Lecture 2
Conception and Pregnancy Loss
Lecture Objectives

• Probability of conception and fecundability

• Pregnancy loss, factors influencing pregnancy loss

• Select appropriate epidemiologic measures of pregnancy loss

• Lactational amenorrhea
Time line of conception and birth outcomes

Conception → Fetal development → Birth outcomes

Infertility

Pregnancy loss

Stillbirth

Reduced fetal growth

preterm birth /low birth weight

Birth defects

Infant mortality/morbidity
Fertilization & Probability of Conception

- Fertile life of gametes: in humans unknown, probably
  - sperm ~ 24-48 hours,
  - ovum ~ 12-24 hours.

- Fertile time in each cycle ~ 30-66 hours

- Maximum probability of conception occurs with intercourse on day of ovulation or 1-2 days prior to ovulation
Conception & Day of Ovulation (0)

Frequency & Timing of Intercourse

- Frequency and timing of intercourse determines the probability of conception per cycle.

- Frequency of intercourse decreases with age, duration of marriage, culture and phase of the menstrual cycle (highest around time of ovulation).
Coital Frequency per Month by Age

Rakai, Uganda Gray et al Lancet 2001
Coitus and Time of Ovulation

Source: Udry JR in Biomed Demographic Determin Reproduction
Timing of Intercourse and Sex Ratio

- Timing of conception may affect sex ratio:
  - Female births more common in conceptions closer to time of ovulation
  - Female births more common with ovulation induction
  - Suggestion that high gonadotrophin levels may increase motility of X bearing sperm?
  - Not much use for sex selection
  - May explain higher male sex ratio in baby booms following wars
Probability of conception

- Probability of conception per month or **fecundability** ($F$).

- $F \sim 0.25/\text{month}$, depending on age, frequency and timing of intercourse (highest $\sim 0.35$)

- Use of waiting times to pregnancy ($W_t$) as a measure of fertility

- $F \sim 1.5/ W_t$

  - Baird et al *Amer J Epidemiol* 1986
Why is the probability of conception so low?

- Failure of ovulation (age, stress etc)
- Failure of fertilization (timing of intercourse, defects in sperm or ova)
- Failure of implantation
- Early pregnancy loss (EPL)
Waiting Time to Conception

- Waiting time to conception is ascertained in women who are not contracepting

- Information ascertained retrospectively or prospectively by two questions:
  - “Did you get pregnant during the first month of unprotected intercourse?” If not,
  - “How many months (cycles) did it take for you to become pregnant?”
Analysis of probability of conception

- Waiting time to conception is useful for identification of reproductive hazards or impairment (e.g. caffeine, smoking, nitrous oxide, injectable contraception, HIV)

- Analysis: Cumulative probability of conception (Kaplan-Meier), proportional hazards (Cox) model for multivariate adjustment
Cumulative Probability of Pregnancy

- Cumulative probability of conception per year:
  - Ages 20-29 years, cumulative probability of pregnancy within one year $\sim$ 90-95%
  - Ages 30-39 cumulative probability $\sim$ 70-80%
  - Failure to conceive $> 1$ year, probability 49%
  - Failure to conceive $> 2$ years probability 14%
  - Affects clinical and epidemiologic definition of infertility
Cumulative Rate of Pregnancy with Nitrous Oxide Exposure in Dental Assistants

Smoking and delayed conception

• Biology:
  – Products of tobacco smoke (benzopyrene, cadmium, cotinine) reach the ovarian follicle and reduce fertilizing ability of the oocyte,
  – reduces ciliary activity of fallopian tubes affecting ovum transport
  – Smoking accelerates estrogen metabolism, reduces ovarian response to FSH/LH,

• Conceptions within 12 months
  – Non-smokers 89.7%
  – Passive smokers 89%
  – Active smokers 86.2%
  – Active + passive 85.8%
    – Hull *Fertil Steril* 2000; 75:725
Pregnancy Loss

- Epidemiology and biology of subclinical and clinical pregnancy loss
- Levels and determinants and methods of measurement of spontaneous abortion
- Pregnancy loss as a marker for environmental hazards
Pregnancy Loss

- **Pre-implantation**
  - Loss of a fertilized ovum prior to implantation (e.g. <7 days post-fertilization), cannot be detected in epidemiologic studies.

- **Subclinical Early Pregnancy Loss (EPL)**
  - Loss before a recognized missed menses. Detected by hCG level between implantation (~7 days after fertilization) and menses.
Early pregnancy losses (EPLs) identified by prospective urinary hCG assays using ultra-sensitive and specific sandwich immunonassays for hCG (avoids cross-reaction with midcycle LH)

- Daily urine samples during the second half of the luteal phase of the cycle (after implantation) and during menstruation (~12 days)
Rate of Early Pregnancy Loss (EPL)


- EPL $\sim 23\%$ in normal women

- Rate of EPL increases with more cycles prior to recognized conception (e.g., EPL $>35\%$ with $>6$ cycles)

- In women with a subfertility history EPLs $\sim 70\%$ (RR = 2.6) Hakim et al *Amer J Obstet Gynecol* 1995
Early pregnancy loss and spontaneous abortions associated with serum DDT

(Venners et al. Amer J Epidemiol 2005;162:709)

<table>
<thead>
<tr>
<th>DDT levels</th>
<th>Early pregnancy Loss</th>
<th>Spontaneous abortion</th>
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<tr>
<td></td>
<td>Rate %</td>
<td>Adj RR</td>
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<tr>
<td>Low</td>
<td>19.0</td>
<td>1.00</td>
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<tr>
<td>Medium</td>
<td>24.0</td>
<td>1.2</td>
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<td></td>
<td>(0.7-2.1)</td>
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<tr>
<td>High</td>
<td>33</td>
<td>2.12</td>
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<td></td>
<td>(1.3-3.6)</td>
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<tr>
<td>Linear trend</td>
<td>10ng/g</td>
<td>1.2</td>
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<td></td>
<td>(1.1-1.3)</td>
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• Spontaneous abortion (SAB)
  – Loss of a recognized pregnancy after a missed menstrual period (e.g. > 4 weeks after the last menstrual period) and before the age of extra-uterine viability (usually up to 20th week gestation).
Pregnancy Loss

- **Stillbirths**
  - deaths of a fetus after time of viability \(\sim 21\) weeks gestation (variable definition used. WHO definition for international comparisons \(28+\) weeks).

- **Induced abortions**
  - purposeful termination of pregnancy at any gestation
  - Often concealed or poorly reported
Measurement of SAB

- Interviews of pregnant women (prospective)
  - Depends on age at gestation at time of interview
- Interviews of women about prior pregnancies (retrospective)
- Problem: omits early pregnancy losses, and recall errors (omissions or timing)
  - 82% SAB recall accuracy < 10 years (Wilcox et AJE)
Measurement of SAB

- Spontaneous abortion (SAB) rates measured as percent of pregnancies lost, or as a life table rate
  - Adjustment for competing risks of induced abortion or ectopic pregnancy (adjust N x 0.5)
  - Adjust for time in gestation when pregnancy first observed (fusion cohort)
  - Cumulative rate of SAB ~10-20% of recognized pregnancies, rates higher in early pregnancy and age > 35
Risk Factors for Pregnancy Loss

- Damage to the gametes (particularly ova), disruption of fetal development or of placenta/uterine unit
- Age: SABs increase after age 35 due to ovum abnormalities
  - Ovum donation from young women to older recipient decreases SABs. Therefore age of ovum not age of the woman is critical.
Spontaneous Abortion Rate by Age (IVF with own or donor ova)

- Pregnancy rate: 35%
- Spontaneous abortion (SAB) rate: 36.4%
- Ovum donated by young women

Diagram shows:
- Spontaneous abortion (SAB) rate increases with age.
- Pregnancy rate decreases with age.
Risk Factors for Pregnancy Loss

- **Chromosomal abnormalities and SABs**
  - Chromosomal anomalies, ~60% in SABs and ~5% in stillbirths
  - Anomalies (trisomy) of larger chromosomes incompatible with life cause SAB earlier in gestation.
  - Smaller chromosomes (e.g., 21 Downs syndrome) are compatible with life and lost later in gestation

- Increased SAB incidence with age involves both chromosomally normal and abnormal fetuses
SAB Rates by Age and chromosomal abnormalities

Estimated rates (%) of spontaneous abortion, euploid abortion and trisomic abortion by maternal age for public patients.
• **Recurrent or prior spontaneous abortions**
  – Due to physical, immunologic, timing of conception and endocrine factors

• **Infections**
  – STDs (particularly syphilis and HIV)
  – Malaria (fever, placental parasitemia)
  – Febrile or chronic illness / malnutrition

• **Occupational / environmental exposures**
  – e.g. glycol ethers, solvents, heavy metals, pesticides
SABs and timing of Conception

Day of conception (estimated day of ovulation = 0)

- 171 women with a history of pregnancy loss
- 694 women with no prior pregnancy loss

Gray Amer J Obstet Gynecol
Risk Factors for Pregnancy Loss Contd.

• **Behavior**
  – Smoking, alcohol, stress, caffeine
  – Infertility: SABs are more frequent in women with prolonged waiting times to conception
  – Subclinical losses are more frequent in women with subfertility

• **IUDs**
  – Pregnancy with IUD *in situ*
Lactation and Lactational Amenorrhea

- Prevalence and duration of lactation, time trends, and differentials
- Endocrinology of lactational amenorrhea and infertility. Effects of feeding patterns and maternal nutrition
- Lactational Amenorrhea Method (LAM) of contraception
Biology of Lactational Amenorrhea

- Suckling stimulus to nipple → CNS causing:
  - Stimulates prolactin (hPrL) from pituitary → increasing milk production
  - Inhibition of GnRH pulses → FSH and LH suppression → anovulation and amenorrhea
Suckling Stimulus

- Effects depend on frequency and duration of suckling episodes, intensity of suckling and duration of time postpartum (responsiveness diminishes with longer duration)

- In traditional societies mothers often sleep with infant at the nipple, persistent nocturnal stimulus
Factors Affecting Lactational Amenorrhea (LAM)

- Poor maternal nutrition may increase the duration of LAM by reinforcing the feedback inhibition, or because reduced milk volume may promote more vigorous infant suckling
- Maternal illness
- Infant illness (failure to suckle)
- Oral contraceptives suppress milk production (estrogen effect)
- Nocturnal suckling
Lactational Amenorrhea Method (LAM) for Postpartum Contraception

- Many societies traditionally used LAM for birth spacing
- LAM as a contraceptive method is a decision tree
  - Amenorrhoeic
  - Exclusive or almost exclusive breastfeeding
  - No bottle supplements
- Efficacy: pregnancy rates ~0.5% < 6 months postpartum
- After 6 months, less reliable
Supplemental Feeding and Weaning

- Supplements needed after 4-6 months to maintain infant nutrition
- Bottle, cup or spoon feeds
- Bottles displace breast (babies satiated)
- Weaning determined by culture, maternal demands of illness (mother or infant)
- Weaning reduces suckling stimulus causing resumption of ovulation and menses
Average Daily Breastfeeds by mode of feeding

Frequency of Supplementary Feeding

• Most mothers supplement breast milk, even in societies with almost universal breast feeding

• Exclusive breast feeding ~ 30% at 4 months, 5-6% at 6 months (in 14 developing countries)