Lecture 14: Conception, Fertility, Early Fetal Loss

- Birth Control (cont.)
- Conception
- What Influences Probability of Conception?
- Early Fetal Loss
- Infertility
- Fertility Enhancement
- Assisted reproduction

Depo-provera

- Injectable contraceptive -- Progestin
- Shot every 3 months
- First year failure rate of 0.3%
- Can delay fertility for 6 months - 1 yr after discontinue
- Used by 30 million women

Norplant

- 6 sticks under skin
- Synthetic progestin
- Lasts up to 5 years
- First year failure rate of 0.05%, 3.7% over 5 years
- Inhibits ovulation, thickens and decreases cervical mucous, thins endometrial lining
- Progestin 4-5x lower than birth control pills
- Used by 3 million women

Implanon

- New birth control similar to Norplant but just 6 stick under skin
- Not yet readily available

The Patch

- Works similar to the pill
- Contains progestin and estrogen
- Delivered through skin
- Put a new patch on once a week
- Reversible

Nuva Ring

- Ring inserted in vagina
- Leave in for 3 weeks - take out for 1
- Contains progestin and estrogen
- Works similar to the pill, but delivers hormones vaginally
- Should be more effective than bill < 1% failure rate
- Reversible
Homunculus in Sperm

Conception

The Ovum
The Ovum

- Shed into peritoneal cavity
- Rising estradiol causes fimbria to sweep ovum into fallopian tube
- Cilia is activated in ampulla
- Ovum moves into fallopian tube and into ampulla
- Ovum continues to ‘ripen’ in ampulla

The Sperm
How do sperm get into Cervix?

- Opening of cervix has cilia to waft sperm through.
- Components of seminal fluid - maybe prostaglandins - stimulate contractions in upper vagina to propel sperm into cervix.
Capacitation

- Change to hyperactivated motility pattern - whip-like beats of tail
- Change in surface membrane -- responsive to signals from oocyte

The Sperm

- Seminal fluid causes contractions of upper vagina
- Cervical mucous changes
- Cilia propel sperm into ampulla where fertilization takes place
- Chemicals surrounding egg may attract sperm
- In ampulla goes through 'capacitation'
Fertilization
Acrosome Reaction

- Fusion with oocyte
- Zona pellucida hardens (Zona reaction)
- Final division of meiosis in oocyte

Perivitelline Space

Binds to Oocyte
Male and Female Pronuclei form

Pronuclei of Male and Female Fuse

Polar Bodies

Cleavage furrow
Fertilization

- Progesterone from granulosa cells causes enzymes in acrosome to leak out and dissolve matrix around egg
- One sperm binds to zona pellucida
- Acrosome reaction
- Microvilli of egg engulf sperm
- Egg enzymes harden zona pellucida
- Final division of oocyte occurs

Implantation

YOU - Day 1!

8 Cell Stage

Morula
Day 5: “Hatching” from Zona Pellucida

Day 8-10: Implantation

Day 11
Implantation

• First forms a morula after initial cell division
• At 8-cell stage differentiates tissues
• Forms blastocyte
  • Trophoblast
  • Inner Cell Mass
• Trophoblast “hatches” out of zona pellucida for implantation

How does the Embryo signal it’s presence to the mother

HCG (Human Chorionic Gonadotropin) Rescue

• Embryo produces HCG to signal the mother
• Mimics LH
• Maintains the corpus luteum

What Influences the Probability of Conception?
Behavior and Conception

Causes of Subfertility

*England*

Infertility: Caffeine

- Caffeine
  - Infertility
  - Miscarriage
  - Birth defects
  - Lower birth weight
  - Earlier births

Infertility: Alcohol

- Alcohol
  - Infertility
  - Miscarriage
  - Birth defects
  - Lower birth weight
  - Earlier births

Alcohol and Conception
Alcohol and Caffeine Consumption

- >50% reduction in probability of conception during a menstrual cycle where alcohol was consumed
- Caffeine enhanced negative effect of alcohol (no independent effect)

Infertility: Smoking

- Smoking
  - Infertility
  - Lower birth weight

Smoking and Conception

- Fecundability Ratio
  - Nonsmokers
  - Female Smokers
  - Male Smokers

Smoking and Caffeine Consumption

- Nonsmokers had a dose response relationship with caffeine
- No dose-response with caffeine in smokers

Male Infertility

- Sperm counts decrease during IVF treatment
Timing of Intercourse?

Timing of Intercourse and Conception

Early Fetal Loss

HCG Concentrations in 5 women with early Pregnancy Loss

Wilcox Study
- 25% chance of conceiving with each cycle
- 31% pregnancies ended in miscarriage
- Doesn’t include loss before HCG secretion detected or if HCG too low
- Risk didn’t increase if had just 1 miscarriage
- No increased loss if conceived in next cycle after miscarriage
- Higher rate of miscarriage in women who eventually conceived

(From Wilcox et al., 1988)
Holman Study

- Observed early pregnancy loss was 34%
- No difference between this and the western sample

Age and Conception

- Fecundity decreases with age

Criticisms:

- Problems with mathematical model
- Fecundability must be almost 100% for this rate of loss

Chromosomal Abnormalities & Age

- Increased chromosomal abnormalities
Age and Down’s Syndrome Risk

- Increased chromosomal abnormalities
- Zona pellucida too dense -- no implantation

Traditional Methods - Fertility Enhancement

**Oral Consumption**
- Consumption of Dill: Rome, 1st Century
- Wild Rue: 11th century Middle East
- Wormwood: 11th century Middle East
- "Hot" Foods (fish, eggs, brown sugar, almonds, dates, ginger, garlic, raisins)

**Intravaginal**
- Ginger: Jivaro of Peru
- Alam: Greco-Roman
- Linseed Oil: Greco-Roman
- Frankincense & Wormwood: 13th century Middle East

**Mechanical**
- Application of vacuumed containers: Greco-Roman, modern Afghanistan
- Wearing of fresh skins: Central Asia
- Massage to move navel: Afghanistan

**Magico-Religious**

Assisted Reproduction

- Clomid
- Perganol
- *in vitro* Fertilization
- Intra-Uterine Insemination
- Sex Selection
- GIFT
- ZIFT
**Fertility Drug: Clomid**
- Fertility drug given to women to promote ovulation
- Ring structure similar to estradiol
- Binds to receptors for estrogen
- Hypothalamus “thinks” estrogen is low and pumps out FSH to make more estrogen
- So causes woman to produce estrogen on her own
  - Multiple births
  - Possibly associated with ovarian cancer (concern for women who donate eggs)

**Fertility Drug: Perganol**
- LH and FSH combined (distilled from menopausal urine)
- Stimulates follicular growth and estrogen production
- Mid-cycle dose of HCG to stimulate ovulation (mimicking action of LH)
- Multiple gestation risk (higher than clomid)

**Fertility Treatment: in vitro Fertilization (IVF)**
- Take fertility drugs to get several eggs to mature
- Ultrasound to watch follicular development
- When follicle mature get dose of HCG (as an LH mimic - to encourage follicular development)
- After 36 hours (just before ovulation would occur naturally) surgically remove 4-12 eggs
- Fertilization outside (in petri dish) of body
- Grow 4-10 cells
- Put back 2-5 in hopes 1 will implant
  - Tubal blockage, as a result of infection
  - Low sperm count (select “best” sperm)

**Fertility Treatment: Intra-Uterine Insemination (IUI)**
- Take fertility drugs to get several eggs to mature
- Ultrasound to watch follicular development
- When follicle mature get dose of HCG (high enough to cause ovulation)
- Inseminate with partner’s sperm in the uterus

**GIFT**
- Gamete Intrafallopian Transfer
- Mix egg and sperm and put back in fallopian tube before fertilization

**ZIFT**
- Zygote Intrafallopian Transfer
- Put zygote in fallopian tube (instead of uterus)
Sex Selection

- Y-sperm lighter can separate out
- Centrifuge
  - Avoid sex-linked recessive diseases

Assisted Reproduction Implications

- Higher rate of multiple births

Assisted Reproduction Implications

- Higher rate of multiple births
- Lower birth weight of singletons AND multiples

Percentage with Low Birth Weight

Possible Causes of Low Birth Weight with Assisted Reproduction

- Human Menopausal gonadotropin (Pergonal) increases insulin-like growth factor-binding protein - intrauterine growth restricts
- Increased rates of structural abnormalities of the placenta
- Pregnancy-induced hypertension
- Increased levels of endometrial proteins
- Elective cesarean section - earlier delivery

Percent Risk of Low Birth Weight & Procedure Type

Schieve et al., 2002

Schieve et al., 2002

Schieve et al., 2002

Schieve et al., 2002
Assisted Reproduction Implications

- Higher rate of multiple births
- Lower birth weight of singleton AND multiples
- Greater risk of short and long term disabilities and death with low birth weight

Assisted Reproduction Implications

- Higher rate of multiple births
- Lower birth weight of singletons AND multiples
- Greater risk of short and long term disabilities and death with low birth weight
- Higher rates of birth defects

Assisted Reproduction & Birth Defects

Possible Causes of Increased Birth Defects with Assisted Reproduction

- Underlying cause of their infertility
- Medications to induce ovulation
- Medications to maintain pregnancy early on
- Freezing and thawing of embryos
- Potential for polyspermic fertilization
- Delayed fertilization of oocyte

Assisted Reproduction & Birth Defects

Singleton Births

- Cardiovascular
- Urogenital
- Musculoskeletal

Possible Causes of Increased Birth Defects with Assisted Reproduction

- 23% success rate
- 2.6 times risk of low birth weight
- Twice the risk of major birth defects
Assisted Reproduction

- 23% success rate
- 2.6 times risk of low birth weight
- Twice the risk of major birth defects

However …

94% will be of normal birth weight
91% free of major birth defects

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Next Time …

- Views of Pregnancy
- Gestational Development
- The Physiology of Pregnancy
- Pica eating
- Pregnancy Sickness
- Energetics of Pregnancy