Induction Ovulation with Gonadotropins

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Introduction into clinical practice in 1961

Extracted from the urine of postmenopausal women (human menopausal gonadotropins [hMG])

Ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) bioactivity is 1:1

Central role in ovulation induction
Since 1996, recombinant human FSH (rhFSH, >99 percent purity) has been available.

Recombinant preparations are appealing due to:

• Ease of administration (subcutaneous rather than intramuscular)
• Purity
• Batch-to-batch consistency
Gonadotropin therapy:

- Exogenous gonadotropin: complex and expensive & are best carried out by experienced clinicians
- FSH, LH, HMG
- Assessment of fallopian tube patency before initiating
- High risk for OHSS
Candidates:

- PCOS women who have not ovulated or conceived with weight loss, clomiphene, or letrozole therapy

- Hypogonadotrophic anovulatory women with hypopituitarism or women with hypothalamic amenorrhea
• Pretreatment evaluation:

- Complete history and physical examination
- Laboratory testing
- Pelvic examination or a pelvic ultrasound to rule out ovarian cysts
- Semen analysis of the partner
- HSG
**Preparations**

**hMG OR FSH**

- No differences in clinical pregnancy or live-birth rates for rFSH and urinary-derived gonadotropins

- No differences in the rates of ovarian hyperstimulation syndrome (OHSS) between rhFSH and urinary-derived gonadotropins
• Hypogonadotrophic hypogonadal women need FSH & LH

• Long-acting rhFSH preparations are currently registered in some countries for use in in vitro fertilization (IVF)
**Protocols:**

✓ The aim of ovulation induction with gonadotropins: formation of a single dominant follicle

✓ Because ovarian sensitivity to FSH stimulation varies among individual women, specific treatment and monitoring protocols are needed to achieve development of a single follicle when exogenous gonadotropin is administered
In spontaneous cycles, this is achieved at the beginning of the cycle by a transient increase in serum FSH concentrations above the threshold value.

Concentrations then decrease due to negative feedback, preventing more than one follicle from undergoing preovulatory development.
In the conventional gonadotropin protocol, the starting dose of FSH is 150 international units/day.

This regimen is associated with a multiple pregnancy rate of up to 36 percent, and ovarian hyperstimulation occurs in up to 14 percent of treatment cycles.
In PCOS:

- Low-dose, step-up protocol
- Low-dose, step-down protocol
In PCOS:

- Low-dose, step-up protocol designed to minimizing excessive stimulation and the risk of development of multiple follicles
- Initial subcutaneous or intramuscular dose of FSH is 37.5 to 75 IU/day
- Dose be increased only if, after 14 days, no response is documented on ultrasonography
- 37.5 IU then are given at weekly intervals up to a maximum of 225 IU/day
- hCG can be given to trigger ovulation
✓ Low-dose, step-down protocol of ovulation induction mimics more closely the physiology of normal cycles

✓ Therapy with 150 IU FSH/day is started shortly after bleeding and continued until a dominant follicle (>10 mm) is seen on transvaginal ultrasonography

✓ Dose is then decreased to 112.5 IU/day followed by a further decrease to 75 IU/day three days later, which is continued until hCG is administered to induce ovulation
Monitoring:

- TVS to measure follicular diameter
- During late follicular phase
- Every two or three days
- If three or more follicles larger than 15 mm are present, stimulation should be stopped, hCG withheld, and use of a barrier contraceptive advised in order to prevent multiple pregnancies and ovarian hyperstimulation
Ovulatory triggers:

- hCG is given as an ovulatory trigger on the day that at least one follicle appears to be mature (follicle diameter of 18 mm)
- Both urinary and recombinant hCG preparations are available
  - 250 mcg of recombinant hCG appears to be equivalent to the standard doses of urinary hCG (5000 units)
  - GnRh Agonist
  - Recombinant LH
✓ Multiple gestation

✓ Ovarian hyperstimulation syndrome