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Occupation and Reproductive Hazards

Reproductive Hazards and Occupational Exposures

- Maternal or paternal occupational exposures can affect reproduction, pregnancy outcome and infant health.
- **Potential hazards:**
 - chemicals,
 - physical agents (eg. 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 (eg. lab technician)
 - Processes change over time
 - Timing of exposure relative to reproductive effects may be problematic (eg. 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 (eg. 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 (Nurminen, 1995)
- **Spontaneous Abortion**
 - Female agricultural workers, different exposures, seasonal. (Nurminen, 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?