

ART as a model to study the effect of environmental exposures on fertility and pregnancy outcomes

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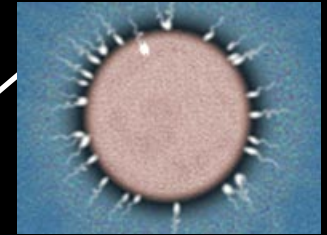
Infertility

- Clinical definition: Inability to conceive after 12 months of unprotected intercourse
 - A live birth is what is important to couples
- In the U.S., 10-15% of reproductive age couples experience infertility (6 - 9 million couples)
 - U.S. National Center for Health Statistics, National Survey of Family Growth
 - From 1982-1995, self-reported fertility problems in women
 - < 25 yrs (42% increase)
 - 25-34 yrs (12% increase)
 - > 35 yrs (6% increase)

FERTILITY & PREGNANCY

Sperm meets Egg

cervical factors
oviduct patency



Fertilization

2 pronuclei



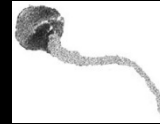
Pre-Implantation Development

embryo quality

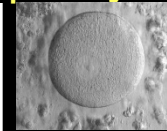


Gametogenesis

semen quality



oocyte quality



Implantation

embryo quality
uterine receptivity



Parturition

pre-term birth

peri-natal
outcomes-
birth defects



Clinical Pregnancy

spontaneous
miscarriage

stillbirth



Post-Implantation Development

early fetal loss <6 weeks

Traditional Reproductive Endpoints in Epidemiologic Studies

- Fertility
 - Semen quality
 - Time to pregnancy
 - Live births
- Pregnancy Outcomes
 - Clinical Pregnancy loss
 - Spontaneous miscarriage
 - Stillbirth
 - Perinatal outcomes
 - Pre-term birth
 - Birth weight
 - Birth defects

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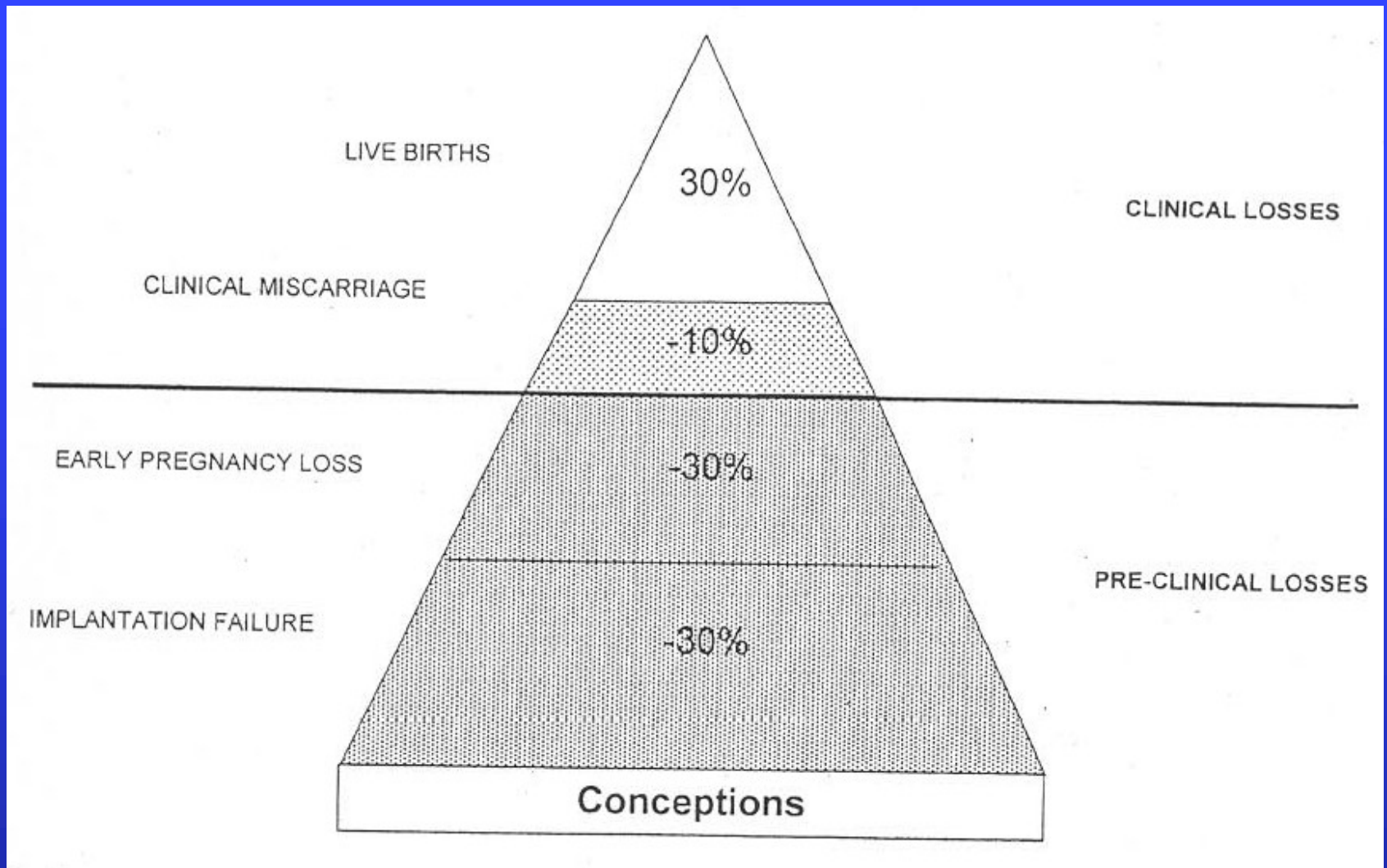


Figure: The Pregnancy Loss Iceberg: an overview of the outcome of spontaneous human pregnancy. A total of 70% of conceptions are lost prior to live birth. The majority of these losses occur prior to the time of the missed menstrual period, and are not revealed. (Macklon et al. Human Reprod Update 2002)

Early pregnancy loss is a frequent event

In animal models, early pregnancy loss is more sensitive to environmental chemicals than late pregnancy loss

However, early (pre-clinical) pregnancy losses are unobservable in humans

Or are they?

Scientific advances have provided us with unique opportunities and challenges in reproductive health

1960's:
Sex without Reproduction

Scientific advances have provided us with unique opportunities and challenges in reproductive health

1980's:

Reproduction without sex

Assisted reproductive technologies (ART)

- Use as a model to study the impact of environmental chemicals on early developmental endpoints not previously observable
 - These include:
 - Folliculogenesis and Oogenesis
 - Fertilization and pre-implantation development
 - Implantation
 - Early (pre-clinical) pregnancy loss

First Human IVF baby

- July 25, 1978
 - 5lb, 12oz. C-section
- Louise Joy Brown
- Fallopian tube obstruction prevented conception
- Laparoscopic egg retrieval in a natural cycle



July 25, 1978: Patrick Steptoe, Jean Purdie, and Louise Brown...in the arms of Bob Edwards

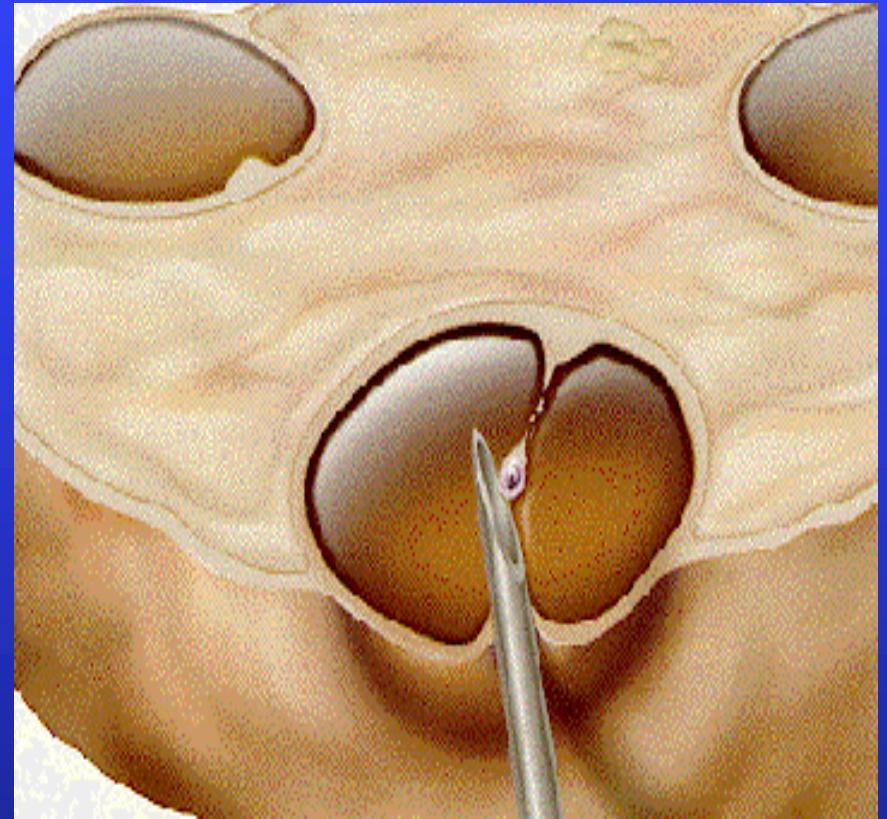


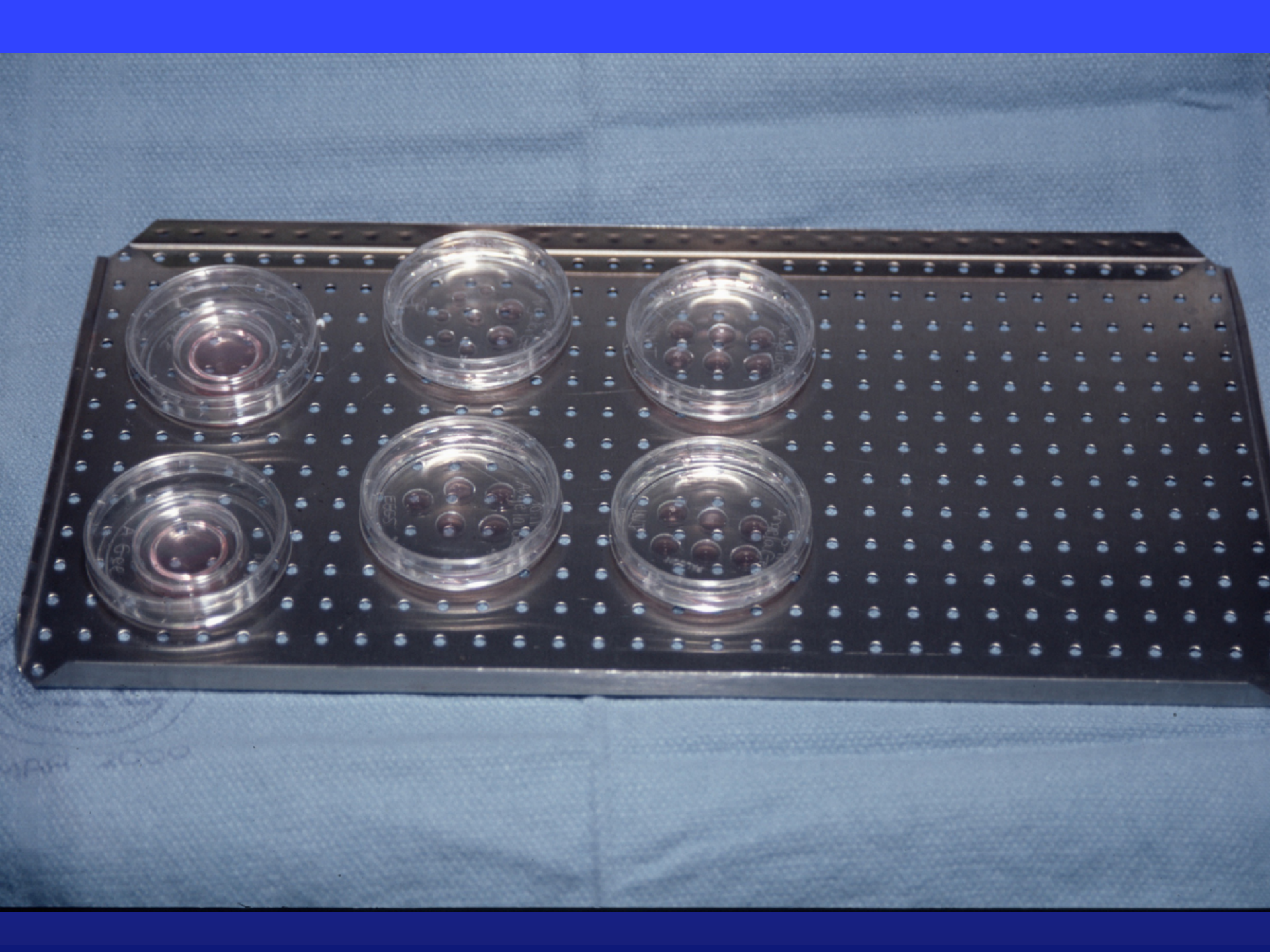
ART Practice Today

- Over 400 Clinics nationwide
- Over 1% of all babies born in the U.S. (approximately 40,000 babies per year)
- In some countries it accounts for over 5% or more of all babies born
- National success rates and those by individual clinic are available to the public

<http://www.cdc.gov/reproductivehealth/art.htm>

Aspiration of the Follicles after Hormonal Stimulation







Human Embryonic Development



MASS. GEN. HOSP. - IVF UNIT

P80

7MHz E721

B8

16.4



GE



CN0
10cm
DR66
G 50

+CRL 3.0mm

5W6D

MI < 0.4

Can common environmental chemicals adversely affect early development and reproductive function?

Endocrine Disruptors

Exogenous Agents That Interfere With the Synthesis, Secretion, Transport, Binding, Action, or Elimination of Natural Hormones in the Body That Are Responsible for the Maintenance of Homeostasis, Reproduction, Development, and/or Behavior.

U.S. EPA 1997

Discussion I

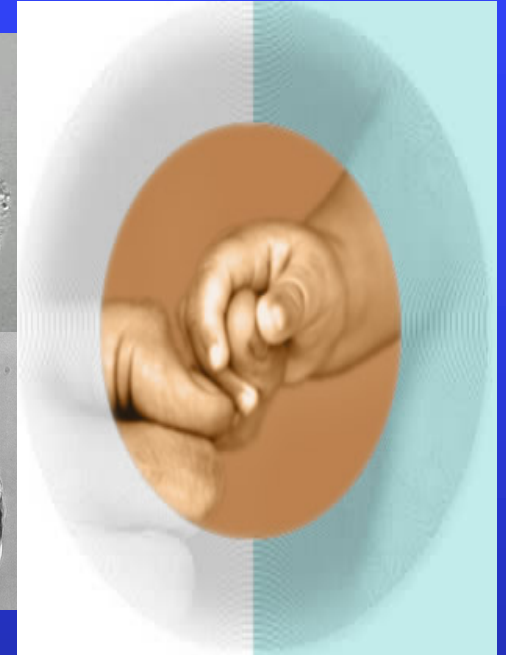
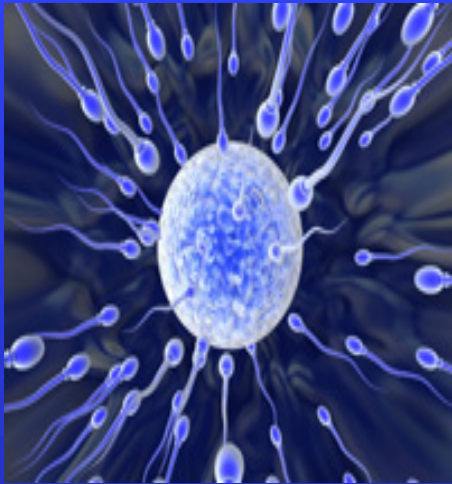
Use ART as a model to study fertility and pregnancy endpoints (a prospective pre-conception pregnancy design)

- Extends traditional epidemiologic endpoints
- Environment and Reproductive Health (EARTH) Study began in 2004 (over 600 couples recruited, 100+ manuscripts)
- Focuses on environmental endocrine disruptors
 - Modern chemicals (phthalates, phenols, flame retardants)
 - Historic chemicals (PCBs, chlorinated pesticides and PBDEs)

Discussion II

- ART designs allows for novel research directions
 - NIEHS funded study of preconception maternal and paternal environmental exposures in relation to children's health (multi-PI with Joe Braun at Brown University)
 - Recruitment ongoing

Thank You!



Questions?