Module 1

Fertility Care Considerations:
Introduction to infertility for the specialty health care pharmacist

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Disclosure: Ann Scalia and Mary Vietzke are employees of Walgreens.

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Objectives

• Review the physiology of the reproductive endocrine system and how various hormones are regulated
• Identify risk factors for infertility in both women and men
• Explain appropriate diagnostic tests for the evaluation of an infertile patient
• Discuss types of assisted reproductive technology (ART) treatment cycles

Infertility

• Infertility is a disease defined by the failure to achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or therapeutic donor insemination
• Earlier evaluation and treatment may be justified for women over the age of 35, based on medical history and physical findings
• Chance of conception decreases dramatically in women over the age of 35 years
Infertility

- 10% - 15% of couples in their reproductive years
- 6.7 million women in the US have impaired fertility
- Estimated 4 million men in the US have reported infertility
- Data suggests up to 600,000 reproductive aged men may have azoospermia
- The male partner is either the sole cause or contributing factor in 40% of couples

Milestones in Assisted Reproductive Technology (ART)

- First baby Louise Brown conceived through ART born in England in 1978
- First IVF baby Elizabeth Carr born in the U.S. in 1981 at Jones Institute in Norfolk
- First child conceived through egg donation was born in 1984
Physiology of the Reproductive Endocrine System

Fertility Potential: Oocyte Production

Women are born with a finite number of eggs

6-7 million by 20 weeks gestation

At birth, ~700,000 primordial follicles

At puberty, only around 300,000 remain

Ovarian reserve diminishes rapidly after age 37 (~25,000)

By menopause, due to the continued atresia, only a few hundred remain
Female Age

- Peaks from late teens through your late 20’s
- Significant decline...35 and over
- Accelerated follicular depletion after age 37
- Pregnancies seldom achieved in women > age 42 without the use of donor egg using IVF

ASRM Web site: http://www.asrm.org/BOOKLET_Age_And_Fertility/. Published 2012.
Van Voorhis B. What to know about the infertile female. 2011:134.

Ovarian Reserve

Describes a woman’s reproductive potential with respect to ovarian follicle number and oocyte quality

Adapted from: Speroff. Clinical Gynecologic Endocrinology and Infertility. 8th ed.
Sperm- Lifetime Production

• Men continuously produce sperm in an adult testis.
• 300 thousand spermatogonia per gonad during embryogenesis
• 600 million per testis by puberty
• 100-200 million per day created in the normal adult male
• Sperm viable for 48-72 hours
• Decreases in sperm quality occur (volume and count) as men age but generally not a problem before a man is in his sixties.

Menstrual Cycle

• Normal reproductive function involves:
  – Repetitive cycles of follicular development
  – Ovulation
  – Preparation of the endometrium for implantation if conception occurs
• Median cycle length is 28 days, with a normal range between 25 and 35 days
• Interval starts to decline between ages of 36-40 with significant variability before menopause
Menstrual Cycle

- Involves recruitment of a group of antral follicles in each ovary during late luteal phase of preceding menstrual cycle
- A single dominant follicle is selected in initial-mid follicular phase, others undergo atresia
- Fluctuations in follicular phase length are primarily responsible for variability in cycles and also may be a function of aging
- Luteal phase duration more constant, lasting between 10 and 16 days in 95% cycles

Menstrual cycle events

- **Menstrual cycle**
- **Follicular phase** Day 1-14
- **Ovulatory phase** Day 14
- **Luteal phase** Day 14-28
The Endocrine System

- Control center for the regulation of all body systems
- Group of glands that maintain and stabilize the body’s internal environment
- Produce chemical - regulating substances called hormones

Reproductive Axis

- Regular ovulatory cycles achieved through integration of stimulatory and inhibitory signals from the hypothalamus, pituitary and ovary
- Initiated by pulsatile secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus into the pituitary portal
- GnRH regulates the synthesis and release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) into the circulation
Hypothalamic Pituitary Axis

- The hypothalamus produces a hormone called GnRH (gonadotropin releasing hormone)
- GnRH stimulates the pituitary to release FSH (follicle stimulating hormone) and LH (luteinizing hormone)
- The ovaries respond to these hormones by developing follicles
- There is a feedback mechanism to the pituitary to regulate the release of gonadotropins: inhibin and estrogen

Normal Hormonal Cycle


Normal Hormonal Cycle

• Estrogen has several effects on the pituitary. Early in the cycle estrogen inhibits FSH release but quickly rising levels later in the cycle serve to stimulate the LH surge which brings about ovulation.

• The ovary, just before ovulation, begins producing progesterone. This prepares the endometrium for implantation.

• If conception occurs, human chorionic gonadotropin is secreted by the fetus. If not, progesterone levels drop and menses ensues.


Follicle Stimulating Hormone (FSH)

• Gonadotropin hormone secreted by the anterior pituitary

• Essential for follicular growth

• Critical for recruitment of follicles and selection

• Induces estrogen and progesterone production at the level of the ovary by activating aromatase and p450 enzymes

• Responsible for initiation/maintenance of spermatogenesis in the male together with testosterone

Luteinizing Hormone (LH)

- Gonadotropin hormone secreted by the anterior pituitary.
- Needed for growth of the preovulatory follicle, luteinization and ovulation of the dominate follicle.
- Early release of LH stimulates production of androgen synthesis by the theca cells in the ovary.
- LH surge initiates the luteinization of the theca and granulosa cells which in turn produces the corpus luteum which contributes to the production of continued progesterone and estrogen.

Estrogen

- Produced at the level of the ovary and is needed for the maturing follicle and oocyte
- Estradiol is the most potent form of estrogen
- Estradiol levels begins to rise significantly by cycle day 7 once the dominant follicle is established
- Derived from androgens produced in the theca cells
- Androgens migrate from the theca cells to the granulosa cells where they are converted to estradiol by aromatase activity

References:
Progesterone

- Steroid hormone produced at the level of the ovary by the corpus luteum
- Rise just prior to ovulation and peaks five to eight days post ovulation
- Induces swelling and secretory preparation of the endometrium during the luteal phase
- Supports embryo development and implantation


Menstrual cycle

Figure 1: Estrogen (estradiol) and progesterone
Figure 2: LH and FSH
Figure 3: Ovarian cycle
Figure 4: Endometrial cycle
Risk factors for infertility

Factors Associated With Infertility

- Abnormalities in:
  - Production of competent oocyte
  - Reproductive tract transport of oocyte, embryo and sperm
  - Implantation process
  - Sperm production (male factor)
- Other conditions that may affect multiple components (immunological).
- Initial infertility evaluations focuses on the above major processes.

Causes of Infertility

- Age
- Hormone dysfunction or insufficiency
- Ovulatory disorders
- Tubal defect
- Uterine abnormality
- Endometrial deficiency
- Poor vaginal environment
- Male factor
- Unexplained or no identifiable cause

ASRM. Fertil & Steril. 2015;103(6):1379-1618

Initial Fertility Evaluation
Diagnostic Evaluation

- Directed toward identifying the cause(s)
- Identify all relevant factors
- Approach evaluation in a systematic, expeditious and cost-effective manner
- Goal: Least invasive methods for detection of the most common causes of infertility

Initial Infertility Evaluation

- Documentation of competent ovulation
  - History regular menses
  - Observation LH surge in urine with predictor kit
  - Midluteal serum progesterone > 3ng/mL
- Documentation of female reproductive tract and tubal patency with assessment of uterine cavity
  - Hysterosalpingogram (HSG)
  - Sonohysterogram
  - Uterine cavity assessment
  - Hysteroscopy
- Evaluation of semen analysis
Assessing Ovarian Reserve

• Age results in changes in oocyte quantity and quality/function
• Ovarian insufficiency or “diminished ovarian reserve”
• Testing for decreased ovarian reserve may include:
  – Cycle day 3 FSH concentration
  – Antimüllerian hormone (AMH) measurement
  – Antral follicle count
  – Clomiphene citrate challenge test


Assessing Ovarian Reserve

• AMH is produced by granulosa cells from pre-antral and antral follicles
• Blood levels of AMH have been shown to correlate with the number of eggs present within the ovaries
• Decreases with age
• An AMH level < 1 ng/mL is associated with poor responses to ovarian stimulation, poor embryo quality and poor pregnancy outcomes in IVF
• Low AMH alone is not enough to rule out treatment

Hormone Reference Ranges Cycle-Day 3 Serum Levels

<table>
<thead>
<tr>
<th>Hormone Test</th>
<th>Reference Range</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicle Stimulating Hormone (FSH)</td>
<td>&lt;10mIU/ml</td>
<td>High values have been associated with poor ovarian stimulation &amp; failure to conceive.</td>
</tr>
<tr>
<td>Estradiol (E2) Day 3</td>
<td>&lt;60-80 pg/ml</td>
<td>An aid to correct interpretation of a “normal” basal serum FSH level.</td>
</tr>
<tr>
<td>Luteinizing Hormone (LH) Day 3</td>
<td>5 - 20 mIU/mL</td>
<td>LH levels are high in ratio to your FSH levels. Could indicate polycystic ovarian syndrome (PCOS).</td>
</tr>
<tr>
<td>Prolactin Level</td>
<td>&lt; 20 ng/ml</td>
<td>Elevated levels can adversely effect ovulation &amp; be caused by hypothyroidism.</td>
</tr>
<tr>
<td>Anti-Mullerian Hormone (AMH)</td>
<td>&lt; 1.25ng/mL</td>
<td>Highly sensitive for detecting women with diminished ovarian reserve.</td>
</tr>
<tr>
<td>Thyroid Stimulating Hormone (TSH)</td>
<td>&gt; 2.5 uIU/mL</td>
<td>Patients with abnormal levels attempting pregnancy are treated.</td>
</tr>
</tbody>
</table>

Van Voorhis, B. What to know about the infertile female. 2011:134-151

Antral Follicle Count (AFC)

- The AFC provides a direct quantitative marker of ovarian responsiveness.
- Count follicles between days 2 and 4 of a spontaneous menstrual or oral contraceptive cycle to avoid the effect of intra-cycle variation.
- Include all follicles between 2-10mm in diameter
- Totals <10 (combination of both ovaries) suggest diminished ovarian reserve (DOR).

Follicular Ultrasound Monitoring

• Evaluates developing follicles
  – Predictive value
  – Size
  – Number
• Progressive growth of follicles
  – Sudden collapse
  – Increase in cul-de-sac fluid volume
  – Evidence of ovulation


Female Reproductive System

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Semen Analysis

• Semen analysis is the cornerstone of the laboratory evaluation for the infertile male.
• Initial evaluation should include one properly performed semen analysis.
• 2-3 days abstinence period
• Should be examined within an hour after collection.
• If initial analysis abnormal a second analysis should be obtained after at least 4 weeks.


2010 WHO Semen analysis reference values:

Values based on men who took 12 months or less to help conceive a child.

<table>
<thead>
<tr>
<th>Description</th>
<th>2010 WHO Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperm volume (ml)</td>
<td>1.5ml</td>
</tr>
<tr>
<td>Total sperm count (no./ejaculate)</td>
<td>39 million</td>
</tr>
<tr>
<td>Sperm concentration (10^9/ml)</td>
<td>15 million/ml</td>
</tr>
<tr>
<td>Progressive motility</td>
<td>32%</td>
</tr>
<tr>
<td>Total motility (PR +NP)</td>
<td>40%</td>
</tr>
<tr>
<td>Normal morphology (%)</td>
<td>4% (strict)</td>
</tr>
</tbody>
</table>

Sperm Morphology

Types of Assisted Reproductive Technology (ART) Treatment Cycles

Adapted from Speroff, L. Clinical Gynecology Endocrinology and Infertility. 2011: 248
Types of treatment cycles

- Ovulation induction (OI)
- Intrauterine insemination (IUI)
- In vitro fertilization (IVF)
- Frozen Embryo Transfer (FET)

Intrauterine Insemination (IUI)

- Bypasses the cervix and places sperm directly into uterus around the time of ovulation.
- IUI timed to take place just prior to ovulation using ovulation predictor kit or LH lab value.
In vitro fertilization (IVF)

- Method of assisted reproduction that allows eggs to be retrieved from the female’s body and either combined with sperm in a laboratory setting to create embryos or frozen unfertilized.
- Fertility medications help ovaries produce multiple oocytes
  - Controlled ovarian hyperstimulation (OHSS)
- Carefully timed steps for IVF treatment cycles
- Close monitoring required

https://www.asrm.org/uploadedFiles/ASRM_Content/Resources/Patient_Resources/Fact_Sheets_and_Info_Booklets/risksofivf.pdf

Ovarian Hyperstimulation Syndrome (OHSS)

- Hyper response to ovarian stimulation medication
- Prevention is goal through close monitoring
  - Ultrasound is used to closely monitor follicular growth response to medications
  - Estradiol levels
  - Medication dosage is based on patient response via ultrasound and estradiol monitoring results throughout cycle stimulation

In vitro fertilization (IVF)

- **Ovarian stimulation** (daily injections of fertility hormones)
- **Retrieval of oocytes/eggs**
- **Eggs and partner or donated sperm combined (through IVF) in lab**
- **Fresh embryo transfer or freezing of embryos/oocyte**
- **ICSI to assist in fertilization**

Transfer Options

**Embryo transfer**
- The ET procedure is the last one of the IVF process.
- Critically important to choose the best quality embryo.
- Either day 2 or 3 after oocyte retrieval

**Blastocyst transfer**
- Transferred on day 5 of oocyte retrieval.
- ↑ Chance of selecting best quality embryo for ↑ chance at pregnancy.
- ↑ eSET

**Freeze all**
- Center preference
- Option for those with OHSS
- Banking embryos for future use
Basic IVF Cycle Timeline

Review the Objectives

• Review the physiology of the reproductive endocrine system and how various hormones are regulated.
  – *Understanding reproductive hormones in the menstrual cycle will allow a greater appreciation for how infertility medications are utilized and prescribed.*
• Identify risk factors for infertility in both women and men.
  – *10% - 15% of couples in their reproductive years maybe affected by infertility*
• Explain appropriate diagnostic tests for the evaluation of an infertile patient.
  – *Approach evaluation in a systematic, expeditious and cost-effective manner*
• Discuss types of assisted reproductive technology (ART) treatment cycles.
  – *IVF is a treatment option that requires careful dosage of injectable infertility medications called gonadotropins*
Thank You

References

References

• Johnson MH. Robert Edwards: the path to IVF. Reproductive biomedicine online. 2011;23(2):245-262.

References

References