Introduction

Infertility is a common disorder that affects 12% of married women in the U.S[1]. Approximately one-third of infertility can be attributed to the male, one-third to the female, and the remainder a combination of problems in both partners or unexplained.

- The most common female fertility factor is an ovulation disorder (the ovaries' inability to produce mature eggs or "ovulate" [release] an egg. Another common cause includes tubal infertility (blocked fallopian tubes preventing the egg and sperm from meeting).
- The most common male infertility factors include azoospermia (no sperm cells are produced) and oligospermia (few sperm cells are produced). The diagnosis of male factors is performed using a semen analysis. Severe male factor is usually treated using intracytoplasmic sperm injection (ICSI). Donor sperm is available commercially, if the couple can accept that the male partner will not be the "biologic father".

In infertile women who have blocked or absent fallopian tubes or whose partners have low sperm counts, in vitro fertilization (IVF) offers a chance at having a baby. In IVF, eggs are removed from the ovary under the guidance of ultrasound and mixed with sperm outside the body in a laboratory dish. These eggs fertilize in the dish and are transferred to the woman's uterus when they have become embryos [embryo transfer (ET)].

Gonadotropin Therapy

The hypothalamus and pituitary gland orchestrate the events leading to ovulation. The hypothalamus releases gonadotropin releasing hormone (GnRH), a messenger that tells the pituitary gland to release follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH primarily makes the follicle grow and produce increasing amounts of estrogen, which then signals the pituitary to shut down FSH production. A surge of LH triggers ovulation.

There are two classes of ovulation drug treatments available in the U.S., clomiphene citrate and human gonadotropins. Clomiphene citrate therapy is usually the first treatment step in anovulatory female infertility patients. However, clomiphene citrate can adversely affect the endometrial lining, and is not applicable for all type of infertility diagnoses.

Gonadotropin therapy usually follows clomiphene citrate therapy but can be the initial therapy in certain patients. This therapy stimulates eggs to mature and be released. Gonadotropins are either purified FSH or FSH/LH combinations. Since the 1980's, IVF programs have used gonadotropin stimulation to increase the number of oocytes and subsequently improve the pregnancy rate. Several side effects including ovarian hyperstimulation syndrome (OHSS), thromboembolic disease and multiple gestation are associated with these drugs used to induce ovulation.

The Division of Reproductive and Urologic Drug Products is assessing the current approval process for gonadotropin therapy. Previous clinical studies have used various clinical populations, methodologies and efficacy endpoints. However, the technology used in the treatment of infertility and the resulting clinical pregnancy rates have improved over the past 30 years as evidenced by the current statistics.[2] The Division is developing a guidance for industry that addresses clinical trial design and analysis for drug products that are seeking the indication of ovulation induction and multiple follicular development in assisted reproductive technology (ART). The Division would like to receive the Committee's input in this process. Enclosed is a briefing package for your consideration.

The briefing package includes:

- ♦ Background Information
- Bibliography
- Labels for Approved Gonadotropin Drug Products

The Division wishes the Committee to discuss the following:

- Study Population
  - The following populations are enrolled for ovulation induction:
    WHO Group I (hypogonadotropic hypogonadism)
    WHO Group II (chronic anovulation)

    Does the committee have any advice on these?

  - The following populations are enrolled for ART:
    Normal ovulatory (defined by serum progesterone levels) women
    WHO Group I (hypogonadotropic hypogonadism)
    WHO Group II (chronic anovulation)

    Does the committee have any advice on these?

    How do we take into account differences in the procedures?
    IVF
    ICSI
    Donor Oocyte

- Study Design
- **What study designs should be used?**
  Blinding
  double or assessor blind
  Comparators
  active or placebo

  Primary Efficacy Endpoint
  Discuss the advantages and disadvantages of the following as primary or secondary endpoints:
  Live birth rate
  Ongoing viable pregnancy (presence of a fetal heartbeat) rate
  Gestational sac development rate
  Rate of Positive ß-hCG
  Ovulation rate [as defined by serum progesterone level(s)]
  Follicular development rate (as defined by two or three criteria)

  How should the primary endpoint(s) be analyzed?
  For Ovulation Induction
  Intent-to-Treat Population
  Per protocol population

For ART
Per treatment initiation?
Per retrieval?
Per embryo transfer?

- Study Analysis

  How should success be defined?

  Superiority to comparator (placebo; active control)
  Equivalence to active comparator
  Non-inferiority to active comparator

- Safety Endpoint Questions

  Discuss the advantages and disadvantages of evaluating the following safety endpoint(s):

  Rate of ovarian hyperstimulation syndrome
  Rate of miscarriages
  Rate of multiple pregnancies
  Rate of ectopic pregnancies

References:

1. Misra,D., The Women's Health Data Book (Third Edition) 2001: 23 – 24.
2. Toner JP. Progress we can be proud of: U.S. trends in assisted reproduction over the first 20 years. Fertil Steril 2002: 78(5): 943- 950.