INDUCTION OF OVULATION FOR TREATMENT OF INFERTILITY

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DIAGNOSIS OF ANOVULATION

• Ovulatory disorders: 18-25% of infertile women
• Women with irregular, unpredictable, or infrequent menses do not require specific diagnostic tests to prove what is already obvious
• BBT recordings having no sustained interval of temperature elevation preceding the onset of menses strongly suggest anovulation

DIAGNOSIS OF ANOVULATION

• Serum progesterone < 3ng/mL implies anovulation, as long as it is appropriately timed
  – Simplest, most common, objective and reliable
  – Normal ovulatory cycle 25-35 days
  – Luteal phase lasting approximately 14 days
  – Ideal timing of serum progesterone level should be one week before the expected menses
CLASSIFICATION OF OVULATORY DISORDERS

• WHO Group I: Hypogonadotropic Hypogonadal Anovulation
  – 5-10% of anovulatory women
  – Low or low-normal FSH
  – Low serum Estradiol levels
  – Absent or abnormal hypothalamic GnRH secretion or pituitary insensitivity to GnRH
  – Examples: hypothalamic amenorrhea (physical, nutritional, emotional, weight loss, excessive exercise, anorexia nervosa), Kallmann syndrome, and isolated gonadotropin deficiency

CLASSIFICATION OF OVULATORY DISORDERS

• WHO Group II: Eugonadotropic Euestrogenic Anovulation
  – 75-85% of anovulatory women
  – Normal serum FSH levels
  – Normal Estradiol levels
  – Normal or elevated LH concentrations
  – PCOS is most common example
  – Screen for Type 2 diabetes before treatment
  – Weight loss best initial treatment for those who are obese
  – Can restore ovulatory function by itself

CLASSIFICATION OF OVULATORY DISORDERS

• WHO Group III: Hypergonadotropic Anovulation
  – 10-20% of anovulatory women
  – Elevated FSH concentrations
  – Most have amenorrhea
  – Classical example: premature ovarian failure
  – Few respond to treatment aimed at ovulation induction
CLASSIFICATION OF OVULATORY DISORDERS

- Hyperprolactinemic Anovulation
  - 5-10% of anovulatory women
  - Inhibits gonadotropin secretion
  - Low to low-normal serum FSH concentrations
  - Low serum Estradiol levels
  - Most have oligomenorrhea or amenorrhea
  - Hypothalamic-pituitary imaging is indicated to exclude mass lesion if hyperprolactinemia can't be attributed confidently to coexisting hypothyroidism

PRETREATMENT EVALUATION

- All anovulatory women deserve at least some preliminary evaluation
- Minimum requirement
  - Serum TSH and serum prolactin
    - Both require further evaluation and specific treatment
  - Endometrial sampling merits consideration due to chronic anovulation risk for endometrial hyperplasia
- Obese anovulatory women with PCOS
  - Screen for impaired glucose tolerance
  - 35% exhibit impaired glucose tolerance
  - 7-10% meet criteria for Type 2 diabetes mellitus
  - Screening semen analysis
    - Prudent as male factors are a contributing cause in 20-40% of infertile couples
  - Preliminary HSG and transvaginal U/S
    - Recommended when medical history or physical exam raises suspicion for co-existing uterine or tubal infertility factors, for women over age 35, and when OI requires exogenous gonadotropins
TREATMENTS

- Best initial treatment for obese anovulatory women is weight loss
  - Dropping 5-10% of body weight often restores ovulatory cycles in obese anovulatory women with PCOS
  - In one study...
    - 90% who lost an average of 10kg/m2 resumed spontaneous ovulation and 78% ultimately achieved pregnancy, 27% without other interventions
  - BMI < 27 is reasonable goal

CLOMIPHENE CITRATE

- 80% of anovulatory women treated with clomiphene citrate achieve ovulation and half of those conceive
- Non-steroidal triphenylethene derivative
- Selective estrogen receptor modulator (SERM)
  - Both estrogen agonist and antagonist properties
  - Usually acts as an antagonist or antiestrogen
  - Only acts as an agonist when estrogen very low

CC PHARMACOLOGY

- 85% eliminated within a week
- Racemic mixture of enclomiphene (62%) and zuclomiphene (38%)
  - Enclomiphene more potent and responsible for ovulation induction actions
  - Enclomiphene - short half-life
  - Zuclomiphene remains detectable for weeks after a single dose and can accumulate over a series of cycles
CC MECHANISM OF ACTION

• Unlike estrogen, clomiphene binds to nuclear estrogen receptors for an extended interval of time
  – Depletes receptor concentrations by interfering with receptor recycling
  – Receptor depletion prevents accurate interpretation of circulating estrogen levels at the hypothalamic level
  – Circulating estrogen levels perceived as lower than they truly are

CC MECHANISM OF ACTION

• Reduced negative estrogen feedback triggers normal compensatory mechanisms that alter the pattern of GnRH secretion and stimulate increased pituitary gonadotropin release which, in turn, drives ovarian follicular development
  • At the pituitary level, clomiphene also might increase the sensitivity of gonatrophs to GnRH stimulation

CC PERIPHERAL ACTIONS

• Quality and quantity of cervical mucus production can be decreased
  – Cervical mucus rarely monitored in clinical practice
  – IUI bypasses the cervix altogether
• Likely, inhibits endometrial growth (for some)
  – Only significant if peak preovulatory EMS <5-6mm
• No clinically relevant direct effects on the ovary or embryo
CC CLINICAL INDICATIONS

• Primarily for WHO Group II
• Typically ineffective for WHO Group I
  – Low endogenous estrogen already not stimulating increased FSH secretion so adding additional negative feedback from clomiphene rarely succeeds
• Short Luteal Phase (poor luteal function)
  – Associated with abnormally low follicular phase levels of FSH
  – CC effective for increasing FSH levels
  – Progesterone levels higher in CC induced cycles
    – Preovulatory follicular development optimized
    – Multiple corpus lutea

CC IN OVULATORY WOMEN

• Efficacy of CC in unexplained infertility
  – Optimized follicular development
  – Superovulation of more than a single ovum
• Empiric treatment is most effective when combined with IUI, in an effort to increase the numbers of both ova and sperm

CC TREATMENT REGIMENS

• Ovulation, conception, and pregnancy outcomes similar when starting anywhere between CD 2-5
• No clinical or laboratory parameter has proven utility for predicting the dose of clomiphene needed to induce ovulation
• Most women who respond to CC will respond to either 50mg (52%) or 100mg (22%)
  – 150mg (12%),
  – I do not go beyond 150mg for treatment
MONITORING REGIMEN

- Serum progesterone > 3ng/mL
  - Speroff recommends between CD22 and 25
- LH surge typically occurs 5-12 days after treatment ends
  - Most often on day 16 or 17 when CC given 5-9
  - Ovulation occurs 14-26 hours after surge detection (almost always within 48 hrs)

CLOMID CHECK/BASELINE US

- Prudent to postpone further treatment when symptoms lead to discovery of a large cyst or grossly enlarged ovaries
- However, routine baseline physical examination or ultrasonography is unnecessary

CC RESULTS

- Induce ovulation in 70-80% of properly selected women
- Women with amenorrhea more likely to conceive than women with oligomenorrhea
  - Oligo women more likely to have other co-existing infertility factors
- Overall cycle fecundability approximately 15%
  - As high as 22% if no other factors (comparable to normal fertility rates)
- Cumulative pregnancy rates of 70-75% can be expected over 6-9 cycles of treatment
  - When pregnancy not achieved within 3-6 cycles, further investigation should be expanded if not already completed
  - Prolonged treatment with CC is inappropriate for women over age 35y/o
CC SIDE EFFECTS

• Common side-effects
  – Transient hot flushes (usually limited to treatment interval) - 10-20% of women
  – Mood swings
• Less common side-effects
  – Headache, breast tenderness, pelvic pressure or pain, nausea
• Visual disturbances (1-2%)
  – Discontinue for persistent “afterimages” (palinopsia) or for light sensitivity (photophobia)

CC RISKS

• Multiple Pregnancy - 7-10%
  – Triplets - 0.3-0.5%
  – Quadruplets - 0.3%
  – Quintuplets - 0.1%
  • Treat with the lost dose to achieve ovulation; higher doses do not improve results and only increase risk of multiples
• No evidence of increased risk for birth defects, developmental delay or learning disabilities
• OHSS is rare and usually mild
• No increased risk of ovarian or breast cancer has been established, but prolonged treatment should be avoided

ADJUVANT AND COMBINATION TREATMENTS

• Clomiphene and Glucocorticoids
• Clomiphene and HCG
• Clomiphene and Metformin
• Preliminary Suppressive Therapy
CLOMIPHENE AND HCG

- Premise: CC may be successful in stimulating the emergence of a preovulatory follicle but ultimately fail to trigger an endogenous LH surge and induce ovulation
- HCG administered too early causes atresia
- Commonly administered when lead follicle reaches 18-20mm
  - However, studies indicate that peak preovulatory diameter when CC is successful range between 18 and 30mm (mean 25mm)

CLOMIPHENE AND HCG

- Insemination timing
  - IUI usually performed on day after detection of spontaneous LH surge using OPK
  - Ovulation generally occurs 14-26hrs after urinary LH surge
  - In some women, LH peak doesn’t reach detection threshold of urinary LH surge kit even though ovulation occurs
    - hCG useful for timing IUI in these women

CLOMIPHENE AND HCG

- Ovulation occurs 36-46hrs after hCG injection
- IUI usually performed 36hrs after injection
**CC AND METFORMIN**

- Biguanide oral insulin-sensitizing agent
  - Primarily reduces hepatic gluconeogenesis
  - Decreases intestinal absorption of glucose
  - Increases peripheral glucose uptake and utilization
- Can increase ovulation rates in some women
  - Insulin resistance and hyperinsulinemia are common features of PCOS
    - Contributing cause of hyperandrogenism and chronic anovulation
  - Anovulatory infertile women with PCOS and hyperinsulinemia are typically more resistant to clomiphene treatment

**CC AND METFORMIN**

- Fasting insulin concentrations and glucose-insulin ratios do not predict response to metformin
- Metformin appears most effective in patients who also respond to clomiphene
- Largest trial
  - Live birth rates
    - Clomiphene 22.5%
    - Metformin 7.2%
    - Clomiphene and Metformin 26.8% (not statistically significant)
  - Metformin treatment did not reduce the dose of clomiphene required to induce ovulation

**CC AND METFORMIN**

- Combined treatment with metformin and clomiphene deserves consideration in women who prove clomiphene resistant before proceeding to ovarian drilling or treatment with gonadotropins
- Side effects: nausea, vomiting, abdominal cramps, diarrhea
- Start at 500mg and increase weekly to 1500-2000mg as tolerance allows
AROMATASE INHIBITORS

- Anastrozole and Letrozole
  - Triazole (antifungal) derivatives
  - Potent, competitive, nonsteroidal inhibitors of aromatase (enzyme that catalyzes the rate-limiting step in estrogen production)
  - Blocks estrogen production in the periphery and in the brain
    - Compensatory increase in pituitary gonadotropin secretion that stimulates ovarian follicular development
  - CC depletes central estrogen receptors, whereas letrozole decreases estrogen production directly

LETRAZOLE

- In theory...
  - Estrogen production in growing follicles increases promptly
  - Quicker negative feedback on gonadotropin secretion
  - Restores the mechanism that normally serves to select and promote development of a single dominant follicle
  - Negative feedback takes longer with CC due to depletion of estrogen receptors

LETRAZOLE

- Transient accumulation of androgen substrate
  - May increase FSH receptor expression and production of IGF-1
    - Amplifying the actions of FSH
**LETROZOLE TREATMENT REGIMENS**

- Most commonly 5mg CD 3-7
- Other described regimens include
  - 2.5mg for 5-10 days starting on CD1
  - Optimal dose probably ranges between 5mg and 7.5 mg daily

**RESULTS WITH LETROZOLE**

- In sum, the available data suggest that aromatase inhibitors should be used as a first-line treatment for ovulation induction in women with PCOS
- Some studies are even indicating it as a replacement for CC in patients with unexplained infertility

**EXOGENOUS GONADOTROPINS**

- For nearly 30 years, human menopausal gonadotropins (hMG, menotropins) were only available exogenous gonadotropins
  - Urine of postmenopausal women
  - 75IU of FSH and 75IU of LH per ampule
  - Initially required IM use due to antigenic urinary proteins
  - Now more highly purified
    - Menopur administered subcutaneously
GONADOTROPIN PREPARATIONS

- Approx 30 years ago, more purified FSH preparations (urofollitropin) - Bravelle
  - 75IU of FSH
  - Contain less than 0.001IU of LH
  - Very low antigenic urinary protein
  - Administered subcutaneously

GONADOTROPIN PREPARATIONS

- Approx 20 years ago, recombinant FSH created through genetic engineering
- Shorter half-life than FSH derived from human urine but stimulate estrogen secretion as or even more efficiently
  - Absence of urinary proteins
  - More consistent supply
  - Less batch-to-batch variation in biologic activity
- Follitropin alpha - Gonal F
- Follitropin beta - Follistim
  - Subtle differences in structure, but functionally the same

INDICATIONS FOR GONADOTROPIN TREATMENT

- Hypogonadotropic Hypogonadism
  - Menotropins is drug of choice
    - Contains both FSH and LH
      - Follicular growth and oocyte maturation can be successfully stimulated with FSH alone
      - However, LH required for normal steroidogenesis, luteinization, and ovulation
      - Endogenous LH levels typically inadequate
    - Unifollicular ovulation is the goal
      - Otherwise normally fertile and high risk for multiple pregnancy
HYPOGONADOTROPIC HYPOGONADISM

- Luteal Phase Support
  - Supplemental hCG (2000-2500IU every 3-4 days)
  - OR progesterone
  - Generally needed to compensate for low levels of endogenous LH secretion that can prove insufficient to support normal luteal function
  - Supplemental hCG also increases risk for OHSS, so empiric progesterone is obvious alternative

CLOMIPHENE-RESISTANT ANOVULATION

- Who Group II generally have normal FSH levels and normal to high LH levels
- Treatment superimposed on erratic endogenous FSH/LH secretion
- FSH treatment alone - theoretical advantage
  - Avoids amplifying endogenous LH hypersecretion
  - Decreased chance of OHSS

CLOMIPHENE-RESISTANT ANOVULATION

- PCOS women generally respond to relatively low doses
- The therapeutic range can be extremely narrow with doses only slightly higher than those proving ineffective causing OHSS
- Unifollicular ovulation remains the objective
- Risk of OHSS and multiple pregnancy greater than in WHO Group I
UNEXPLAINED INFERTILITY

- Superovulation most effective when combined with IUI
- Risk of multiple pregnancy even greater than clomiphene-resistant anovulatory women

GONADOTROPIN TREATMENT REGIMENS

- Safe use of exogenous gonadotropins depends heavily on the experience and clinical judgment of the treating clinician
  - Direct relationship between BMI and dose requirement
  - However, dose threshold can’t be predicted reliably

- Initial attempts to induce ovulation should begin with a low daily dose (75IU daily) in a step-up treatment regimen
  - Estradiol level with/without ultrasonography after 4-7 days of stimulation
    - Dose of gonadotropins maintained or increased
  - Once serum estradiol level begins to rise, ultrasound to determine size and number of developing follicles is essential every 1-2 days
    - hCG to trigger ovum release when lead follicle reaches 16-18mm
    - Ovulation expected to occur 36-48hrs later
GONADOTROPIN TREATMENT REGIMENS

- PCOS often exquisitely sensitive to low doses of gonadotropin stimulation
- **Low-slow** treatment regimen starting 37.5-75IU daily with small increments and longer duration of stimulation
  - Most stimulations span interval of 7-12 days but low-dose in PCOS can take longer
  - Insulin-resistant women may be less sensitive to gonadotropins
    - Metformin treatment before and during stimulation can help improve response, limit the number of smaller developing ovarian follicles, and reduce the likelihood of cycle cancellation for excessive stimulation

GONADOTROPIN TREATMENT REGIMENS

- **Sequential** treatment with clomiphene and gonadotropins
  - Standard course of clomiphene 50-100mg daily
  - Followed by low dose FSH or hMG (75IU daily) beginning on the last day of clomiphene or the next day
  - Lower total dose/duration of gonadotropins with cycle fecundity approaching gonadotropins alone

MONITORING GONADOTROPIN THERAPY

- Achieve ovulation
- Avoid ovarian hyperstimulation
- Minimize risk of multiple pregnancy
- Must monitor gonadotropin therapy with serial estradiol levels and ultrasonography
SERUM ESTRADIOL LEVELS

- Gonadotropins generally given 5-8pm
- Serum estradiol levels usually obtained early morning
- Follicles <10mm produce relatively little measurable estrogen
- Larger follicles secrete progressively more as they grow and approach maturity
- E2 levels rise at a constant exponential pace
  - Doubling every 2-3 days over the days before peak follicular development is achieved
  - A shallower or steeper slope suggests the need to increase or decrease the level of stimulation

SERUM ESTRADIOL LEVELS

- In a natural cycle
  - E2 levels peak between 200-400pg/mL just before the LH surge
  - Comparable levels of E2 should be expected in gonadotropin-stimulated cycles, for each mature follicle observed
  - Cycle fecundity increases with E2 levels
  - But so does risks of
    - Multiple pregnancy
    - Ovarian Hyperstimulation
  - Best results are generally obtained when E2 peaks between 500 and 1500pg/mL with pregnancies uncommon at levels below 200pg/mL

ULTRASONOGRAPHY

- In a normal ovulatory cycle
  - Recruited cohort of antral follicles can be identified by CD 5-7
  - Dominant follicle emerges by CD 8-12
  - Grows approximately 1-3mm per day thereafter
    - Most rapidly over the 1-2 days immediately preceding ovulation
  - Measures approx 20-24mm when LH surge occurs
  - Lesser follicles rarely exceed 14mm
ULTRASOUND

- Likelihood of ovulation increases with follicular diameter
  - <14mm occasionally
  - 15-16mm 40%
  - 17-18mm 70%
  - 19-20mm 80%
  - >20mm virtually all
- hCG should not be administered when the risk of multiple ovulation is high and the goal of treatment is unifollicular ovulation

ULTRASOUND

- Stimulation cycles in presence of ovarian cysts are often less successful
  - Possibly due to errors in interpretation of U/S
  - Many believe that suppressive therapy with OCPs speeds the regression of residual ovarian cysts
    - There is no evidence that such treatment is more successful than observation alone
- Endometrial thickness
  - Few pregnancies result from cycles in which endometrial thickness is less than 7mm on the day of hCG-induced ovulation

RESULTS OF GONADOTROPIN TREATMENT

- Induces ovulation in over 90% of WHO group I/II women
- WHO group I - 25% cycle fecundity -> 90% cumulative pregnancy rate after 6 cycles
- WHO group II - 5-15% cycle fecundity -> 30-60% cumulative pregnancy rate
  - Poorer prognosis for hyperandrogenic chronic anovulation
### RESULTS OF GONADOTROPIN TREATMENT

**Multiple Pregnancy**
- 1.25% of spontaneous pregnancies
- 5-8% of clomiphene pregnancies
- 25% of gonadotropin pregnancies
- Monozygotic twinning
  - 0.3-0.4% normal frequency
  - 3-fold increase using exogenous gonadotropins

**Spontaneous Miscarriage**
- 20-25% in gonadotropin-induced pregnancies
  - Moderately higher than the 15% general population
- There is no evidence that gonadotropin therapy is associated with any increased prevalence of congenital anomalies

### Risks - Multiple Pregnancy
- Risk of multiples increases with serum E2 concentrations, the total number of developing ovarian follicles, and with decreasing maternal age, but does not correlate well with the number of larger preovulatory follicles
- hCG should be withheld when E2 rises above approximately 900-1400pg/mL or U/S reveals more than 4-6 follicles larger than 10-14mm
  - This would cancel up to 1/3 of exogenous gonadotropin-stimulated cycles
- Multifetal pregnancy reduction is an effective management tool for the complication of high-order multiple pregnancy
OVARIAN HYPERSTIMULATION SYNDROME

- Occasionally observed in clomiphene cycles
- Rare cases in spontaneous pregnancies (generally with supraphysiologic concentrations of hCG -> multiples and molar pregnancies)
- Recurrent OHSS can be associated with mutation in the FSH receptor resulting in loss of ligand specificity that permits activation by hCG

OHSS

- Normally self-limited and resolves spontaneously within several days, but can be severe
- Increased capillary permeability -> fluid shift from intravascular to extravascular spaces -> possibly from increased ovarian secretion of VEGF

OHSS RISK FACTORS

- Young age
- Low body weight
- PCOS
- Higher doses of gonadotropins
- Previous OHSS
- High serum estradiol levels
- Large number of developing ovarian follicles
- Use of supplemental doses of hCG for luteal phase support
MILD OHSS

- Characterized by: ovarian enlargement, lower abdominal discomfort, mild N/V, diarrhea, abdominal distention, occurs in 1/3 of superovulation cycles
- Treated with oral analgesics and counseling for s/s of progressive illness
- Avoid intercourse due to risk of ovarian rupture

OUTPATIENT MANAGEMENT

- Persistent or worsening symptoms or ascites signal progressing illness
- Additional treatment with anti-emetics and more potent oral analgesics
- Outpatient management must include monitoring of daily weights and urinary frequency
- Serial clinical exam to detect ascites and lab evaluation of hematocrit, electrolytes, and serum creatinine

OUTPATIENT MANAGEMENT

- Oral fluid intake no less than 1L/day
- Electrolyte supplemented commercial drinks to help maintain electrolyte balance
- Avoid strenuous physical activity to avoid torsion -> but no bedrest due to VTE risk
- Weight gain > 2lbs daily and decreasing urinary frequency require prompt clinical and laboratory re-evaluation
- Pregnant women with OHSS merit close monitoring as rapidly rising hCG levels increase risk for progression to severe illness
SEVERE OHSS

- Uncommon but not rare - 1% incidence
- Severe pain
- Rapid weight gain
- Tense ascites
- Hemodynamic instability
- Respiratory difficulty
- Progressive oliguria
- Laboratory abnormalities
- Hypotension from intravascular volume depletion
- Oliguria from reduced renal perfusion from low vascular volume and/or tense ascites
- Dyspnea from ascites or hydrothorax

SEVERE OHSS

- Hemoconcentration, reduced peripheral perfusion, and inactivity increase risk of thromboembolism
- Severe OHSS patients should be observed and treated in an inpatient setting

THE END