Reproductive Hazards and Occupational Exposures

• Maternal or paternal occupational exposures can affect reproduction, pregnancy outcome and infant health.

• **Potential hazards:**
  - chemicals,
  - physical agents (e.g., radiation, lifting, heat),
  - psychosocial (stress)

• **Exposures**
  - Total number of persons with potential exposure is substantial, but numbers with specific exposures are often low due to small numbers of workers in high risk jobs
  - Multiple exposures are common and complicate identification of hazards
  - Animal toxicology studies have limited utility for predicting human reproductive hazards
  - Epidemiologic studies have serious limitations in establishing causality
Endpoints and Expected Frequencies

- Subfertility/Infertility (~ 9-10%)
- Early Pregnancy Loss (hCG detected ~ 23%)
- Spontaneous abortion (~ 10-15%)
- Stillbirth (~ 2%)
- Prematurity (~ 6-9%)
- Low Birthweight (5-7%)
- Major defects at birth (~ 3-4%)
- Hard to study in small populations due to lack of power
Healthy/Unhealthy Worker Effects

- **Selection effects** ("healthy/unhealthy") worker effects
  - healthy workers may leave the workplace because of normal pregnancy/childbearing, causing over-representation of “unhealthy” workers
  - “Unhealthy” workers may leave job due to illness
  - Need to study voluntary terminated ex-employees of persons on leave of absence
  - Difficult to study long-term exposures due to selection
Employment during pregnancy

• Effects of work in Pregnancy and PTD
  – Studies contradictory
  – Selection: “unhealthy/healthy worker effect”
  Socioeconomic benefits of employment
  – Most associations are with prolonged standing, heavy lifting, long working hours, shift work, work with industrial machines
Reconstructing Occupational Exposures

- **Job history** is difficult
  - Recall of jobs or chemicals poor (process information)
  - Job titles are non-specific (e.g., lab technician)
  - Processes change over time
  - Timing of exposure relative to reproductive effects may be problematic (e.g., subfertility), timing of exposure in relation to pregnancy
  - Hard to categorize jobs (job title, task analysis, processes) need to be linked to specific agents (Industrial Hygiene)

- **Exposure assessment**
  - Dose, duration and timing of exposures
  - Route of exposure (inhalation, dermal, ingestion)
  - Threshold effects (problem with quantifying exposure)
Regulation of exposures

• Regulatory:
  – Define “Threshold Limit Value” (TLV) lowest level of permitted exposure

  – NIOSH (National Inst Occupational Safety and Health) recommend TLVs

  – Legal and commercial factors affect TLV

  – OSHA (Occupational Safety and Health) regulates TLVs
Epidemiologic Study Designs

• **Retrospective Cohort or Case-control studies**
  – Problems of exposure/outcome timing
  – Recall of occupation and specificity of exposures poor
  – Job titles (nonspecific), processes, chemical/physical agents
  – Event frequency low (e.g. specific birth defects)
  – Need medical record validation
  – Pregnancy outcome studies exclude infertility effects

• **Prospective Studies**
  – Recognized waiting time to conception/pregnancy loss (sample size, cost). Allow concurrent exposure assessment
  – Use of hCG to detect early losses or hormonal disturbances using daily urine samples. Sample size, cost, compliance
Evidence of Occupational Hazards

- Solvents
- Anticancer drugs
- Anesthetics
- Pesticides
- Herbicides
- Heavy metals
- Radiation
- Physical stressors
Fertility and Male Exposures

- Belgian studies of men in smelters and battery manufacturing, using biologic measurement of exposure (Gennant 1992)
  - Male fertility reduced with
    - High level cadmium
    - Lead at all levels
- Ethylene glycol ether metabolites in urine associated with infertility OR 3.1 (Veulemans 1993)
- DBCP Fungicide caused testicular atrophy
- Heat (outdoor work, lack of air conditioning) reduced fertility
Fertility and Female Exposures

- **Health Care Workers**
  - Dental assistants exposed to nitrous oxide
    - Reduced fertility increased pregnancy loss (Rowland *NEJM* 1992)
  - Anesthetics gases increase spontaneous abortion (RR = 1.5) Figa-Talamanca *Epi Reviews*;2000.

- Antineoplastic drugs increase spont abort, birth defects, menstrual dysfunction

- Microwave exposures increase SABs (Quellet-Hellstrom *Am J Edpid* 1993)
Work Stress

• Some association of night work or shift work with SABs

• High stress vs low stress jobs in nurses
  (Hatch *Scand J Work Environ Hlth* 1999;25:144)
  – Long cycles OR = 4.3
  – Anovulation OR = 5.5

• Heavy lifting increase SABs (OR = 3.2. Florack *Epidemiol* 1993)
Solvents

- **Microchip manufacturing**
  - reduced fertility
  - increased spontaneous abortion
  - mainly in subgroups working with solvents such as short chain ethylene glycol ethers (EGEs)
Short Chain Ethylene Glycol Ethers (EGE)

- Were widely used (microchips, paint, printing, electronics)
- Low volatility (most exposure is dermal)
- Penetrate most rubber gloves
- Animal studies show reproductive and teratogenic effects
- Biological mechanism: Metabolized to alkoxy acetic acid which prevents DNA synthesis during cell division, detectable in urine (biomarker)
Three studies of Female EGE Exposures in Microchip manufacturing

- EGEs used in manufacture of microchips
- **Spontaneous abortions**
  - OR 2.4 (Pastides, 1988)
  - OR 2.8 (Gray 1996)
  - OR 2.3 (Swann, 1996)
- **Subfertility**
  - OR 4.6 (Gray 1996)
Cardiac Defects and Solvents
(Baltimore Washington Study, Ferencz 1993)

• Population based case-control study
• Type of exposure and type of defect varied
• Aortic stenosis
  – Any solvent OR = 3.2
  – Degreasing solvents OR = 12.5
• Coarctation of the aorta
  – Any solvent OR = 3.4
  – Degreasing solvents OR = 3.0
• Specific defects may result from highly specific exposures or from generalized exposures to a family of agents
Pesticide Exposures in Agriculture

- **Malformations**
  - Several organ systems (Nurmininen, 1995)
- **Spontaneous Abortion**
  - Female agricultural workers, different exposures, seasonal. (Nurmininen, 1995)
- **Stillbirths**
  - Agricultural workers in Sudan (Taha Gray)
- **Subfertility**
  - Female
    - Agricultural workers, manufacturing
  - Male
    - DBCP (testicular damage)
DDT and Reproduction

• Measure DDE (metabolite of DDT) in serum (Longnecker *Lancet* 2001;358:110)
  – PTD: Adjusted OR increased from 1.8 to 4.0 with DDE 15-29 ug/L to >60 ug/L (p<0.0001).
  – SGA: Adjusted OR increased 1.9 to 2.6 with increasing DDE (p = 0.04)
Sex ratio and exposures

• Seveso, Italy 1976. Explosion in herbicide plant released dioxin (Mocarelli Lancet 2000)
  – Men under 19 exposed at time of explosion subsequently fathered more girls than boys
  – sex ratio m/f = 0.38 CI 0.3-0.47
  – No effects in exposed females
Sex ratio and PCB exposure Taiwan

- PCB exposure via contaminated cooking oil
- Males <19, Sex ratio m/f = 0.85 (p = 0.04)
- Males >19 and females no effect
  - Similar effects observed in rats
  - Mechanism??
- Del Rio Lancet 2002;360:143

- Also observed oligospermia, abnormal sperm morphology and inability to penetrate oocyte in vitro (Huang JAMA 2003;289:2943)
Accidental Exposures

- Highest dose exposures often related to accidents
  - Spills
  - Explosions
  - Contamination of food and water
- Hard to document
Health Protection

• Exclude from “high risk” jobs
• Move pregnant women to low risk jobs
• Problems:
  – Identify hazards (problematic); what is low risk
  – Identify limits of exposure Threshold limit value (TLV), known for < 13% of potential hazards
  – Protection of “average worker” versus vulnerable subgroups
  – “Cautionary principle” (UN 1992), suspicion is sufficient, lack of scientific “certainty” should not be used to perpetuate exposures
  – Economic costs, limitation of women’s choices?