JOHNS HOPKINS
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SCHOOL of PUBLIC HEALTH

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
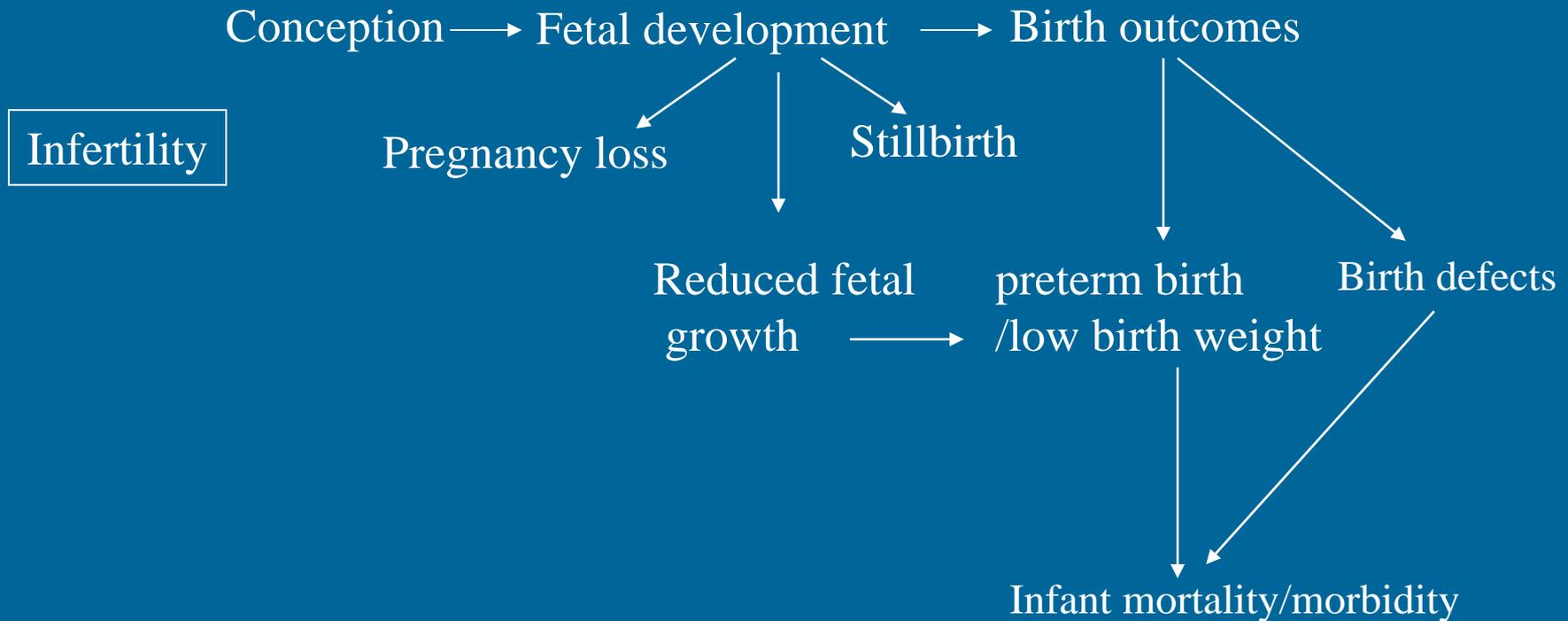
Fertilization & Probability of Conception

- 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)
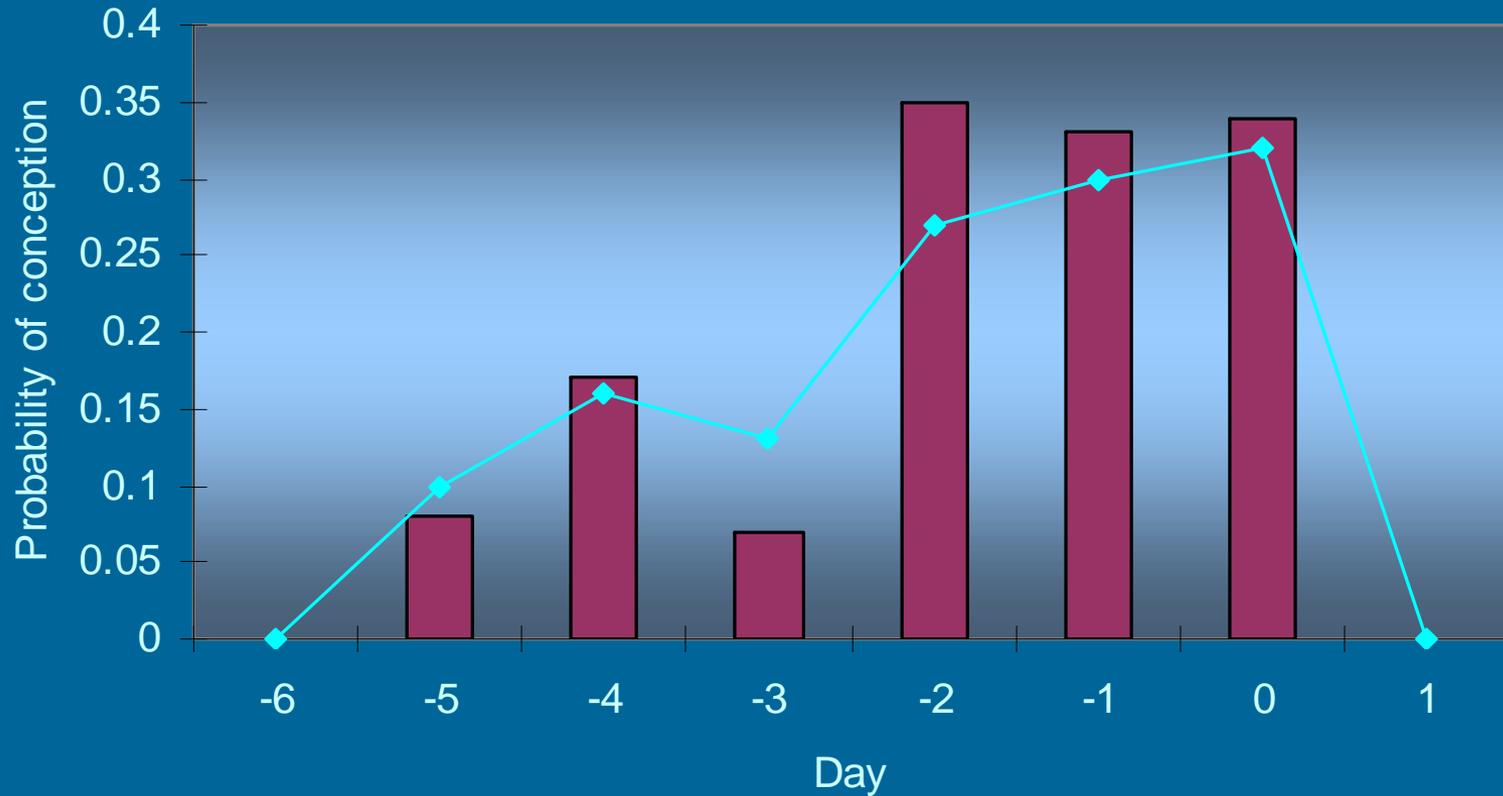
Source: Wilcox et al. New Engl J Med 1995;333:1517-1521.

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
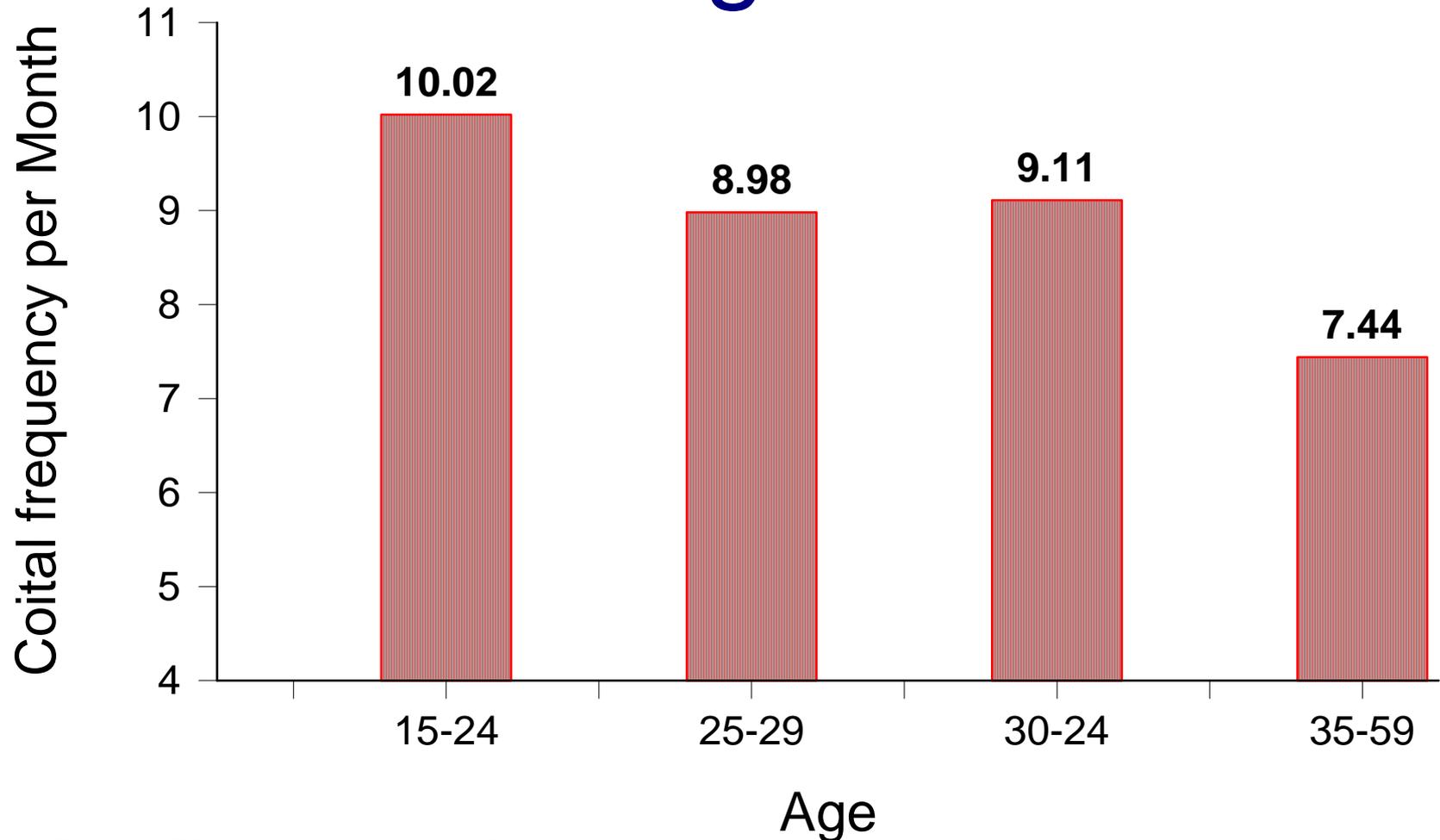
Rakai, Uganda Gray et al Lancet 2001

Coitus and Time of Ovulation
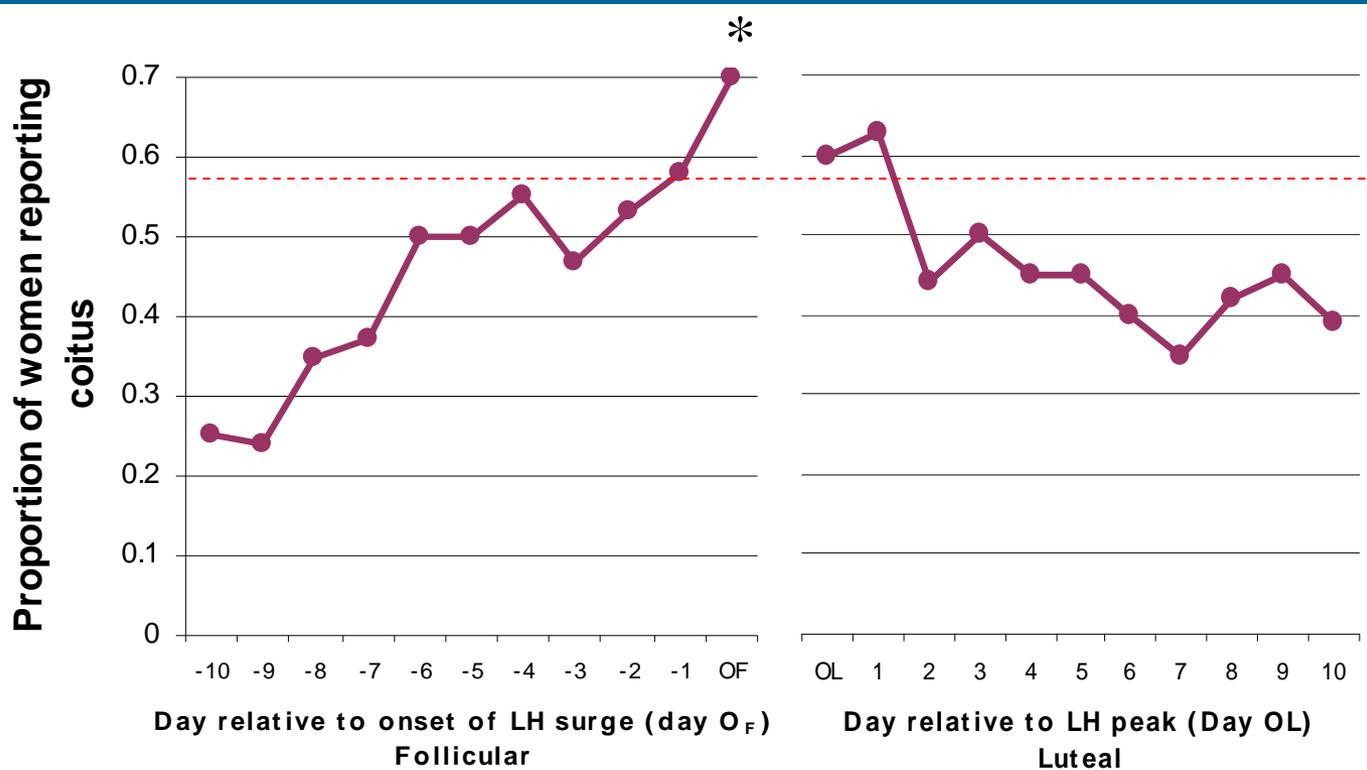
Source: Udry JR in Biomed Demographic Determin Reproduction

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).**

- $F \sim 0.25$/month, depending on age, frequency and timing of intercourse (highest ~ 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 ~ 90-95%
  - Ages 30-39 cumulative probability ~ 70-80%

  - Failure to conceive > 1year, 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
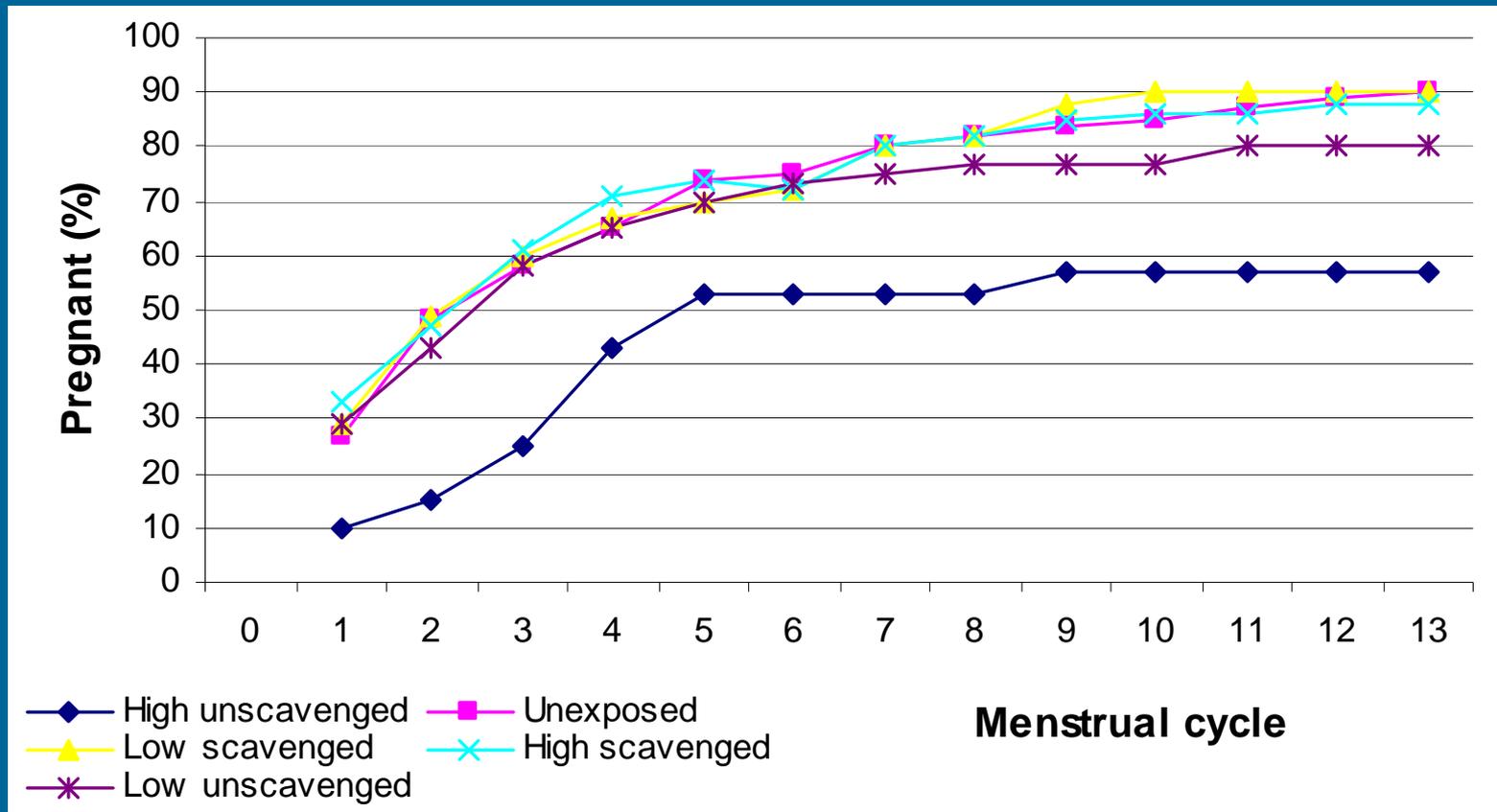
Source: Rowland et al. New Engl J Med 1992;327:993-997.

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.

Measurement of Early Pregnancy Loss (EPL)

- **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)

- Four prospective studies >1000 women and 3000 cycles (Wilcox *NEJM* 1988, Zinaman *Fertil Steril* 1996, Hakim *Amer J Obstet Gynecol* 1995, Wang *Fertil Steril* 2003)

- EPL ~ 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 ~ 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)

DDT levels	Early pregnancy Loss		Spontaneous abortion	
	Rate %	Adj RR	Rate %	Adj RR
Low	19.0	1.00	10	1.0
Medium	24.0	1.2 (0.7-2.1)	10	1.2 (0.5-1.3)
High	33	2.12 (1.3-3.6)	10	1.3 (0.5-3.1)
Linear trend 10ng/g		1.2 (1.1-1.3)		1.1 (0.9-1.3)

Spontaneous Abortion

- 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 ~ 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)
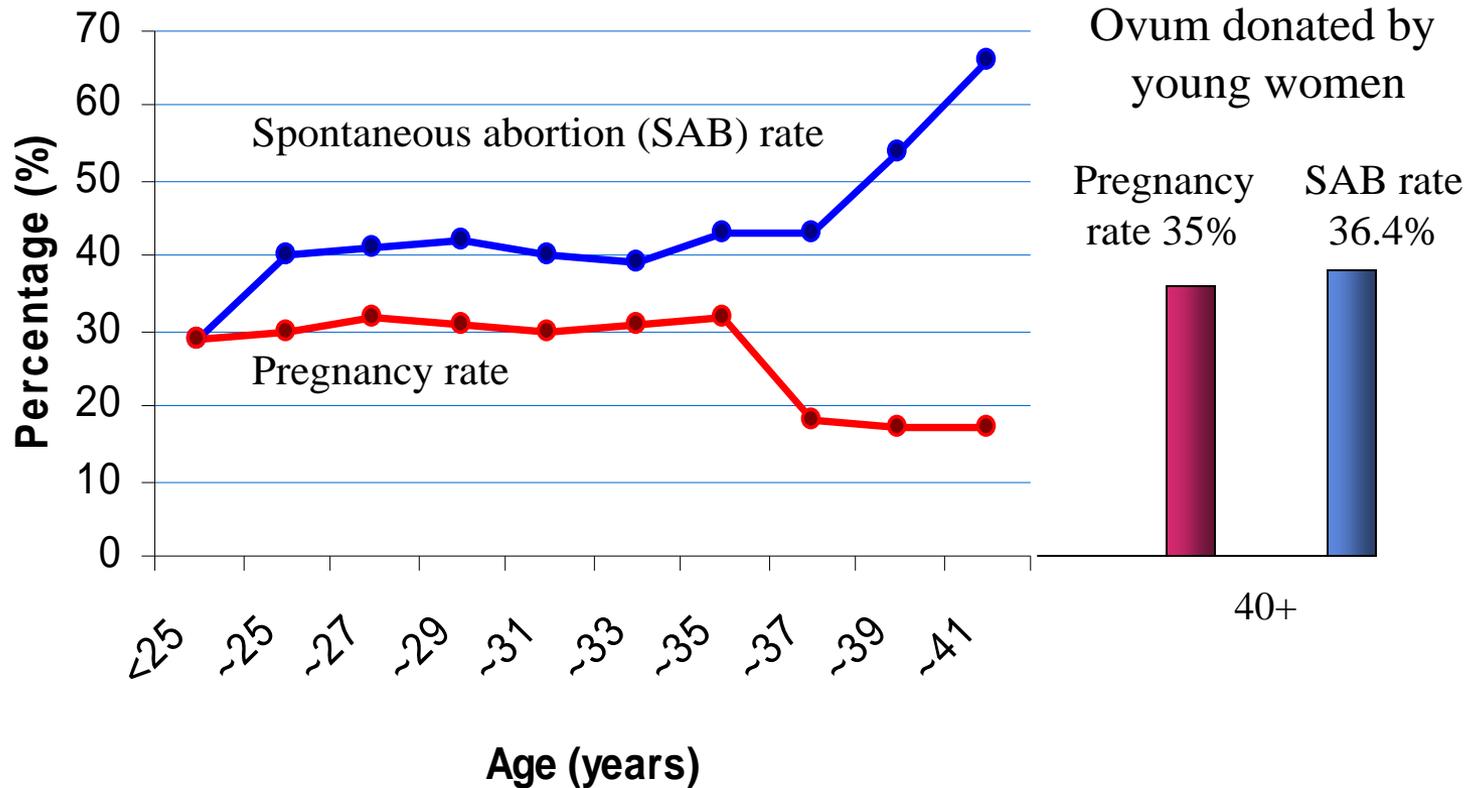
Risk Factors for Pregnancy Loss

- 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
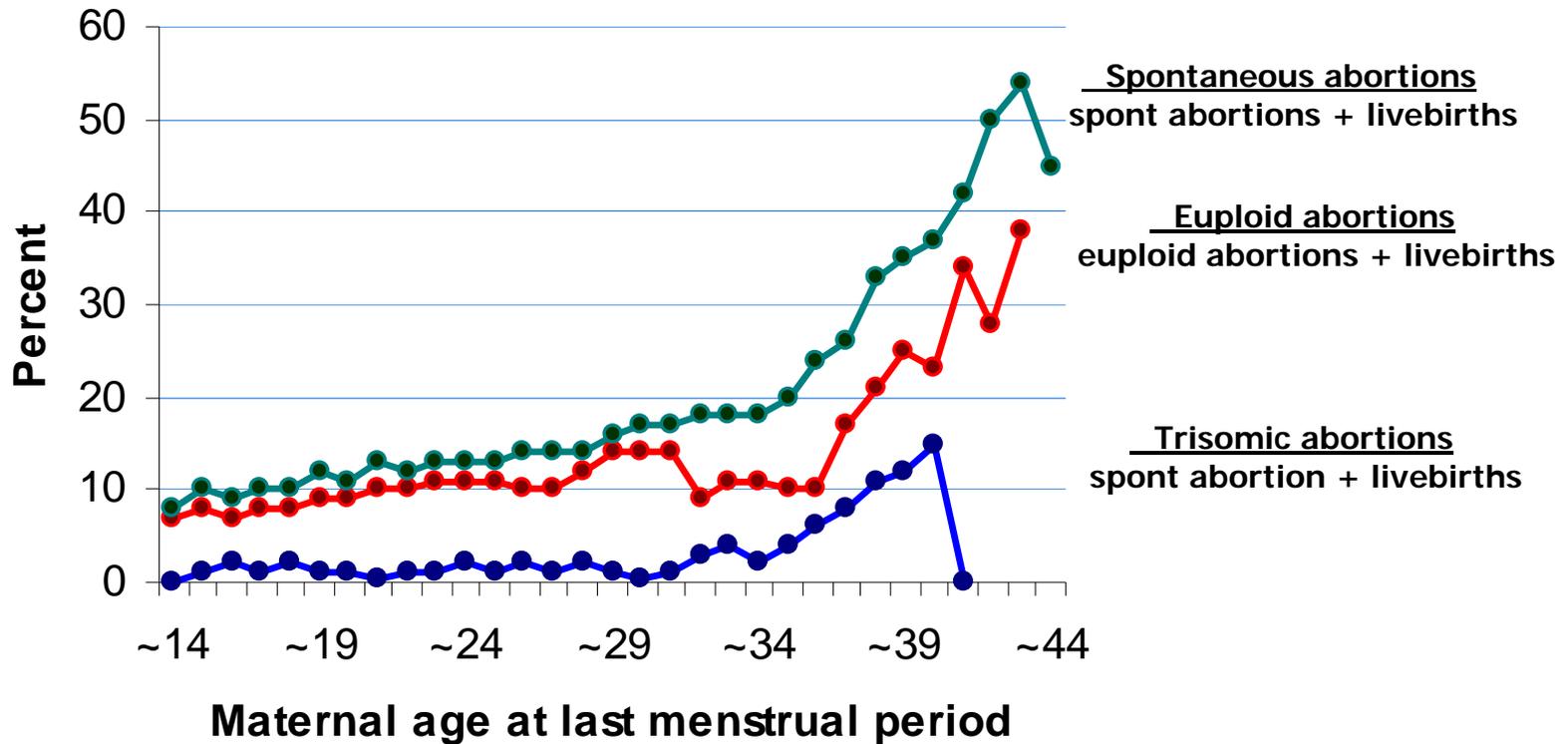
Estimated rates (%) of spontaneous abortion, euploid
abortion and trisomic abortion by maternal age for public patients

Risk Factors for Pregnancy Loss Contd.

- 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

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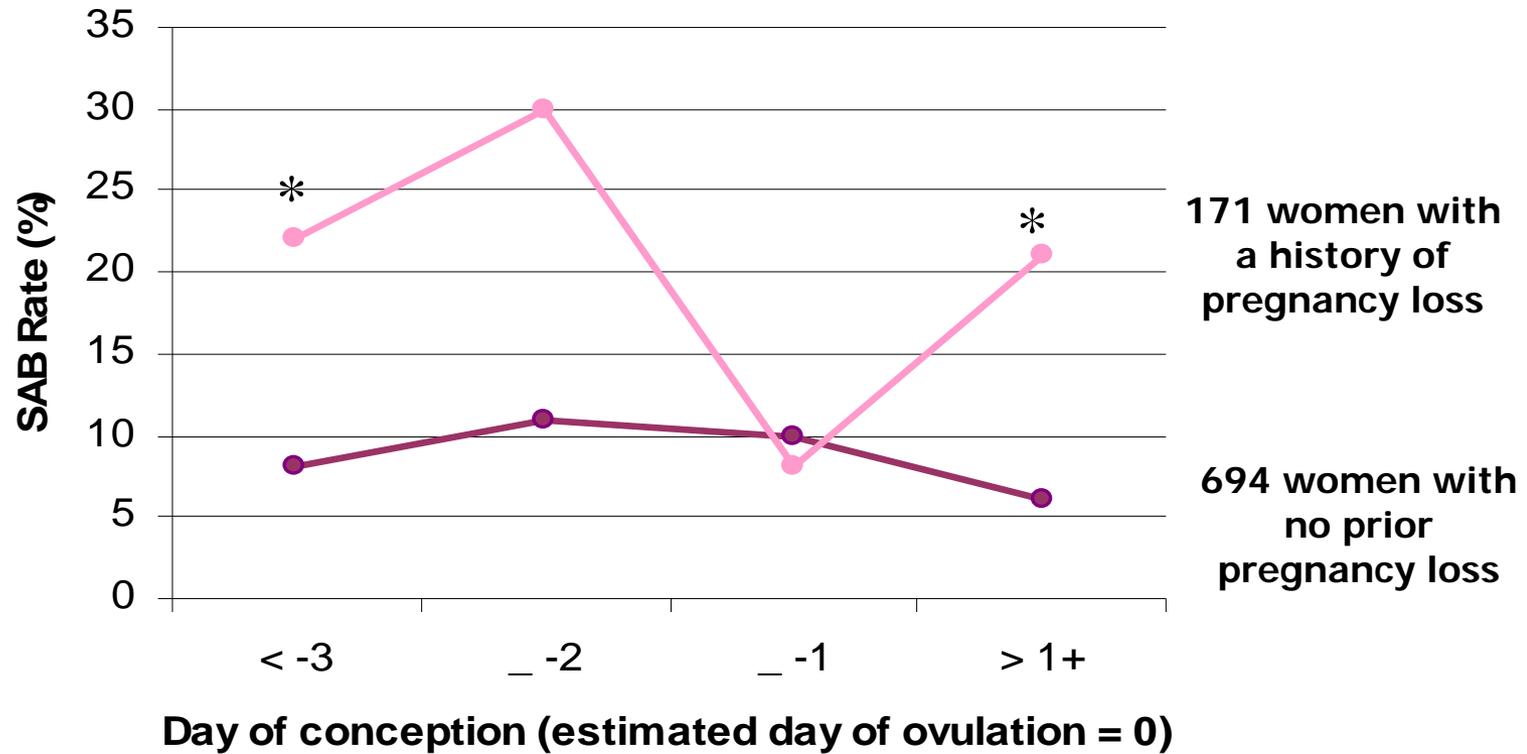
Risk Factors for Pregnancy Loss Contd.

- **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 $\rightarrow$ CNS causing:

- Stimulates prolactin (hPrL) from pituitary $\rightarrow$ increasing milk production

- Inhibition of GnRH pulses $\rightarrow$ FSH and LH suppression $\rightarrow$ 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
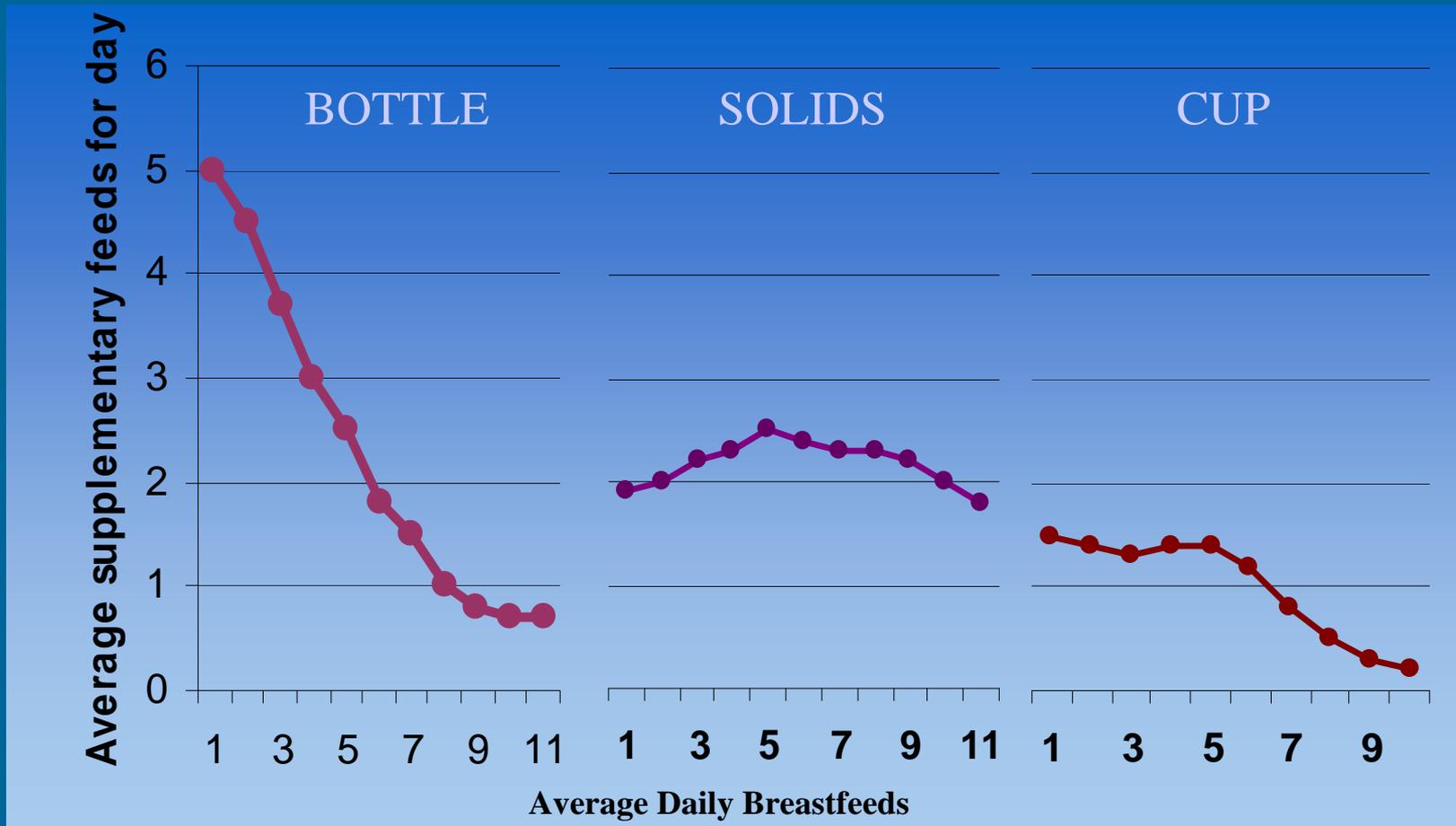
Source: Campbell and Gray. Am J Obstet Gynecol 1993; 169(1):55-60 .

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)