and chest to improve ventilation
  – oxygen – 10L/min with nonrebreather face mask or CPAP; consider intubation
  – continuous pulse oxymetry and cardiac monitoring
  – IV access; consider arterial line or central line
  – ID risk factors, modify if possible

• Monitoring
  – input/output
  – BP, fetal heart rate
Pulmonary edema

• Pharmacologic therapy
  – Morphine sulfate – 3-5mg IV (avoid if altered LOC, increased ICP or severe COPD)
  – Furosemide 20-40 mg IV, repeat prn, do not use >120mg/hr and give slowly to prevent ototoxicity
  – Nitroglycerin (2 in of paste or 1 pill 1/150 until IV access obtained)
  – Hydralazine 5-10mg IV if severe HTN is causing the pulmonary edema