**PHARMACOEPIDEMIOLOGY OF DRUG INDUCED BIRTH DEFECTS**

**Definitions**

* Birth defects: those that are life threatening, require major surgery, or present a significant disability
* Affect approximately 2-6% of liveborn infants
* Teratogenism: unique adverse drug effect, affecting an organism (the fetus) other than the one for whom the drug was intended (the mother).
* Whatever benefit/risk accrues to the mother, only the fetus is at risk for birth defects

**Clinical problems to be addressed through pharmacoepidemiological research**

* Since roughly half of pregnancies (at least in the US) are unplanned, teratogenic concerns extend to women who might become pregnant while taking a medication.
* teratogenic effects can be prevented by avoidance of pregnancy, and the birth of a malformed infant can be avoided by termination of pregnancy

Teratogenic drugs

* Fall under two categories:
* 1. High risk: which produce major effects in high proportion. Eg. thalidomide, isotrenitoin
* 2. Moderate risk: increase the rate of specific birth defects. Eg. Carbamazepine and neural tube defects
* Most known teratogens, such as phenytoin and valproic acid, pose moderate risks balanced by clinical benefits.

**Methodological problems to be addressed through pharmacoepidemiological research**

Sample size

* Birth defects” is not a single, homogeneous outcome, and teratogens do not uniformly increase the rates of all birth defects, but rather increase the rates of selected defects.
* Birth defects vary according to :
* Time of exposure
* Sensitivity of end organ (embryonic tissue)
* Teratogenic mechanism

Exposure to non-prescription drugs

* women of childbearing age view OTC drugs as safer than prescription products, and they may assume that the same is true for use of these drugs in pregnancy
* Same with herbal products

Recall bias

* Because of feelings of guilt, the mother of a malformed infant may be more likely than the mother of a healthy infant to accurately recall her pregnancy exposures
* difference in recall accuracy could lead to false positive associations
* Open-ended questions invite differential recall between mothers of malformed and normal infants, whereas focused questions are more likely to yield complete information.

Outcome

* Though birth defects are often classified by organ system (e.g., “musculoskeletal”), whenever possible they should be classified on the basis of the embryologic origin for a given defect.
* For example, neural crest cells form various structures of the face/ears, heart, and neural tube

**Currently available solutions**

Studies designed to follow large populations exposed to various agents

* An example is the US Collaborative Perinatal Project (CPP), which enrolled over 58 000 women between 1959 and 1965, obtained detailed information on their pregnancies, and followed the children until age 7
* Such a cohort may be large enough to identify some highrisk teratogens, but power is usually inadequate to identify moderate-risk teratogens among commonly used drugs, and power is routinely inadequate to identify such teratogens among the vast majority of other drugs

Use of data sets created for other purposes

* All have the advantage of identifying exposures independent of knowledge of the outcome, some may include large populations, and a few may have good reporting of malformations
* Despite their overall size, these databases may include few subjects with specific malformations who were exposed to a particular drug *in utero*.

Follow up of Selected Exposures

* enrolling pregnant women in pregnancy registries
* identify a woman exposed to a drug of interest early in pregnancy and, most importantly, identify and enroll the woman before the pregnancy outcome is known.

Case control studies

* obtaining information directly from the mother, they also can capture information on critical covariates, such as smoking, alcohol, diet, and use of non-prescription drugs
* High statistical power
* Eg. National Birth Defects Prevention Study through surveillance.
* **CASE EXAMPLE 27.6: TESTING**
* **HYPOTHESIZED TERATOGENIC EFFECTS**
* **Background**
* • In the late 1970s, the antinausea drug Bendectin®(Debendox®; Lenotan®: doxylamine, dicyclomine, and pyridoxine) was widely used to treat nausea and vomiting in pregnancy.
* • Legal claims based on allegations of the drug’s teratogenicity ultimately resulted in the manufacturer removing it from the market.
* **Issue**
* • Concern about the possible teratogenic effects of the drug were raised by studies that suggested increased risks of selected cardiac defects and oral clefts among the babies of mothers who had taken the drug in the first trimester.
* • In both studies, exposure among mothers of cases was compared to exposure among mothers of normal infants, and there were questions about the rigor and symmetry regarding collection of exposure information.
* **Approach**
* • Utilizing data from an ongoing case–control surveillance program of specific birth defects in relation to medication use in pregnancy, researchers identified cases with selected cardiac defects and cases with two kinds of oral clefts and compared maternal Bendectin exposure among those cases to that among mothers of controls with various malformations other than those in the cases.
* **Results**
* • Among the 970 malformed controls, the prevalence of first trimester exposure was 21%.
* • Case groups ranged in size from 98 to 221 infants.
* • Risk estimates ranged from 0.6 to 1.0.
* **Strengths**
* • The existence of the case–control surveillance database provided sufficient power (for this common exposure) to test the hypotheses without the need for further data collection.
* • Sample sizes were large enough to provide tight confidence bounds.
* • Direct interviews with mothers of study subjects provided information on important potential confounding variables.
* • Use of malformed subjects as controls minimized the risk of biased recall.