Fertility Clinical and Managed Care Considerations for the Specialty Healthcare Pharmacist

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DISCLAIMER

- The information within this CME/CE activity is for continuing education purposes only, and is not intended to substitute for the medical judgment of the healthcare provider. Recommendations for use of any particular therapeutic agents or methods are based upon the best available scientific evidence and clinical guidelines. Reference in this activity to any specific commercial products, process, service, manufacturer, or company does not constitute its endorsement or recommendation.
Ann Scalia has served as senior CES for Specialty Clinical Services at Walgreens since 2003. She brings more than 30 years of nursing experience in multidisciplinary settings, including reproductive endocrinology, ambulatory surgery, management, marketing and education. Ann is the author of multiple continuing education courses related to women’s reproductive health, and she has presented in a variety of educational venues nationally. Ann started her nursing career in the operating room and has been specialty certified in perioperative nursing since 1983.

Prior to working at Walgreens, Ann was the director of surgical services at Boston IVF, where she had experience transitioning an IVF facility into a fully accredited – AAAHC (Accreditation Association for Ambulatory Health Care) – freestanding ambulatory surgery center, specializing in IVF and gynecology procedures.

She is an active member of many well-respected fertility associations, including the ASRM, NPG, NEFS (New England Fertility Society), NENRM (New England Nurses for Reproductive Medicine), ONS and AORN (Association of periOperative Registered Nurses). Ann can be reached at ann.scalia@walgreens.com.
DISCLOSURES

- I do intend to discuss an off-label use of a product during this activity.

- I currently have the following relevant financial relations to disclose:
  
  - Employee of Walgreens Specialty Pharmacy
OBJECTIVES

1. Differentiate between the pathophysiology of the various types of infertility
2. Identify risk factors for infertility in both women and men
3. Explain appropriate diagnostic tests for the evaluation of an infertile couple
4. Identify monitoring parameters for a patient undergoing treatment for infertility
5. Discuss recommended appropriate non-pharmacologic and pharmacologic plans to address infertility
6. Identify barriers to adherence and compliance to treatment plan for infertility
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\(^1\)
- Earlier evaluation and treatment may be justified for women over the age of 35, based on medical history and physical findings\(^1\)
- Chance of conception decreases dramatically in women over the age of 35 years

INFERTILITY

- 6.7 million women in the US have impaired fertility\(^1\)
- 7.4 million women have used infertility services\(^1\)
- 1.5 million married women that are infertile
- 10% - 15% of couples in their reproductive years
- Estimated 4 million men in the US have reported infertility\(^2\)
- Data suggests up to 600,000 reproductive aged men may have azoospermia\(^2\)
- The male partner is either the sole cause or contributing factor in 40% of couples

\(^1\)CDC, Faststats Infertility
MILESTONES IN ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

- First baby Louise Brown conceived through ART born in England in 1978 (Steptoe & Edwards)
- First IVF baby Elizabeth Carr born in the U.S. in 1981 at Jones Institute in Norfolk
- First child conceived through donor egg born in 1984 (Trounson et al)

CDC collects the data from all fertility clinics in the United States and calculates standardized success rates for each clinic. This enables potential ART patient an idea of their average chances of success. 451 clinics performing assisted reproductive technology (ART) services in US are annually required to report success rates and outcomes. 163,038 ART cycles performed in the US resulted in 47,849 deliveries and 61,610 infants. 1.6% of all US births were conceived using ART.

OOCYTES

- Women are born with a finite number of eggs
- 6-7 million by 20 weeks gestation\(^1,2\)
- At birth, a woman has approximately 700,000 primordial follicles\(^2\)
- At puberty, only around 300,000 remain\(^1,2\)
- Ovarian reserve diminishes rapidly after age 35\(^2\)
- 400-500 eggs will ovulate during a woman’s reproductive years\(^1,2\)

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 CLINICAL CHARACTERISTICS

- Normal reproductive function involves:
  - Repetitive cycles of follicular development
  - Ovulation
  - Preparation of the endometrium for implantation if conception occurs\(^1,2\)
- Median cycle length is 28 days, with a normal range between 25 and 35 days\(^1,2\)
- Little cycle-to-cycle variability for majority of reproductive life\(^1\)
- Interval starts to decline between ages of 36-40 with significant variability before menopause\(^1\)

MENSTRUAL CYCLE CLINICAL CHARACTERISTICS

• 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

- Follicular Recruitment
- Selection of Dominant Follicle
- LH Surge
- Ovulation
- Implantation

**Follicular Phase**
- Day 1
- Day 7

**Luteal Phase**
- Day 14
- Day 21-22
  or
- Day 20-24

**Window of Receptivity**

Reference:
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 GONADAL AXIS

Estradiol (-) → Hypothalamus → GnRH → Pituitary Gland → LH/FSH → Ovary/Testis

Testosterone (+) → Pituitary Gland

Inhibin (-) → Hypothalamus

Estradiol (+) → Ovary/Testis
NORMAL HORMONAL CYCLE

- 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

- Estrogen has several effects on the pituitary. Early in the cycle estrogen inhibits FSH release but quickly rising levels later in the cycle serves 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
- The granulosa cells also produce a substance called inhibin which will contribute to the suppression of FSH
- 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 and luteinization and ovulation of the dominate follicle
- Early release of LH stimulates production of androgen synthesis by the theca cells in the ovary
- Stimulates proliferation of these cells and increases LH receptors on the granulosa cells
- 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
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

Days 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
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
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

FACTORS ASSOCIATED WITH INFERTILITY

- Abnormalities in production competent oocyte
- Abnormalities in reproductive tract transport oocyte, embryo and sperm
- Abnormalities in implantation process
- Abnormalities sperm production (male factor)
- Other conditions that may affect multiple components (immunological)
- Initial infertility evaluations focuses on these five major processes

DIRECTED TOWARD IDENTIFYING THE CAUSE(S)

• Approach evaluation in a systematic, expeditious and cost-effective manner

• Identify all relevant factors through a thorough history/physical

• Age results in changes in oocyte quantity and quality/function

• 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

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
- Represents the number of granulosa cells in growing 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 specific to rule out treatment

HORMONE REFERENCE RANGES

- Normal day 3 FSH level should be <10mIU/ml
- Early follicular phase E2 level <80 pg/ml
- Normal day 3 LH levels are 5 - 20 mIU/mL
  - LH levels are high in ratio to your FSH levels Could indicate polycystic ovarian syndrome (PCOS)
- Normal prolactin level is < 20 ng/ml
- AMH < 1.25ng/mL is highly sensitive for detecting women with DOR
- AACE New TSH Guidelines -
  - New target TSH reference range of 0.3 to 3.0
  - Hypothyroidism diagnosed before pregnancy AACE recommends TSH level not higher than 2.5 mIU/liter.

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

- Antral follicle count (AFC) is currently considered to be the best single predictor of ovarian response to stimulation in ART, and it can be used in clinical practice for pretreatment counseling purposes.
- The antral follicle count 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).

ANTRAL FOLLICLES/BASELINES

Reproductive Science Center, San Ramon, California
FEMALE REPRODUCTIVE SYSTEM

- Fallopian tube
- Ovulation
- Follicle
- Uterus
- Cervix
- Sperm
- Vagina
- Ovary
SEMEN ANALYSIS

- Semen analysis is the cornerstone of the laboratory evaluation of 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

On at least two occasions

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

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<th>2010 WHO Values</th>
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<td>20 million/ml</td>
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<td>&gt;14% normal –Kruger Strict Criteria/WHO 1999</td>
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TREATMENT STAGES

Treatment of Infertility

Oral Medication
clomiphene citrate

Natural intercourse
every other day
mid-cycle

Timed Intercourse
LH urine testing

IUI
1 day after + LH
Mid-cycle ultrasound
INTRAUTERINE INSEMINATION (IUI)
ADVANCED TREATMENT STAGES

Injectable Medication
hMG, uFSH and rFSH

TIMED INTERCOURSE
follicular monitoring
hCG injection

IUI
follicular monitoring
hCG injection

IVF
follicular monitoring
hCG injection
egg retrieval

Treatment of Infertility
IN VITRO FERTILIZATION

Process whereby a couple’s gametes (eggs and sperm) are fertilized in a laboratory setting and the embryos are placed back into a woman’s uterus.
OVULATION INDUCTION MEDICATIONS: TWO FOLD

Correct ovulatory dysfunction

- Irregular periods
- Irregular ovulation

Controlled ovarian hyperstimulation

- IUI
- IVF
- Donor Egg/Third Party

ASRM. Fertil & Steril. 2012;98(2):302
ANTI-ESTROGENS

- Initial treatment of choice for most anovulatory or oligo-ovulatory infertile women desiring pregnancy
- Most widely used anti-estrogen for treating anovulatory women is clomiphene citrate (CC)
- In ovulatory women, CC treatment increases GnRH pulse frequency
- Has estrogenic and antiestrogenic actions so give lowest dose possible due to antiestrogenic effects on cervical mucus and endometrium which are counterproductive to initiation of pregnancy

CLOMIPHENE CITRATE TABLETS, USP (CC)

- Clomiphene citrate is administered typically for 5 days starting on the 2nd to 5th day after the onset of spontaneous or progestin induced menses.
- Given in the early-mid follicular phase, it causes a rise in endogenous FSH level.
- Usual starting dose is 50mg daily increasing by 50mg increments in subsequent cycles until ovulation induced.
- Doses in excess of 100 mg/d are not approved by the US Food and Drug Administration (FDA).

CLOMIPHENE CITRATE TABLETS, USP (CC)

- Ovulation most often occurs from 5 to 10 days after a course of clomiphene citrate \(^1,^2\)
- Timed intercourse is therefore advised for a week from the 5\(^{th}\) day following end of CC administration\(^3\)
- Once ovulation has been established, each course of clomiphene citrate tablets USP should be started on or about the 5th day of the cycle \(^2\)
- If ovulation does not occur after three courses of therapy, further treatment with clomiphene citrate tablets USP is not recommended and the patient should be reevaluated \(^2\)

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The first human menopausal gonadotropins (HMG) were extracted from urine of post-menopausal women. After numerous purification techniques, there was still some LH in the final product. There was also batch-to-batch variation in potency. They were also given IM (intramuscularly).

Exogenous gonadotropins have been widely used since 1958.

The next generation of gonadotropins exhibited significant improvements in purification (less LH and less protein contaminants) but were still urinary based.

First urinary preparation containing only uFSH became available in 1983.

HISTORY OF GONADOTROPINS

- Recombinant DNA technology led to development of human recombinant FSH (recFSH)
- Genetically engineered hamster ovary cells produce pure human FSH
- Available in the form of follitropin alpha and follitropin beta since 1996
- No LH or other protein contaminants
- Subcutaneous route of administration
- Now available in ready to use pens that eliminate the need for reconstitution

THE ROLE OF GONADOTROPINS

- Indicated for women that do not respond to clomiphene citrate
- Indicated for use with ART-IVF to stimulate multiple follicles
- Act directly on the ovary
  - FSH stimulates follicle recruitment, growth, and maturation
  - LH supports development and maturation of the follicle
- Ovarian function must be documented
- Must be given by injection
- Careful monitoring and evaluation

MIDCYCLE FOLLICULAR ULTRASOUND MONITORING

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

ASRM. Fertil & Steril. 2012;98(2):302
Both hMG (uFSH) and recFSH products are called gonadotropins. They are used alone or in conjunction with one another in all ovulation induction and IVF fertility cycles.

RECOMBINANT (FSH only)
- Follistim® (follitropin beta injection)
- Gonal-f® (follitropin alpha injection)
- Gonal-f ® RFF (follitropin alpha injection)
- Gonal-f ® RFF Redi-Ject (follitropin alpha injection)

URINARY (hMG)
- Menopur® (menotropins for injection) (FSH/LH)
- Bravelle® (urofollitropin for injection purified)(FSH)

ROLE OF CHORIONIC (HCG)GONADOTROPIN

- Given as a “trigger” shot
- Simulates the LH surge for final oocyte maturation
- HCG causes eggs in the developing follicles to mature and detach from the wall of the follicle
- HCG is given the night of gonadotropin cessation and stays in the body for about 14 days
- Ovulation will occur within 36-40 hours after injection

CHORIONIC GONADOTROPIN [package insert]. Schaumburg, IL: APP PHARMACEUTICALS.; 2008
CYCLE TIMELINE

- GnRH agonist long protocol
  - leuprolide acetate

- Micro-dose or half-dose GnRH agonist short protocol
  - leuprolide acetate

- Possible birth control pills

- Progesterone

- Consult
- Day 1
- Ovulation
- Day 21
- Day 1
- Day 3

- Opportunities for Patient Education

- GnRH Antagonist
  - Ganirelix
  - Acetate
  - Cetrodile

- Human Chorionic Gonadotropin (HCG)
  - Novarel
  - Ovidrel PreFilled Syringe
  - Pregnyl

- Gonadotropin Stimulation Medication
  - Follistim
  - Gonal-fRFF
  - Gonal-f RFF Redi-ject
  - Gonal-f Multi-Dose
  - Bravelle
  - Menopur
  - Repronex

- Egg Retrieval
- Blastocyst Transfer

- Pregnancy Test

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ORAL CONTRACEPTIVES

- Oral contraceptive pills (OCP), aka birth control pills, may be prescribed to regulate a patient’s menstrual cycle
- In an IVF cycle, OCPs allow physician to manipulate the patient's cycle to fit into a set schedule and the make the treatment dates more predictable
- Combination hormonal OCPs
  - Progestin component of a combination pill prevents ovulation by inhibiting gonadotropin secretion of LH; also alters endometrium
  - Estrogenic component suppresses FSH
An agonist binds to a receptor and exhibits a desired response

GnRH agonists are used in IVF cycles to prevent a premature rise in LH preventing ovulation from occurring

When an agonist is given, first the pituitary is initially stimulated to release FSH and LH, but soon the gland becomes suppressed: “down regulation”

Once gonadotropin meds are added, the ovaries are stimulated to make multiple follicles, while the GnRH agonist suppresses the normal “one egg per month” process/ premature ovulation

Known as the “long protocol” that became the standard of care

Most commonly used is leuprolide acetate in various dosages

ROLE OF GONADOTROPIN RELEASING HORMONE (GnRH) ANTAGONIST

- An antagonist binds to a receptor and inhibits another molecule from binding to the receptor, thus inhibiting the desired response.
- GnRH antagonists are used in IVF cycles to prevent a premature rise in LH preventing ovulation from occurring.
- GnRH agonists are used to “suppress” or down-regulate the pituitary prior to administering gonadotropin medications.
- Known as the “long protocol” that became the standard of care.
- Most commonly used is leuprolide acetate in various dosages.

ROLE OF (GnRH) ANTAGONIST

- No stimulatory action on pituitary; acts by blocking the GnRH receptors on the pituitary gonadotrope and subsequent transduction pathway\(^1\)
- Immediate suppression (down regulation) of endogenous FSH and LH release
- Antagonists are started when lead follicle is 12-14mm or by CD 6
- Available as Ganirelix Acetate Injection or Cetrotide\(^\circledR\) (Cetrorelix)

ROLE OF CHORIONIC (HCG)GONADOTROPIN

- Given as a “trigger” shot
- Initiates the LH surge for final oocyte maturation
- HCG causes eggs in the developing follicles to mature and detach from the wall of the follicle
- HCG is given the night of gonadotropin cessation and stays in the body for about 14 days
- Ovulation will occur within 36-40 hours after injection
- Available as Generic Chorionic Gonadotropin for injection, USP (HCG ), Pregnyl, Novarel
ROLE OF PROGESTERONE

- Progesterone for luteal phase support of the endometrium is needed in stimulation cycles
- Used to build up lining of endometrium for successful implantation
- Many routes are available: vaginal gel, vaginal insert, vaginal suppositories, capsules, compounded micronized progesterone that can be used vaginally or orally, troches, and oil-based intramuscular (IM) injections available in various strengths
- Administration begins the day of egg retrieval and continues until pregnancy test

STRESS IN INFERTILITY

- Stress in the REI professional and patient are > other fields such as oncology or cardiology
INFLUENCING THE TREATMENT PLAN

- Age
- Insurance coverage
- Financial ability
- Schedule / career constraints
- Emotional / ethical concerns
- Awareness / assertiveness
PROFILE OF AN INFERTILITY PATIENT: UNDER STRESS

- $12,000 - $25,000 per cycle if no insurance coverage
- Success rates of approximately <50%
- Hormonal Roller Coaster
- Sense of loss and grief related to lack of fertility
- Marital strain
- Loss of intimacy
- Feelings of isolation
- Sense of loss of control
- Other common emotions of anger, fear and resentment
## FINANCIAL STATE: COVERAGE

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INFERTILITY PHARMACY CARE IS UNIQUE WITHIN SPECIALTY PHARMACY

- Providing effective fertility pharmacy is based on an acute care model with much shorter fulfillment timelines
- Fertility pharmacy involves high patient turnover. Only about 15 percent of prescriptions are "refill" with the clear majority (85%) being "new" RXs
- Response time for RX order filling is measured in hours or sometimes minutes
INFERTILITY PHARMACY CARE IS UNIQUE WITHIN SPECIALTY PHARMACY

- Relationships with reproductive centers are critical.
- Specialty fertility pharmacists know these physician protocols and are able to quickly receive these complex orders.
- Pharmacists often can rectify mistakes before they occur due to their knowledge of physician preferences and what components a proper fertility cycle "should" contain.
- Medication compliance is critical. One mistake could result in a cancelled cycle.
- Understand that these patients can be very emotional and treat them with empathy, support and provide additional education if necessary.
This program has been brought to you by The National Association of Specialty Pharmacy and its education provider The Specialty Pharma (session codes are located in your program guide on the activity sheet page)

*All users must complete the pre & post test to receive statement of credit.*
THANK YOU