Lecture 12a: Complications of Pregnancy

Complications of Pregnancy

- Antenatal care (ANC) is intended to detect and treat or prevent complications of pregnancy
  - Ectopic pregnancy
  - Toxemia (pregnancy induced hypertension PIH), precursor of eclampsia
  - Diabetes
  - Infections
  - Anemia
  - Birth defects/chromosomal anomalies screening

Ectopic Pregnancy

- Extra-uterine pregnancy in fallopian tubes, ovary or abdominal cavity
- Rate 1.3-2% of pregnancies
- Mortality:
  - US 1970 = 35.5, 1990 = 3.8/10,000
  - Developing countries 100-300 deaths/10,000
- Presentation:
  - Pelvic pain and vaginal bleeding (> 5-8 weeks early)
  - Shock, hemorrhage, acute abdominal emergency (late presentation)
  - Woman with a missed period or known pregnancy

Risk factors for ectopic pregnancy

(Farquhar *Lancet* 2005;366:583)

Risk factor	Range of Odd ratios
Tubal surgery, sterilization	4.7-21.0
PID	2.5-21.0
>1 sex partner	2.1-2.5
Induced abortion	~ 2.8
Smoking	2.3-2.5
Age > 40	~2.9
IUD	4.2-45.0
Sterilization	4.9-18.0
Prior ectopic	6.0-11.5
DES	2.4-13.0

Diagnosis of ectopic pregnancy

- Clinical suspicion (bleeding or lower abdominal pain in a pregnant woman)
- Serial hCG (normal hCG increases exponentially, attenuated with ectopic)
- Progesterone (lower in ectopic than normal pregnancy)
- Transvaginal ultrasound

Trends in ectopic Pregnancy

- Ectopic pregnancy increased in industrialized countries during 1970s and 80s, and declined in 1990s
- Risk factors:
  - PID (chlamydia)
  - Sterilization (15-20% of sterilization failures are ectopic)
  - Increased age at first pregnancy (increased ectopics with age)
  - Improved early diagnosis (hCG and ultrasound)
  - IUD use? (increased proportion of pregnancies with IUD are ectopic. Differential efficacy for intra- versus extra-uterine pregnancies)
  - Ovulation induction

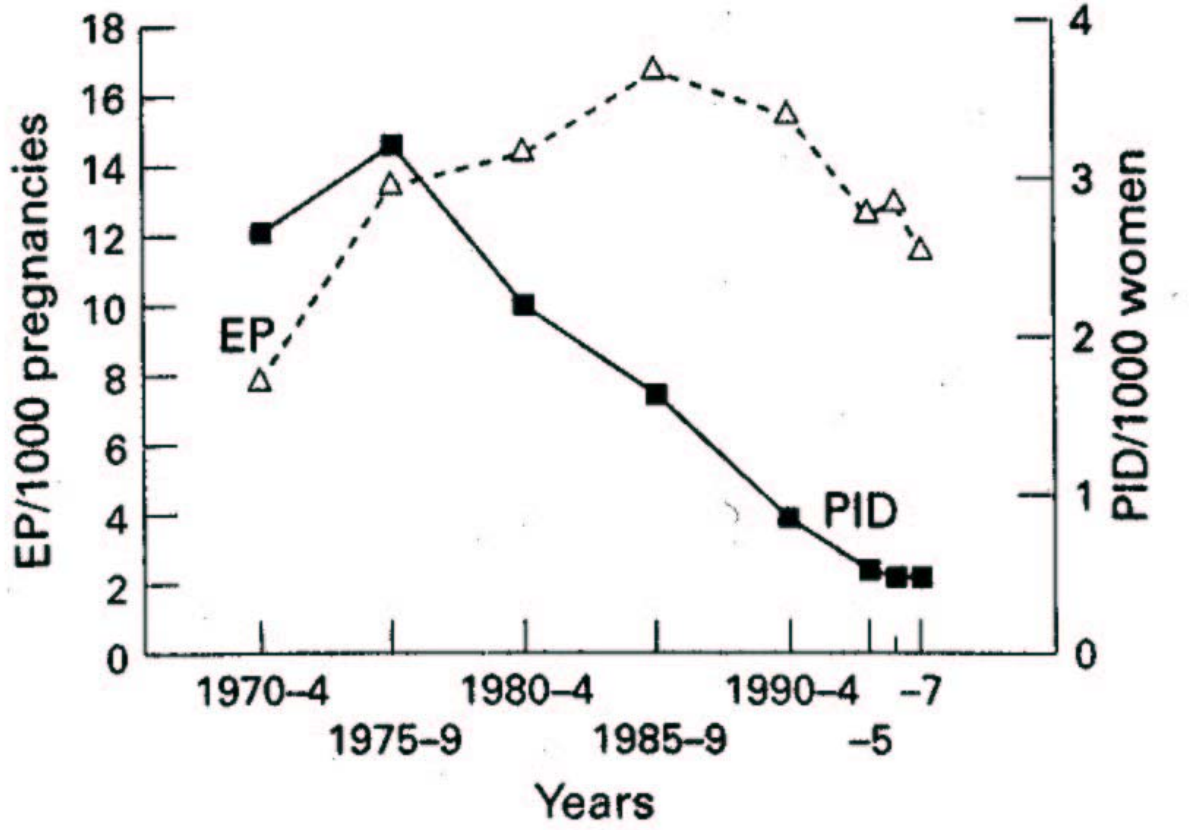

Figure 1 The incidence rates of ectopic pregnancy (EP) per 1000 pregnancies and acute pelvic inflammatory disease (PID) per 1000 women in Örebro county (catchment area for Örebro Medical Centre Hospital) from 1970 to 1997. Incidences were calculated per 5 year period from 1970–94 and then per year from 1995–7.

Ectopic Pregnancy: Treatment

- Early unruptured ectopics
  - Salpingostomy
  - Methotrexate
- Ruptured or later ectopics, or ovarian/abdominal ectopics
  - Laparotomy

Hypertension in pregnancy

- Pre-existing hypertension before pregnancy or < 20 weeks gestation; 3-5% of pregnancies)
- Pregnancy associated hypertension (PAH) >20 weeks; no proteinuria; ~6-7% of pregnancies
- Pre-eclampsia, hypertension with proteinuria 5-6% of pregnancies
- Superimposed hypertension. 25% of women with pre-existing hypertension develop pre-eclampsia
- Eclampsia, convulsions in a woman with hypertension and proteinuria.

Preeclampsia and Eclampsia

- Preeclampsia (toxemia, pregnancy induced hypertension, PIH)
  - BP ≥ 140 mm Hg systolic or ≥ 90 diastolic
  - Proteinuria ≥ 0.3 g per 24 hours
  - Edema +/-
  - Placental insufficiency 30%
  - Disturbances of coagulation and liver function

    Usually > 20 weeks gestation

    Early onset suggests preceding hypertension
- Major risk to mother (eclamptic convulsions)
- Risk to fetus (IUGR/PTD, placental abruption, stillbirth) due to placental insufficiency or maternal convulsions

Eclampsia

- **Maternal/fetal death**
  - Rate ~ 0.05% in developed countries
  - Rate ~ 0.06-1% in developing countries
  - ~50,000 maternal deaths due to eclampsia

Pathophysiology

Unknown (“disease of theories”).

- Endothelial functional abnormalities, possibly related to immune reaction to paternal antigen in the placenta,
- genetic factors (some men present greater risk)
- dietary deficiency (calcium)

Risk Factors for Pre-eclampsia and Eclampsia

- Previous pre-eclampsia (OR ~ 11)
- Nulliparous (OR ~ 5)
- Paternal factors (some men increase risk)
- Genetic factors, familial history
- Calcium deficiency
- History of spontaneous abortion (multiparous only, OR ~ 0.3)
- African American (nulliparous only)
- Higher body weight
- Ovum donation
- Smoking (OR ~ 0.45)

Eskanazi *JAMA* 1991;266:237, Walker *Lancet* 2000;356:1260

Pre-eclampsia Prevention Trials

- **Primary prevention by**:
  - Low-dose aspirin
  - Calcium supplementation
- **Secondary prevention**
  - Magnesium sulphate
  - Anticonvulsants
- **End points**
  - Maternal condition
  - Infant outcomes

Early Low-dose Aspirin Primary Prevention Trials

- Six trials before 1991 meta-analysis of small trials (n = 394)
  - PIH RR = 0.35 (0.22-0.55)
  - LBW RR = 0.56 (0.36-0.88)
  - Fetal/neonatal death RR = 0.88 (0.32-2.46)
  - No maternal side effects

Imperiale *JAMA* 1991;266:260

Low-Dose Aspirin Prevention Trials

(Sibai *NEJM* 1993; 329:1213)

- Low-dose aspirin vs placebo (n=3135)
  - PIH RR = 0.7 (CI 0.6-1.0)
  - Women with preceding hypertension on enrollment PIH 5.9% in aspirin vs 11.9% control (RR = 0.50)
  - No effects on PTD or LBW

- Conclusion: aspirin is indicated for women with preceding hypertension

Low-Dose Aspirin Prevention Trials

CLASP Trial Low-Dose Aspirin (*Lancet* 1994;343:619)

- Low-dose aspirin for prevention of PIH (n =9364)
  - PIH (RR = 0.87 ns)
  - PTD (RR = 0.88 ns)
- Low-dose aspirin for treatment of PIH
  - PIH (RR = 0.88 ns)
  - PTD (RR = 0.79 ns)
- Conclusion
  - No support for routine aspirin prophylaxis
  - May be warranted for high risk women?

Calcium Supplementation Trials

- Animal studies suggest that calcium depletion can cause PIH
- Observational studies suggest an inverse association between dietary calcium and BP in pregnancy
- 14 trials, mainly in Latin America (<1994), relatively small numbers (14-588), many not placebo-controlled, mainly high-risk women (e.g., prior hypertension or PIH)
- **Meta-analysis** (Bucher *JAMA* 1996;275:1113)
  - Reduction of systolic BP –5.40 mm Hg (-7.81, -3.00)
  - Reduction of diastolic BP – 3.44 mm Hg (-5.20, -1.68)
  - PIH OR = 0.38 (0.22-0.65)

NICHD Trial (US) Calcium for Pre-ecalmpsia Prevention (CPEP)

Levine *NEJM* 1997;337:69

- 4,589 healthy nulliparous women 13-21 weeks gestation randomized to 2 g calcium or placebo
  - Preeclampsia RR = 0.94 (0.76-1.16)
  - Pregnancy associated hypertension RR = 0.88 (0.78-1.01)
  - BP Calcium vs placebo: Systolic –0.3 mm, diastolic = 0.03mm (ns)
  - No effects on PTD, LBW, SGA

Meta-analysis 1999

DeSimonian, Levine *JAMA* 1999;282:664

- 6 trials with placebo control, separated into populations at low and high risk of calcium deficiency
- **Low-risk populations** (n = 1357)

  RR = 0.79 (0.44-1.42)
  - Preeclampsia in controls = 3.8% (3-7%)
  - Calcium intake 600-1200 mg/day

- **High-risk populations** (n = 225)

  RR = 0.19 (0.08-046)
  - Preeclampsia in controls = 29% (24-44%)
  - Calcium intake 300-600 mg/d

Calcium supplementation and Pre-eclampsia: Relative Risk Estimates for Placebo-Controlled Trials

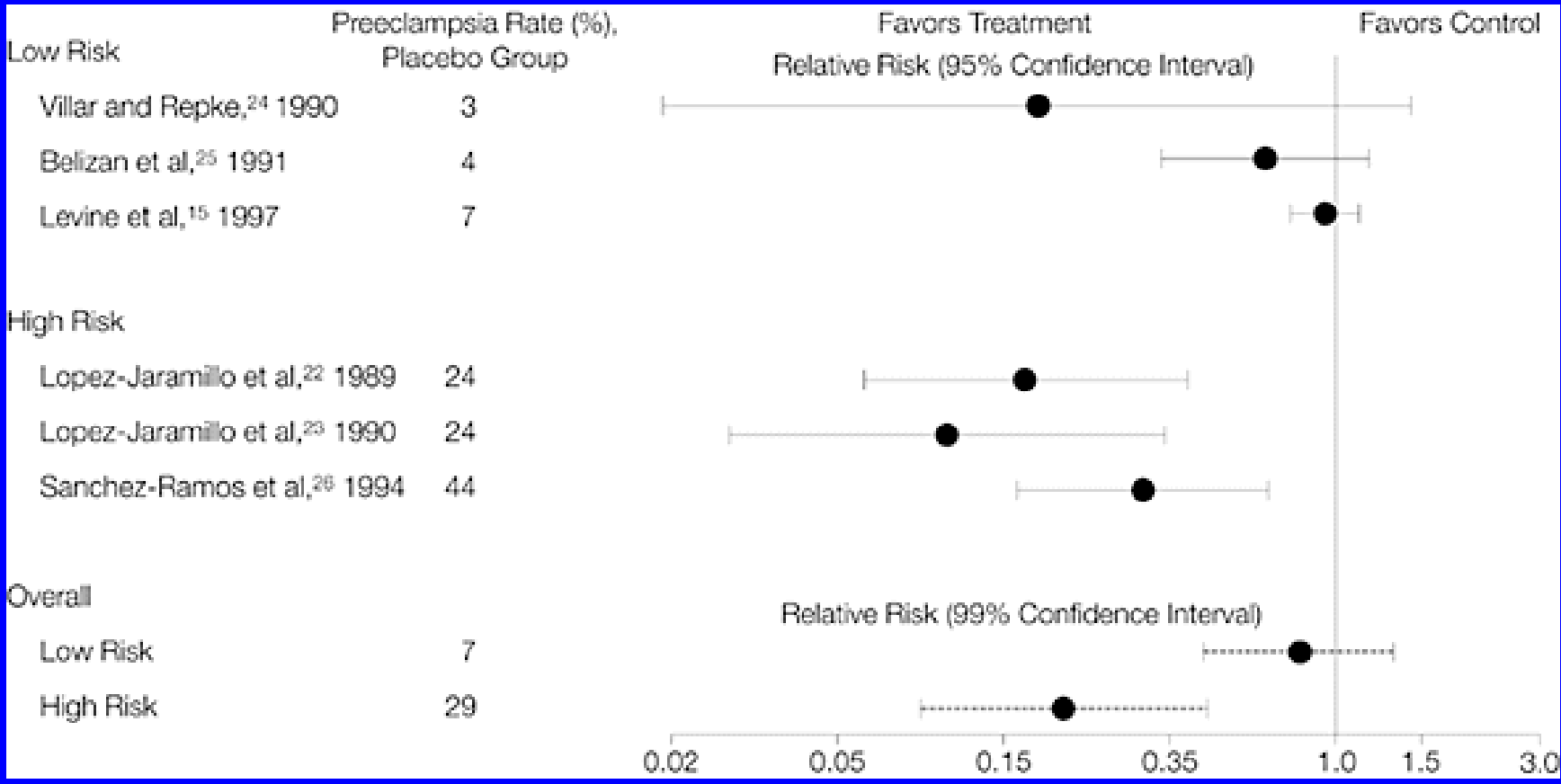

Figure 1. DerSimonian R, et al. Resolving Discrepancies Between a Meta-analysis and a Subsequent Large Controlled Trial. JAMA 1999;282:664-670.

Calcium Supplementation for Pre-eclampsia: Conclusions

- No evidence of benefit in low-risk women
- Probable benefit in high-risk women
  - Need multiple trials in different nutritional settings
  - Need placebo control
  - Need sub-group analyses
  - Need more trials of high risk

Vitamin C and E supplementation

(Briley Lancet 2006; 367:1145)

- 2410 women at risk of pre-eclampsia randomized to vitamin C and E or placebo

- No effect on pre-eclampsia, increased LBW (RR = 1.15, CI 1.02-1.30)

Management of pre-eclampsia

- BP ~150 systolic and 90-105 diastolic
  - Antihypertensives reduce eclampsia
  - may reduce neonatal complications

- BP >160/100
  - Antihypertensives indicated
  - Reduces fetal and neonatal complications

Magnesium Sulphate for **Established Eclampsia**

- 1687 women with eclampsia randomized to magnesium sulphate IV, or anticonvulsants (diazapam, phenytoin) IV or IMI

- Recurrent convulsions
  - Mag sulph vs diazepam RR = 0.48 (0.36-0.63)
  - Mag sulph vs phenytoin RR = 0.33 (0.21-0.53)

  - Mag sulph reduced infant complications

Magnesium sulphate for treatment of **pre-eclampsia** (Magpie trial, Lancet 2002;359:1877)

- 10,110 pregnant women with BP > 140/90 and proteinuria randomized to magnesium sulphate IV or placebo (saline)

- Eclampsia RR = 0.42 (0.29-0.60)
- Maternal death RR = 0.55 (0.26-1.14)
- Perinatal death RR = 0.99 (0.88-1.11)

Magnesium Sulphate for neuroprotection before preterm birth

(JAMA 2003;290:2669)

- 1062 women at risk of preterm birth <30 weeks. Magnesium sulphate vs placebo

- Severe motor dysfunction or death in infants RR = 0.75 CI 0.59-0.96

Gestational Trophoblastic Disease

- **Hydatidiform mole**
  - Neoplasm of the placenta (chorion), forming grape like cysts. Usually no fetus or dead fetus
  -
- **Choriocarcinoma**
  - Malignant cancer of the placenta

Palmer *J Reprod Med* 1994;39:155

Hydatidiform Mole

- **Incidence**
  - US, Europe ~ 1/1000 pregnancies
  - Japan and East Asia 2/1000 pregnancies
- **Risk factors**
  - Older maternal age (>35)
  - Previous hydatidiform mole (RR ~ 10)
- **Treatment**
  - dilation and curettage
  - Monitor for choriocarcinoma

Choriocarcinoma

- **Incidence**
  - US and Europe ~ 0.05/1000
  - Japan and East Asia ~ 0.08-0.23/1000
- **Risk factors**
  - Prior hydatidiform mole (RR ~1000)
  - Older maternal age (> 35)
  - Type A blood group
- **Treatment**
  - Chemotherapy

Diabetes in pregnancy

Galernau et al Obst and Gynecol Clin of Nth Amer 2004;31:907

- Pre-gestational diabetes
  - Pre-existing type 1 or 2 diabetes in a pregnant woman (~ 4% in US)
  - Rates increasing due to obesity and delayed child bearing
- Gestational diabetes
  - Diagnosed in pregnancy (~7% in US)
  - Due to insulin resistance
  - Risk factor for subsequent diabetes

Complications due to gestational diabetes

- Maternal
  - Increased hypertension and preeclampsia (RR 2-4)
  - SAB (RR ~ 3)
- Infant
  - Macrosomia (birth weight > 4 kg),
  - Shoulder dystocia
  - Birth defects (CNS, cardiovascular) RR ~ 8 vs nondiabetics
  - Metabolic abnormalities, Respiratory Distress Syndrome (RDS)
  - Subsequent diabetes in offspring (5-15%)

Violence During Pregnancy

- Maryland 1993-98 enhanced surveillance of maternal deaths
  - (Horon and Cheng *JAMA* 2001;285:1455)

- 247 pregnancy associated deaths identified by record linkage and medical examiner records
  - Homicide leading cause of pregnancy associated death death (20%)
  - Cardiovascular disease (19%)