Case Study 1

- 25 y, Oligomenorrhea with hirsutism, male factor infertility
- Plan Femara ovulation induction with IUI
- Femara 7.5 mg; (was resistant to 2.5 and 5 mg)
- Day of trigger: E2 800
- US: 17, 18, 19, 20
- Counseled about cancellation
- Two weeks later, patient called with a positive pregnancy test

Case Study 1

- OB Scan: quadruplets
Fertility Treatments and Multiple Births in the United States

Annette D. Kalkundi, M.B., B.S., M.P.H., Denise J. Jamieson, M.D., M.P.H., Howard W. Jones, Jr., M.D., Dorothy M. Klein, M.D., M.P.H., Mario F. Galli, Ph.D., Mauricio Macaluso, M.D., Dr.P.H., and E.T. Addai, M.D.

N ENGL J MED 369:23 NEJM.ORG DECEMBER 5, 2013
IVF: Singleton, twins, Triplets

Principles of safe ovulation induction

- Understand the diagnosis
- Optimize pregnancy rate
- Reduce multiple pregnancies, specially high order multiple gestations
- Reduce the risks of ovarian hyperstimulation syndrome

Anovulation

- Anovulation is the most common cause of female infertility
- Clinically:
  - Typically associated with amenorrhea or oligomenorrhea
- Ovulation:
  - Monthly menses
  - Moliminal symptoms: breast tenderness and dysmenorrhea
How to diagnose anovulation

- Methods of diagnosis of anovulation:
  - BBT
  - Cervical mucus
  - Serum progesterone
  - Endometrial biopsy
  - LH urine testing
  - Mid-follicular ultrasound

Body basal temperature

- Increased body temperature by 0.6 F
  - Before ovulation < 98 F
  - After ovulation more than 98 F

- At least 10 days in length
- Cheapest method but not often used
- BBT charts
Serum progesterone

- Mid to late luteal phase: day 21
- Greater than 3 ng/mL
- Problem with pulsatile nature (pulsatile LH)

Endometrial biopsy: rarely used

Presumptive signs of ovulation

- LH testing
  - Detection of LH surge in the urine
  - Ovulation occurs 24 hours after LH peak
  - 7% false positive (no ovulation on endometrial bx)

- Ultrasound monitoring:
  - Detection of pre-ovulatory follicle: 20-25 mm in diameter

Cervical mucus

- Cervical mucus: Cheap and effective

<table>
<thead>
<tr>
<th>Feeling</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Dry, rough and itchy or nothing felt</td>
<td>Nothing seen</td>
</tr>
<tr>
<td>2- Damp</td>
<td>Nothing seen</td>
</tr>
<tr>
<td>3- Damp, yellowish, or sticky</td>
<td>Mucus is thick, creamy, whitish,</td>
</tr>
<tr>
<td>4- Wet, slippery, smooth, stretchy</td>
<td>Mucus is transparent, like raw egg elastic, liquid, watery, or reddish</td>
</tr>
</tbody>
</table>
Principles of Ovulation induction

1. Get an accurate diagnosis:
   - WHO classification:
     - WHO I: Hypogonadotropic hypogonadism
     - WHO II: Eu-estrogenic ovulatory function
     - WHO III: Hypergonadotropic Hypogonadism

Initial work up

- TSH, Prolactin
- FSH and estradiol
- AMH
- If indicated:
  - Androgens: free and total T
  - Pelvic ultrasound (PCO ovaries)

WHO I: Hypogonadotropic Hypogonadism

- Most common cause: functional

- Other causes
  - Infiltrative disease such as lymphoma histiocytosis
  - Pituitary disease: prolactinoma, Sheehan, Cushing, acromegaly, and other tumors
Hypothalamic amenorrhea

- Three main causes: “energy deficit”
  - Stress
  - Weight loss
  - Exercise
- Female athlete triad: low energy availability, amenorrhea, and osteoporosis
- Suppression of GnRH

Hypothalamic amenorrhea

- Hormonal profile
  - Low estradiol
  - Low or normal FSH and LH
  - No response to Provera challenge test
- MRI indicated if presence of neurological symptoms
- Ferritin level to rule out hemochromatosis

Treatment options

- Life style modifications
- If no success: gonadotropin ovulation induction and luteal support
- Clomid or other antiestrogen are usually not effective because of the pituitary suppression
Case study 2
- 35 years old, G0P0 Amenorrheic for many years.
- FSH <0.2, LH < 0.2 AMH: 3
- Plan
- FSH ovulation induction:
  - After 13 days of Stimulation:
    - E2 level Unknown, patient could not afford
    - US: 17mm, 16, 14, 13,13,13
    - Trigger ovulation

Case study 2
- Quintuplets

WHO III: Hyperandrogenic Hypogonadism
- Ovarian insufficiency and ovarian failure
  - Genetic
  - Autoimmune
  - Chemo therapy/radiation
  - Surgical
  - Infectious (TB)
WHO III: Hyperandrogenic Hypogonadism

- Ovarian insufficiency: (Premature ovarian failure)
  - Results from follicular depletion
  - Before age 40
  - Amenorrhea for 4 months or more
  - FSH: two levels 1 months apart in menopausal range
- Causes: 90% idiopathic
- FMR1 mutation, anti 21 hydroxylase antibodies and Karyotype

Diagnosis of ovarian insufficiency

- Elevated FSH, Normal or low Estradiol
- Very low AMH
  - If Day 3 FSH is normal, but Estradiol is high (above 50), repeat, and always get an AMH
- Treatment: very poor prognosis, likely need IVF with donor oocytes
- 5-10% lifetime spontaneous pregnancy

WHO II: Euestrogenic ovulatory function

- Most common causes:
  - PCOS: hyper-androgenism
  - Hypothyroidism
  - Idiopathic
Consensus on diagnostic criteria for PCOS

Rotterdam 2003 criteria 2/3.

1. Oligo- and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries on ultrasound
4. Exclusion of other etiologies

ESHRE and ASRM 2003

Ovulation induction: Clomiphene

- Agonist –antagonist of estradiol
- Effect on hypothalamus and pituitary:
  - 40-50% increase in FSH and LH
- Side effects
  - Vasomotor 20%
  - Adnexal tenderness 5%
  - Nausea 3%
  - Headaches 1%
  - Visual changes: Discontinue permanently

Ovulation induction: Clomiphene

- Start 50 mg daily on day 2, 3, 4 or 5 for five days
  - If failed, increased to 100 daily, followed by 150 daily
- Ovulation monitoring
  - Temperature charting
  - Serum Progesterone (day 21)
  - LH kit
  - Transvaginal ultrasound
Clomiphene: Step-up protocol


Aromatase inhibitors

- Letrozole (FEMARA) 2.5-7.5 mg on days 3-7
- FIRST LINE
- NOT FDA APPROVED: OFF LABEL USE

Dexamethasone: Clomid resistant patient

<table>
<thead>
<tr>
<th></th>
<th>CC+ Dex n = 40</th>
<th>CC+ placebo n = 40</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation rate</td>
<td>75%</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>40%</td>
<td>5%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Elnashar et al, Hum Reprod, 2006
Common problems:

- Overlapping Clomid treatment with Provera
- Not establishing an ovulation monitoring method
- Increasing Clomid dose, despite ovulation, if no pregnancy
- Extending treatment more than 4-6 months

Metformin: Ovulation induction

![Graph showing rate of live birth over days from randomization.](Legro et al, NEJM, 2007)

Laparoscopic ovarian drilling (LOD)

- **Type:**
  - Wedge resection
  - Monopolar
  - Laser
- **Procedure:**
  - 4-5 holes using monopolar cautery
  - No difference between 5 VS 10
  - Setting 30-40 watts
  - 3mm wide, 3mm deep, duration 3-5 seconds

![Diagram of laparoscopic ovarian drilling.](Unlu C, Atabekoglu C.S. Curr Opin Obstet Gynecol, 2006)
Laparoscopic ovarian drilling (LOD)

- Ovulation rate: 54 - 95%
- Pregnancy rates: 28 - 78%
- Need for ovulation induction agent:
  - 3-6 months
  - 17.5 - 22.6%
- Failure rates: 20-30%
  - Obese
  - Hyperandrogenism
  - Infertility of more than 3 years

Unlu C, Atabekoglu CS. Curr Opin Obstet Gynecol. 2006

Amer et al. Hum Reprod. 2004

Laparoscopic ovarian drilling (LOD)

- Adhesion formation

Saravelos H and Li TC. Hum Reprod 1996

- Reduced ovarian reserve
  - AMH levels
  - LOD (4.60 +/- 3.16 ng/ml) vs
  - PCOS (5.99 +/- 3.36 ng/ml) groups
  - Day-3 FSH: PCOS < LOD
  - AFC: PCOS > LOD

Case study 3

- 35 years old, Obese, irregular cycles, hx of PCOS, and large ovarian cysts
- 5 years of infertility
- Ultrasound: multiple large ovarian cysts
- Plan: Laparoscopic cystectomy and ovarian drilling
Case study 3

- Post op AMH: undetectable!
- FSH 50
- Plan for IVF donor oocyte

AMH after ovarian cystectomy


Unexplained infertility

1.8 Unexplained infertility

1.8.1. Do not offer an ovarian stimulation agents (such as clomiphene citrate, aspirin/coumadin) to women with unexplained infertility [new 2016]

1.8.2. Inform women with unexplained infertility that clomiphene citrate as a standard treatment does not increase the chances of a pregnancy or a live birth [new 2016]

1.8.3. Advise women with unexplained infertility who are having regular unprotected sexual intercourse to try to conceive for a period of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered [new 2016]
Thank you