Purpose: To provide sufficient background regarding various ovarian stimulation protocols for In Vitro Fertilization cycles.

Goal: To assist staff in understanding the various approaches to ovarian stimulation for IVF allowing for a more informed discussion with members undergoing treatment and to provide guidance to providers.

Detailed Steps/Screen Shots

<table>
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<th>TOPIC</th>
<th>NOTES</th>
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| 1. Background Information | • Ovarian stimulation for in vitro fertilization (IVF) cycles involves highly individualized protocols based upon:  
  – Age  
  – Ovarian Reserve  
    • Tests of ovarian reserve include baseline FSH and estradiol, levels of antimullerian hormone (AMH), antral follicle count  
    • Poor ovarian response (POR) may be defined by at least 2 of the following:  
      – Advanced maternal age (≥40) or any other risk factor  
      – A previous POR (≤3 oocytes)  
      – An abnormal ovarian reserve test (<5-7 antral follicles or AMH <0.5-1.1 ng/ml)  
  – Weight  
    • Obesity may warrant an increase in the initial gonadotropin dosage  
    • Previous response to gonadotropins  
    • The goal of ovarian stimulation is to recover a synchronous cohort of mature oocytes while minimizing the risk of complications such as ovarian hyperstimulation syndrome  
    • Response to stimulation may be characterized as high, intermediate, or low based upon the pattern of estradiol and follicular responses  
      – Low responder  
        • Basal FSH > 10 mIU/ml  
        • Estradiol > 90 pg/ml  
        • Reduced number of antral follicles  
        • Previous IVF cycle with peak estradiol < 900 pg/ml, retrieval of <5 mature oocytes, previous cancellation due to poor folliculogenesis (<4 dominant follicles)  
      – High Responder  
        • Peak estradiol > 3000 pg/ml  
        • > 20 follicles with a high preponderance of small to intermediate size follicles (<10mm-14mm) on the day of ovulation “triggering”  
    – Women with Polycystic Ovarian Syndrome (PCOS) are prone to hyperrespond and are at risk for multiple gestation and ovarian hyperstimulation syndrome |
• No one stimulation protocol has proven to be superior to another
  – Step-down: higher initial doses of FSH in the follicular phase followed by lower doses
    • Appears to result in greater follicular synchrony
  – Step-up: lower initial doses of FSH in the follicular phase followed by higher doses
    • May be useful for the patient who does not respond to initial lower doses
    • May be required in the face of excessive ovarian suppression following the use
      of oral contraceptives and/or GnRH analogues
  – Fixed dose: constant dose of FSH throughout the cycle
• Numerous gonadotropin products are available on the market
  – No one product has proven to be superior to another
  – Cost may vary considerably among various preparations
• GnRH agonists and/or antagonists are commonly utilized in conjunction with gonadotropin
  stimulation in order to
    – Improve the synchrony of the developing follicular cohort
    – Prevent a premature LH surge needed
    – Decrease cycle cancellation rates
• There are a variety of GnRH analogue protocols
  – GnRH agonists may be started in the late luteal phase of the cycle preceding the IVF cycle
    (long protocol) or in smaller doses just prior to the onset of stimulation (flare protocol)
  – GnRH antagonists may be initiated based upon a specific day following the onset of
    stimulation (fixed protocol) or based upon follicular development (flexible protocol)
• GnRH antagonists appear to yield comparable pregnancy rates compared to GnRH agonists while
  reducing the duration of stimulation and the total amount of gonadotropin utilization
  – A GnRH agonist may be utilized in lieu of hCG to induce ovulation in antagonist cycles
  – and may thus decrease the potential risk of ovarian hyperstimulation syndrome
  – Antagonist protocols may be beneficial for poor responders
• Oral Contraceptives
  – May enhance ovarian suppression and follicular synchrony
  – Used often as a cycle scheduling tool
• The addition of LH to the stimulation regimen is controversial
  – LH is beneficial for women diagnosed with hypogonadotropic hypogonadism
  – LH may be beneficial for women in the face of GnRH analogue suppression
  – LH may be administered in the form of urinary menopausal gonadotropins, recombinant
    LH or micro-dose hCG
• The duration of stimulation in a typical IVF cycle ranges from 8 to 14 days (average 10-12)
• There is no proven benefit to exceeding a total daily dose of FSH of 450 IU/day
  – Higher doses of gonadotropins, while perhaps decreasing the cycle cancellation rate, may
    adversely affect the clinical pregnancy and live birth rate
• Consideration should be given to minimal stimulation protocols
  – Aim to limit the number of mature oocytes obtained to < 8
  – Typically incorporate GnRH antagonist and rFSH 150 IU daily
  – Cumulative pregnancy rates need to be evaluated
  – Aneuploidy rates may be increased with excessive ovarian stimulation
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<th>2. Client/Target Population</th>
<th>• This guideline applies to all women undergoing ovarian stimulation for an in vitro fertilization cycle</th>
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<td>Clinical Management</td>
<td>3. Initial Evaluation for Protocol Determination • Complete history and physical including a history of response to any previous gonadotropin stimulation • Basal FSH, estradiol, antimullerian hormone levels and antral follicle count</td>
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<td>Medical Treatment</td>
<td>4. Medical Treatment • Before any intervention is initiated, preconception counseling should be provided emphasizing the importance of folic acid supplementation, lifestyle modification, especially weight reduction and exercise in overweight women, smoking cessation, and control of alcohol consumption (i.e., 1 or fewer drink equivalents per day) • Weight loss should be recommended as the first line therapy in obese women seeking pregnancy • Gonadotropin dosing should reflect optimal stimulation to achieve an acceptable number of mature oocytes while minimizing the risk of a hyperresponse. • Daily starting dose of FSH should be based upon the anticipated response with adjustments made thereafter based upon the individual response – Intermediate Responder: 225 – 300 IU/day – High Responder: 75-150 IU/day i. Women prone to a high response are excellent candidates for eSET and frozen embryo transfer cycles 1. High oocyte yield can be expected 2. A frozen transfer cycle may be beneficial in providing a uterine environment that is more conducive to implantation, given the likely high estrogen levels during a fresh stimulation cycle – Low Responder: 375 – 450 IU/ day – Either step-up (increasing the dose based upon response), step-down (decreasing the dose based upon response) or fixed (maintaining a constant dose) protocols are acceptable • Hyperresponse may be addressed by – The use of antagonist protocols with a GnRH agonist to induce ovulation – Withdrawing gonadotropin support prior to hCG (coasting) – Decreasing the ovulatory dose of hCG – Cycle cancelation prior to the administration of hCG – Cryopreservation of all ensuing embryos</td>
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5. **Best Practices and Medical Director Escalation**

- Provide preconception counseling, including a discussion of risks for multiple gestation with ovulation induction
- High response patients should be ideal candidates for elective single embryo transfer
- Consideration should be given to promoting a frozen embryo transfer cycle in lieu of a fresh transfer in the face of a hyperresponse, given the expected high levels of estrogen and possible altered uterine environment that may be detrimental to implantation
  - The risk of ovarian hyperstimulation syndrome may be reduced or its duration shortened by not transferring embryos on the fresh cycle
- Anticipated total gonadotropin dosing >4500 IU over a 10 day period (> 450 IU/Day) requires review by the medical director

6. **Case Example**

A 36 year old member presents with unexplained infertility of 2 years duration. She understands that an empiric trial of gonadotropin/IUI yields a low chance for a successful outcome and is not cost effective. She agrees to move forward with an IVF cycle. Her initial evaluation reveals a BMI of 22, FSH=6.5, estradiol = 45, AMH = 1.8 and an antral follicle count of 8 on each ovary. In the absence of any signs of PCOS or diminished ovarian reserve, a long GnRH agonist protocol utilizing 225 IU of FSH as the starting dose in a step-down fashion to 150 IU was chosen. Following successful ovarian suppression, stimulation was begun. Following 6 days of stimulation, few follicles > 10 mm were noted and her estradiol was 320 pg/ml. Instead of decreasing her dose, the FSH was increased to 300 IU with little change in her response 3 days later. The cycle was cancelled. Two months later she made another attempt again with a long GnRH agonist protocol, but this time starting with 375 IU as the initial dose. On day 6 of stimulation, she had over 20 follicles all < 12 mm in diameter and an estradiol of 2600 pg/ml. The FSH dose was lowered to 75 IU. After an additional 3 days of stimulation, she had 10 follicles that measured >15 mm in diameter and an estradiol of 4800 pg/ml. Gonadotropin therapy was withheld (she was coasted) but her estradiol climbed to over 6000 pg/ml. She was advised of the risk for ovarian hyperstimulation syndrome and the alternatives of cancelling the cycle, proceeding with an egg retrieval but cryopreserving all the resulting embryos for a later frozen embryo transfer cycle. Due to a lack of insurance coverage for embryo cryopreservation as well as a limited lifetime benefit maximum, she elected to cancel the cycle. Two months later, she initiated her third IVF stimulation attempt. This time, she was started on FSH 300 IU and utilized a flexible GnRH antagonist protocol. She mounted a robust follicular response with over 20 follicles, 12 of which were 18 mm or greater in diameter. Her estradiol level peaked at 3800 pg/ml. Although she was again advised of the potential for ovarian hyperstimulation, she also understood that utilizing a GnRH agonist instead of hCG to trigger ovulation would reduce the likelihood of this complication. She underwent an egg retrieval which yielded 18 oocytes, 12 of which were mature. Ten eggs fertilized successfully with standard fertilization and 8 continued to develop to the blastocyst stage. She elected to participate in a novel benefit program that allowed her to undergo an elective single embryo transfer and to cryopreserve the remaining good quality blastocysts for use in a subsequent frozen transfer cycle at no additional cost to her should the fresh cycle not be successful. This member had a positive pregnancy test and an ultrasound later confirmed the presence of a viable singleton gestation. She plans to utilize a cryopreserved embryo sometime in the future when she is ready to expand her family.
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