Mechanisms of Action of Hormonal Contraceptives

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**Mechanisms of Action of Hormonal Contraceptives**

**Outline of presentation**

1. Learning objectives
2. History of contraception, focusing on HCs
3. Efficacy of HCs
4. Non-contraceptive benefits of HCs
5. Types of modern HCs
6. Adverse effects of HCs
7. Female hypothalamic-pituitary-gonadal axis
8. Menstrual cycle
9. Fertilization/No fertilization
10. HC mechanism of action
11. Summary and prospectus
Mechanisms of Action of Hormonal Contraceptives

Learning Objectives

1. Describe action of hormonal contraceptives in hypothalamus and anterior pituitary

2. Describe primary and secondary effects of hormonal contraceptives in reproductive tract

Primary mechanism of action of hormonal contraceptives is generally independent of formulation and route of administration.
Mechanisms of Action of Hormonal Contraceptives

1. **Within brain:**
   - Inhibit ovulation by suppressing LH surge at mid-cycle,
   - LH is necessary for terminal stages of follicular maturation and rupture.

2. **Within UGT:**
   - Thicken cervical and endometrial mucus forming a mechanical barrier, and
   - Create hypoplastic endometrium that is not hospitable for implantation
Seminal moments in the history of hormonal contraception; Part 1

1851 BC
Ancient Egypt
Sodium Carbonate
Acacia tree sap
Crocodile dung
Sour milk
Honey
Lint
Various barriers

384 - 322 BC
Aristotle proposes using cedar oil, lead ointment, and frankincense as spermicides

1725 - 1798
Casanova uses empty rind of half a lemon as a cervical cap

1827
Scientists discover the existence of the ovum—the dawn of reproductive medicine

1832
Charles Knowlton invents birth control solution that is injected into uterus after intercourse (salt, vinegar, liquid chloride, zinc sulfate, aluminum potassium sulfite)

1838
Friedrich Wilde invents "Wilde Cap" to cover cervix between menstrual cycles; forerunner to diaphragm

1839
Charles Goodyear invents technology to vulcanize rubber; manufacturers condoms, IUDs, douching syringes and womb veils (diaphragms)

1843
Scientists link penetration of egg by sperm to conception
Seminal moments in the history of hormonal contraception; Part 2

1873
Comstock Law
Congress makes all forms of contraception illegal (anti-obscenity act, 1873-1965)

Margaret Sanger
Opens family-planning and birth-control clinic and lands in prison for 30 days

1916
Disinfectants
Most popular "contraceptive" in US
Problems: doesn't work, women allegedly die from using it, others suffer severe inflammation and burns

1920 - 1960
Margaret Sanger
Gregory Pincus
John Rock
Katharine McCormick
Karl Djerassi
Russell Marker
Develop concept of and synthesized PO progestins as "magic pills"

1951 - 1953
Pincus and Rock run 1st "fertility" study with 50 women (POP); not a single patient ovulates

1954
Rock submits Enovid (Searle) for FDA approval; clinical trials set up in Puerto Rico
"Enovid gives 100% protection against pregnancy" but many side effects

1956
FDA approves Enovid for treatment of severe menstrual disorders; requires warning that Enovid will prevent ovulation

1957
Seminal moments in the history of hormonal contraception; Part 3

1959
- Over 500K women taking Enovid for off-label use
- Searle applies for FDA approval to use Enovid as contraceptive

1960
- Searle receives FDA approval to market Enovid as contraceptive at original, high dose and eventually receives approval for lower doses
- 13 major drug companies work to develop OCs

1962
- Second (EE) contraceptive is approved
- VTEs and MIs linked to OC use
- 2.3M women taking pill

1963
- 6.5M women taking pill

1965
- 12.5M women taking pill

1967
- 6.5M women taking pill

PBS: The Pill
Seminal moments in the history of hormonal contraception; Part 4

1967 - 1968
- Sales of the pill: $150M
- Concurrent smoking identified as major risk factor for blood clots and other side effects of pill
- Congress holds hearings on side effects of pill
- Release of mini-pill

1970s
- 10.7 US women taking pill
- 50 - 80M women worldwide taking pill
- Very low-dose contraceptives introduced
- High-dose contraceptives removed from market

1980s
- Depo-MDP officially approved as long-term contraceptive

1992
- Emergency contraception approved

1998 2000 - 2010
- New products: Patches, Rings, Hormonal IUD, Extended-cycle OCs
- Used by 100M women worldwide and 12M in US

PBS: The Pill
Enovid

- Approved on June 10, 1957 by FDA for menstrual disorders
- Approved on June 23, 1960 by FDA for use as an OC
- Withdrawn from US market in 1988, along with other first-generation, high-estrogen combined oral contraceptive pills
- Active ingredients:
  - Mestranol $150 \mu g$
  - Norethynodrel 10 mg
Hormonal Contraceptives

Combined OCs
- Perfect use: 0.3 pregnancies per 100 women
- Typical use: 9 pregnancies per 100 women
- Effective but not as effective as IUDs, P4 implants/injections or sterilization

Non-contraceptive health benefits (mostly COCs)
- Reduction in acne
- Reduction in androgens, hirsutism in PCOS
- "Normalization" of menstrual cycle
- Reduction in dysmenorrhea, menorrhagia (EV/dienogest)
- Reduction in premenstrual dysphoric disorder (Dros only)
- Reduced risk of endometrial, ovarian and colon CA
Hormonal Contraceptives

- **Estrogen**: ethinyl estradiol (mostly)

- **Progesterone**: four generations of contraception
  1. Norethindrone (Norethisterone), Norethindrone acetate
  2. Norgestrel, Levonorgestrel
  3. Desogestrel, Gestodene, Norgestimate
  4. Drospirenone, Dienogest
  5. Ulipristal—not really a progestin, but a SPRM

All progestins are equal with respect to primary MOA in contraception. Not equal with respect to other activities, some of which may also be involved in contraception.
<table>
<thead>
<tr>
<th>Progestins</th>
<th>Activities</th>
<th>Progestin</th>
<th>Estrogen</th>
<th>Androgen</th>
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<td>Ethynodiol</td>
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<td><strong>Second Generation</strong></td>
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<td>Levonorgestrel</td>
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<td><strong>Third Generation</strong></td>
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<td>Dienogest</td>
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<td>0</td>
<td>Antagonist</td>
</tr>
</tbody>
</table>
1. MI and ischemic stroke
   - Clearly was a problem with early, high-dose HCs (E2)
   - MI/IS is less of a problem/no problem with modern, low-dose HCs in young, non-smokers who are otherwise healthy

2. VTE and cerebral venous thrombosis
   - Risk of VTE (pulmonary embolism and DVT) is increased by a factor of 3-4 among current HC users
   - Related to E2 dose (affects clotting factors) but progestins play a role—risk is highest: 4th = 3rd > 2nd > 1st generation
   - Risk increases with age, body mass, smoking, childbirth
   - Risk not increased with progestin-only HCs

3. Compromised lactation (E2 mostly)
Mechanisms of Action of Hormonal Contraceptives

Female hypothalamic-pituitary-gonadal axis
Menstrual cycle
Fertilization/No fertilization
HC mechanism of action
Regulation of Reproduction via the HPG Axis

Hypothalamus

Preoptic area

GnRH

Anterior Pituitary

Gonadotrope

LH

FSH

Gonadal Tissue

Ovaries

Testes

FSH

Aromatase

5α SR

P

E2

T

DHT

Negative Feedback
Follicular maturation and formation of corpus luteum

- **Primary Unilaminar Follicle**: Granulosa cells + ovum
- **Primary Multilaminar Follicle**: More Granulosa cells + ovum
- **Graafian Follicle**: Granulosa cells + Thecal cells + ovum
- **Ovulation**: Lutein cells + Thecal cell
- **Corpus luteum**
  - P4
  - E2
- **Corpus albicans**

**Fertilization/implantation**
- HCG
- LHR
- P4
- E2

**No fertilization/implantation**
- LH (surge)
- LHR
- P4
- E2

- Testosterone → Estradiol
- Aromatase
Function of corpus luteum +/- fertilization/implantation

- Menstruation
  - De-repression of FSH/LH secretion
- Ovulation
  - FSH
  - LH
  - E2
  - Post-ovulation
  - HCG
  - Corpus luteum
    - E2: proliferation
    - P4: differentiation to secretory phenotype
  - Corpus albicans
    - No Fertilization
    - No E2/P4

- Corpus luteum
  - E2
  - Post-ovulation
  - HCG
  - LH
  - De-repression of FSH/LH secretion
A pathway that is highly drugged

**GnRH**: fertility
**GnRH analogs**: endometriosis
**GnRH antagonists**: fertility

**FSH**: fertility
**LH (HCG)**:
- fertility
- ovulation kits
- home pregnancy tests

**Brain**

**Ovary**

**Gonad (ovary)**

**Estrogens**: HRT, osteoporosis, contraceptives
**SERMs**: HRT, Osteoporosis, BrCA, fertility
**NERMs**: BrCA
**Aromatase inhibitors**: BrCA, fertility

**Circulatory System**

**Gonadotrope**

**Anterior Pituitary**

**GnRH**

**Preoptic Area** (hypothalamic nucleus)
### Wiring in the Female Reproductive System

- **Preoptic Area (Nucleus)**
  - **GnRH** neuron
  - **Kisspeptin** neuron

- **Infundibular Nucleus**
  - **FSH/LH**
  - **ERα**, **PR**
  - **KNDy** neuron

- **Median Eminence**
  - **Leptin**

- **Anterior Pituitary**
  - **GnRH**
  - **FSH/LH**
  - **Primordial**, **Primary Unilaminar**

- **Circulatory System**
  - **Gonadotrope**

- **Gonad (ovary)**
  - **Ovarian follicles**
  - **Corpus luteum**
  - **FSH**, **LH**
  - **E2**, **P4**
GnRH

FSH/LH

Preoptic Area (Nucleus)

Infundibular Nucleus

Median Eminence

Anterior Pituitary

Circulatory System

Gonad (ovary)

Brain

Ovary

Kisspeptin neuron

ERα

PR

Kisspeptin

GnRH

(+)

Hormonal Contraceptives

Kisspeptin-Neurokinin B-Dynorphin

(-)

KNDy neuron

Leptin

Adipose Tissue

Gonadotrope

FSH/LH

FSH

LH

GnRH

(+)

(+)

(+)

E2

P4

Corpus luteum

Ovarian follicles
FSH
E2
LH
P4

Hormonal contraceptives

Follicle
Endometrium

Day 2 4 6 8 10 12 14 18 22 26 28 2

Meno  Proliferative  OV  Secretory  Meno
**Mechanism of Action of Hormonal Contraceptives**

**Learning Objectives**

1. **Describe action of hormonal contraceptives in hypothalamus and anterior pituitary**
   - Activation of negative feedback pathway
     - activation of estrogen and progesterone receptors in KNDy neurons in infundibular nucleus → suppression of kisspeptin release by these hypothalamic neurons
     - Reduced GnRH and LH secretion; no LH → NO OVULATION

2. **Describe primary and secondary effects of hormonal contraceptives in reproductive tract**
   - **Primary effect**
     - suppression of ovulation in ovary—latter stages of follicular maturation and rupture requires LH
   - **Secondary effect**
     - production of viscous cervical and uterine secretions that impairs access of sperm to fertilization-competent ovum (mainly progestin-only preps)
Mechanisms of Action of Hormonal Contraceptives

Summary and Prospectus

1. HCs represent a highly effective means of contraception when taken correctly.

2. The contraceptive effect of HCs is primarily due to suppression of ovulation but local effects on cervical and endometrial mucus also play a role.

3. Modern HCs have side effects, the most relevant of which is VTE and related disorders.

4. The incidence of VTE (and MI and IS) in patients taking HCs is increased by smoking, body mass, and age.

5. Other pathways (e.g. Kisspeptin) represent attractive targets for contraceptives in the future but the safety and efficacy of targeting these pathways are unknown.
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