Why do we worry about pregnancy testing?
Teratogens and teratogenic risk

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Outline

• Background
  – Clinical trials
  – The scientific evidence for teratogenic potential
  – Managing teratogenic risk
Clinical Trials

Stages of Clinical Trials

- **Preclinical**
  - Lab Studies: Several Years
  - Human Safety: Days or Weeks

- **Phase I**
  - Expanded Safety: Weeks or Months
  - Efficacy & Safety: Several Years

- **Phase II/III**
  - Efficacy & Safety: Several Years

- **Phase III**

Percentage of Participants by Phase (n=334,551)*

- Phase Unsupervised: 46% Female, 54% Male
- Phase 3: 45% Female, 55% Male
- Phase 2/3: 58% Female, 42% Male
- Phase 2: 48% Female, 52% Male
- Phase 1/2: 22% Female, 78% Male
- Phase 1: 25% Female, 75% Male

Percentage of Participants by Phase (n=334,551)*

International partnership for microbicides [http://www.ipmglobal.org](http://www.ipmglobal.org)

[http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ParticipatinginClinicalTrials/ucm197788.htm](http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ParticipatinginClinicalTrials/ucm197788.htm)
Human Data

- 15-20% of recognized pregnancies will end in miscarriage
- There is a 2-3% risk of a birth defect with every live birth
- For most the causes are genetic or unknown

and there’s a 97% chance your baby is perfect
Teratogen
Any substance, agent, or process that interferes with normal prenatal development, causing the formation of developmental abnormalities of the embryo or fetus

_All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy_  

Paracelsus (1493-1541)
Teratogenicity can happen anytime

KL Moore, The Developing Human
Human Data

Human teratogens (examples)

- Maternal disease, or condition
  - insulin dependent diabetes
  - folic acid deficiency
  - hyperthermia
  - alcohol, smoking

- Radiation
  - atomic weapons, radiiodine,
  - therapeutic high doses (not diagnostic X-rays)

- Intrauterine infection
  - rubella, toxoplasmosis

- Environmental Agents and Drugs
  - heavy metals; lead, mercury
  - anticonvulsants, retinoic acid, warfarin
Timeline of development

Days Gestation

0 280

Trimesters

First Second Third

Periods

Egg Embryo Fetus

Key Events and Phases

Fertilization Cleavage Blastulation Implantation Gastrulation

Primary Morphogenesis Organogenesis

Examples:
- Neural Tube Defects
- Gastrochisis
- Single Outflow Tract
- Phocomelia

Examples:
- Mental Retardation
- Hearing Loss
- Hypoglycemia
- Cardiomyopathy
- Lung Immaturity

Teratogenic Exposure Outcomes

Miscarriage Major Structural Defects

Abnormal Organ Differentiation, Growth, and Function

Scientific Evidence for Teratogenicity

- Biological Plausibility
  - Based on what you know, is it a reasonable possibility?

- Animal data
  - Evaluates the full range of developmental endpoints (e.g., survival, teratogenesis, behavior and learning)
  - Assess hazards that cannot be assessed in clinical trials
When is a drug a teratogen? Gathering the scientific evidence

- Reproductive and developmental toxicity studies
  - Investigate exposure of mature adults and all stages of development from conception to sexual maturity.
  - Pre-mating → conception → implantation → end of pregnancy (birth) → weaning → sexual maturity

- Most common study designs*
  - Fertility and Early Embryonic Development (one species)
  - Embryo/Fetal Development (two species)
  - Prenatal and Postnatal Development (one species)

*International Conference on Harmonization (ICH) Detection Of Toxicity To Reproduction For Medicinal Products & Toxicity To Male Fertility S5(R2)
Types (Classes) of Data

- **Reproductive toxicity** refers to structural and functional alterations that affect reproductive competence in sexually mature males and females.
  - male fertility
  - female fertility
  - parturition
  - lactation.

- **Developmental toxicity** refers to adverse effects on the developing organism that result from exposure prior to conception, during the prenatal period, or postnatally up to the time of sexual maturity.
  - mortality
  - dysmorphogenesis (structural abnormalities)
  - alterations to growth
  - functional impairment.

Taken from FDA guidance: Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns.
Integration of Data

• Positive signals are evaluated to estimate the likelihood of increased reproductive or developmental risk for humans

• All relevant information considered
  – reproductive and developmental toxicity data
  – general toxicology data as well as human and animal pharmacodynamic and pharmacokinetic data.
  – The analysis accounts for the quality and type of data.

• A weight of evidence approach is applied to arrive at an overall conclusion for reproductive or developmental toxicity

Taken from FDA guidance: Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns.
Guidances: International Conference on Harmonization [ICH]

- Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals [ICH M3(R2)]
  - Reproduction toxicity studies can be staged but **must be performed before large scale or long duration clinical trials are initiated**
  - Reproduction toxicity and genotoxicity studies **must be completed** to include women of childbearing potential not using ‘highly effective birth control’ or whose pregnancy status is unknown
Data from animal studies

Carcinogenicity studies

Safety
Pharmacology
genetic toxicology,
general toxicology
(short duration)

General toxicity studies (increasing duration) Reproductive and
developmental toxicity studies

Managing a Teratogenic Risk

• Risk management options
  – Avoid treatment
    • use other non-teratogenic products
    • interrupt treatment until after pregnancy ends
  – If treatment necessary/unavoidable
    • inform/educate stakeholders about risks and safe use conditions
    • ensure safe use through measures to
      – avoid/minimize fetal exposure
      – prevent pregnancy
Summary

• Females of Reproductive Potential participate in all phases of clinical trials.
• The understanding of risks for teratogenicity is developed over time and is not usually known prior to the conduct of clinical trials
• Teratogenicity is not just a first trimester event
• The focus for clinical trials is pregnancy prevention
  – Pregnancy testing