Reproductive Endocrinology in Daily Practice

Jennifer Glueck, MD
Case 1

• 17 yo woman presents with oligomenorrhea and difficulty losing weight; LMP 6 month ago
• No hair/skin changes, no temp intolerance, no breast symptoms, neck symptoms. No changes in energy level/mood
• Normal puberty in timing and development; menarche @ 13 yo, always had irregular menses, menses q 4-6 months, no menorrhagia or dysmenorrhea
• Wt: started to notice increase in weight about age 11 yo, never seemed to stabilize her weight. She is very active and exercises daily and plays multiple sports
• BMI 29- otherwise normal exam, including note from GYN with normal pelvic exam; no androgen excess
Case 1 - Labs

- negative HCG
- FSH 66, E2 20, AMH 0.014
- T 18, SHBG 55, DHEAS 171, 17OHP 32, hba1c 5, TSH 0.82, TPO neg
- 46 X,X; 21 hydroxylase ab neg; AM cortisol 14
- 1 year later, TSH >150, TPO 15
Objectives- secondary amenorrhea

• Basic work up of secondary amenorrhea
• Specific issues in premature ovarian insufficiency
• Decision making regarding OCPs vs physiologic replacement of estrogen
Secondary Amenorrhea

• Menstrual cycle is as much a "vital sign" as blood pressure, pulse rate, or temperature as an indicator when assessing a woman's overall health

• Over 50% of cases of secondary amenorrhea result from perturbations in the hypothalamic-pituitary-ovary (HPO) axis

• Majority of secondary amenorrhea cases are accounted for by four conditions: the polycystic ovary syndrome, hypothalamic amenorrhea, hyperprolactinemia, and primary ovarian insufficiency

• It is inappropriate to attribute amenorrhea to stress without further evaluation
Figure 2.

Potential hormonal mediators of amenorrhea and infertility. Physical, emotional, or nutritional stress may increase CRH levels, which suppress GnRH release. Cortisol levels, which increase in the setting of stress and Cushing's syndrome, also suppress GnRH release and likely decrease LH responsiveness to GnRH. Starvation results in low leptin levels and increased FGF-21 levels in animal models; the low leptin levels and increased FGF-21 levels likely suppress GnRH release by decreasing kisspeptin expression. In primary hypothyroidism, TRH levels are increased and stimulate prolactin release. Hyperprolactinemia suppresses GnRH release by decreasing kisspeptin expression, and possibly through a CRH-mediated pathway. High androgen and progesterone levels may be seen in CAH, and these hormones likely suppress GnRH release. kiss, kisspeptin.
46 X,X Premature ovarian insufficiency

• Preferred name is POI – not premature menopause or premature ovarian failure

• POI is different from menopause in that there is varying and unpredictable ovarian function in approximately 50% of cases, and about 5 to 10% of women conceive and deliver a child after they have received the diagnosis

• Represents a continuum of impaired ovarian function rather than a dichotomous state

• Primary ovarian insufficiency affects 1 in 10,000 women by age 20, 1 in 1000 by age 30, and 1 in 100 by age 40
Presentation and Diagnostic Criteria

• Because there is intermittent ovarian function rather than complete cessation of ovarian function, these patients are expected to have irregular and unpredictable menses rather than complete amenorrhea.

• There is no menstrual history that is characteristic; most women present after a normal puberty, although primary amenorrhea may be the presenting feature in about 10% of cases; Most commonly, there is a prodrome of oligomenorrhea, or dysfunctional uterine bleeding.

• Symptoms of estrogen deficiency (vasomotor symptoms, vaginal dryness, dyspareunia) are present in many but not all women.

• Diagnostic criteria include age <40 yo, ≥4 months of disordered menses in setting of menopausal levels of FSH.
Etiology/Mechanisms

• 90% of cases are idiopathic

• Majority are spontaneous POI but can be part of a syndrome (Fragile X disorder, Autoimmune polyendocrine syndrome, type 1 AIRE - Adrenal insufficiency, hypoparathyroidism, chronic mucocutaneous candidiasis; Autoimmune polyendocrine syndrome, type 2 - Adrenal insufficiency, type 1 diabetes mellitus, autoimmune thyroid disease

• Single gene mutations as well as abnormalities in the X chromosome have been implicated in nonsyndromic POI

• Occurs through two major mechanisms: follicle dysfunction and/or follicle depletion
Indicated tests for further evaluation in POI

• Karyotype (count 30 cells) – to evaluate for mosaic chromosome abnormalities
• Adrenal antibodies - 4% of women with primary ovarian insufficiency screen positive for adrenal antibodies, which indicates steroidogenic cell autoimmunity and lymphocytic autoimmune oophoritis
• FMR1 premutation - fragile X premutation is found in approximately 2% of women who have isolated spontaneous 46, XX primary ovarian insufficiency and in 14% of women with a familial presentation
• Pelvic ultrasound – evaluate for enlarged, polycystic ovaries
• Bone mineral density – establish baseline
OCPs vs physiologic E2/P for ovarian insufficiency or failure of any cause

• Contraceptive steroidal hormone agents provide supraphysiologic levels of more potent forms of synthetic estrogen and progestin needed to suppress ovulation in normally cycling women

• Thus, by definition these agents provide more steroid hormone than is required to replace ovarian production rates as is the goal in POI, Turner Syndrome, early, surgical or even natural menopause

• Mounting evidence that physiologic replacement results in better bone protection and likely increased CV health compared to OCPs

• These women will be on HRT for decades risks so seen with OCPs including increased risk of VTE, CVA, increased BP, unfavorable lipid profiles, insulin resistance, and breast cancer need to be avoided or limited

• In patients with FHA, OCPs mask/prevent return of spontaneous menses and do not protect against ongoing bone loss
Treatment

- HRT – symptom relief AND physiologic hormone replacement until average age of natural menopause (50 yo)
- Provide bone and CV protection from hypoestrogenism
- It is invalid to apply the results of the Women’s Health Initiative to young women with primary ovarian insufficiency in determining the risk/benefit ratio for women of reproductive age
- Main goal of hormone therapy is to mimic normal ovarian function; average serum estradiol level during the menstrual cycle in normal women is approximately 100 pg
- Usually transdermal or transvaginal e2 and cyclic progesterone
- Pregnancy testing should be done if menses are delayed; spontaneous remission is not rare and 5-10% of women have spontaneous pregnancy
Infertility/Family planning options

• Await spontaneous conception
• Child-free living
• Adoption/Foster
• Oocyte donation
• Embryo donation
Case 2

• 41 yo presents with low libido, no ED; lack of motivation and fatigue ongoing for 10 years; has a 3 year old with current spouse, no fertility issues/no delay in conceiving; 40 lb gradual weight gain in past 7-8 years

• Normal puberty in timing and development, although never had to shave very often; wants another child

• Exam is normal, well virilized, no gynecomastia; BMI 28

• Initial labs with PMD: Total T 184, free T 35.2 (lower limit is 35 pg/mL)

• Rpt labs, AM/fasting: Total T 240, free T 46.5, SHBG 12, FSH/LH 0.8/1.3; other pituitary hormones normal

• MRI: Partially empty sella with otherwise homogeneous and diffuse enhancement of the pituitary gland. No mass lesion
Objectives: Hypogonadism in young men

• Which patients truly have hypogonadism?
• Guidelines for diagnosis and pitfalls
• Clomid use for hypogonadism
Etiology of Hypogonadism

Table 1. Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism

<table>
<thead>
<tr>
<th>Primary Hypogonadism</th>
<th>Secondary Hypogonadism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORGANIC</td>
<td></td>
</tr>
<tr>
<td>KS</td>
<td>Hypothalamic/pituitary tumor</td>
</tr>
<tr>
<td>Cryptorchidism, myotonic dystrophy, anorchia</td>
<td>Iron overload syndromes</td>
</tr>
<tr>
<td>Some types of cancer</td>
<td>Infiltrative/destructive disease</td>
</tr>
<tr>
<td>chemotherapy, testicular radiation/damage, orchidectomy</td>
<td>of hypotalamus/pituitary</td>
</tr>
<tr>
<td>Orchitis</td>
<td>Idiopathic hypogonadotropic</td>
</tr>
<tr>
<td>Testicular trauma, torsion</td>
<td>hypogonadism</td>
</tr>
<tr>
<td>Advanced age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FUNCTIONAL</td>
</tr>
<tr>
<td>Medications (androgen synthesis inhibitors)</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>Opioids, anabolic steroid use, glucocorticoids</td>
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<tr>
<td></td>
<td>Alcohol and marijuana abuse*</td>
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<tr>
<td></td>
<td>Systemic illness*</td>
</tr>
<tr>
<td></td>
<td>Nutritional deficiency/excessive</td>
</tr>
<tr>
<td></td>
<td>exercise</td>
</tr>
<tr>
<td></td>
<td>Severe obesity, some sleep disorders</td>
</tr>
<tr>
<td></td>
<td>Organ failure (liver, heart, and lung)*</td>
</tr>
<tr>
<td></td>
<td>Comorbid illness associated with aging*</td>
</tr>
</tbody>
</table>

*Combined primary and secondary hypogonadism, but classified to usual predominant hormonal pattern. Adapted with permission from Bhasin et al. (7).
Disease Mongering

- US pharmaceutical sales of testosterone inc from $324 mill in 2002 to $2 billion in 2012 and projected to be $6.5 billion by 2020
- Direct and indirect marketing campaigns use catchy phrases such as “low T”, “andropause”, “manopause”
- All studies evaluating testosterone prescription trends in the USA demonstrated an increase between 1.8- and 4-fold over the last 2 decades

Diagnosis and prevalence of hypogonadism

• ES guidelines recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated)

• Without consideration of associated symptoms, or number or type of serum tests before diagnosis, prevalence is up to 76.8% of men

• In the Massachusetts Male Aging Study and Boston Area Community Health Survey, when symptomatic clinical criteria are added to serum laboratory values, prevalence of hypogonadism ranges from 5.6% to 6.5%

• In the European Male Aging Study, when defined by at least 3 sexual symptoms associated with low total T (<317ng/dL), and low free testosterone (<6 ng/dL) the prevalence of hypogonadism was 2.1% age 40-79; (0.1% in men 40-49)
<table>
<thead>
<tr>
<th>Specific</th>
<th>Suggestive</th>
<th>Nonspecific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete or delayed sexual development</td>
<td>Reduced sexual desire (libido) and activity</td>
<td>Decreased energy, motivation, initiative, and self-confidence</td>
</tr>
<tr>
<td>Loss of body (axillary and pubic) hair</td>
<td>Decreased spontaneous erections, erectile dysfunction</td>
<td>Feeling sad or blue, depressed mood, persistent low-grade depressive disorder</td>
</tr>
<tr>
<td>Very small testes (6 mL)</td>
<td>Breast discomfort, gynecomastia</td>
<td>Mild unexplained anemia (normochromic, normocytic)</td>
</tr>
<tr>
<td></td>
<td>Eunuchoidal body proportions</td>
<td>Reduced muscle bulk and strength</td>
</tr>
<tr>
<td></td>
<td>low sperm count</td>
<td>Increased body fat, body mass index</td>
</tr>
<tr>
<td></td>
<td>Height loss, low-trauma fracture, low BMD</td>
<td>Poor concentration and memory</td>
</tr>
<tr>
<td></td>
<td>Hot flushes, sweats</td>
<td>Sleep disturbance, increased sleepiness</td>
</tr>
</tbody>
</table>
Technical considerations when assessing testosterone:

• Glucose and food intake suppress T levels—measure after overnight fast
• Testosterone concentrations exhibit significant diurnal and day-to-day variations; repeat morning levels on two occasions
• Large inter-assay and inter-laboratory variability occurs with TT and FT measurements; need to use accurate and reliable methods, optimally, an assay that has been certified by CDC; TT by LC MS-MS and FT by equilibrium dialysis
• Quest and Labcorp have LC-MS-MS assays that are certified by the CDC
• In men who have conditions that alter SHBG, or whose initial total testosterone concentrations are at or near the lower limit of the normal range, should determine free testosterone concentrations either directly from equilibrium dialysis assays or by calculations that use total testosterone, SHBG, and albumin concentrations
• Testosterone binds primarily to SHBG or albumin; the unbound, or free testosterone, is considered the active component that has androgenic effects and reflect the “body store” or biologically active testosterone that is available to the cells to use
Many (most) men need to have FT measured:

<table>
<thead>
<tr>
<th>Table 2. Conditions in Which Measurement of FT Concentration Is Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Conditions that are associated with decreased SHBG concentrations</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Use of glucocorticoids, some progestins, and androgenic steroids</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Acromegaly</td>
</tr>
<tr>
<td>Polymorphisms in the SHBG gene</td>
</tr>
<tr>
<td>2. Conditions associated with increased SHBG concentrations</td>
</tr>
<tr>
<td>Aging</td>
</tr>
<tr>
<td>HIV disease</td>
</tr>
<tr>
<td>Cirrhosis and hepatitis</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Use of some anticonvulsants</td>
</tr>
<tr>
<td>Use of estrogens</td>
</tr>
<tr>
<td>Polymorphisms in the SHBG gene</td>
</tr>
<tr>
<td>3. Total testosterone concentrations in the borderline zone around the lower limit of the normal range (e.g., 200–400 ng/dL)</td>
</tr>
</tbody>
</table>

Adapted with permission from Bhasin et al. (8).
Case 2 cont

• No baseline SA was done but he was treated with CC 25 mg every other day with very good response

• TESTOSTERONE
  250 - 1,100 ng/dL 431

• FREE TESTOSTERONE
  35.0 - 155.0 pg/mL  87.7

• FSH
  1.6 - 8.0 mIU/mL  1.5 (L)

• ESTRADIOL
  < OR = 39 pg/mL  37

• Symptoms improved, most prominent improvement for him was improved motivation and “feeling more aggressive at work”

• Conceived 2\textsuperscript{nd} child again without difficulty
Clomiphene therapy in IHH/FHH

• Testosterone restoration therapy rather than replacement
• Clomiphene selective estrogen receptor modulator (SERM) with predominant antagonist activity at the hypothalamus and pituitary estrogen receptor (ER)
• 62:38 mixture of enclomiphene (trans-isomer, E2 antagonist) and zuclomiphene (cis-isomer, mixed E2 agonist)
How long to continue CC?

TABLE 1 Baseline and follow-up hormone, symptom and BMI data for patients (data are means ± sd)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total T, ng/dL</td>
<td>228 ± 48</td>
<td>612 ± 212</td>
<td>562 ± 201</td>
<td>582 ± 227</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH, IU/mL</td>
<td>2.0 ± 1.6</td>
<td>8.6 ± 3.2</td>
<td>7.2 ± 4.0</td>
<td>8.2 ± 1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oestradiol, pg/mL</td>
<td>37 ± 16</td>
<td>48 ± 22</td>
<td>42 ± 13</td>
<td>50 ± 30</td>
<td>0.02</td>
</tr>
<tr>
<td>ADAM (+ responses)</td>
<td>7 ± 2</td>
<td>3 ± 2</td>
<td>5 ± 2.5</td>
<td>5 ± 3</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>32 ± 8</td>
<td>31 ± 9</td>
<td>29 ± 11</td>
<td>28 ± 4</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

FIG. 1. Breakdown of bone densitometry diagnoses at baseline and over the course of CC therapy (BD, bone density).
Case 3

• 33 yo woman, G0; diagnosed with PCOS several years prior; unprotected intercourse for 6 months trying to conceive
• Menarche @10, always had oligomenorrhea/amenorrhea up to 6 months, generally menses q3-6 months; has bothersome hirsutism, hair thinning, no acne; no FH of T2DM
• BMI 39, +hirsutism primarily at back and abdomen, no AN, no striae
• Total testosterone 41 (2-45ng/dL), free testosterone 8.2 (0.1-6.4 pg/mL), SHBG 17, DHEAS 211, 17OHP 49, PRL 8; AMH 5.9; TSH 1.0, hba1c 5.5
• Normal HSG, normal pelvic ultrasound, partner with normal SA
Objectives: Infertility in PCOS

• What should the endocrinologist do?
• Efficacy and role of metformin for fertility in PCOS
• Role of weight loss for fertility in PCOS
• Other ovulation induction medicines
What is the role of metformin in women with PCOS trying to conceive?

• Studies beginning in the 1990s showing that metformin improves ovulation and pregnancy rates

• Exact role remains controversial

• Meta-analyses have shown that compared to placebo, metformin decreases circulating androgens, improves ovulation rates and increases live birth rates  
  Fertility and Sterility® Vol. 108, No. 3, September 2017

• No differences in ovulation rates based on type of metformin IR vs ER

• Dose 1500-2550 mg studied in PCOS
Metformin is not an ovulation induction medicine

- Head to head, metformin is inferior to CC; no studies have compared metformin to letrozole

![Bar chart showing live birth/ovulation comparison between CC, Met, and Comb groups.](Image)
Metformin as adjuvant therapy:

- Significant heterogeneity in studies
- Comparing combination therapy with metformin + CC vs CC alone; meta-analyses show improvement in ovulation and clinical pregnancy but not live birth rate
- Recent Cochrane review suggest that metformin may increase the live birth rate among women undergoing ovulation induction with gonadotrophins
Metformin as adjuvant to ovulation induction medications

**FIG. 3.** Live birth rates in the metformin and placebo groups in the whole population and in the nonobese and obese subjects.

J Clin Endocrinol Metab, May 2012, 97(5):1492–1500
Does weight loss improve fertility in PCOS?

• Benefit of weight loss in obese patients with unexplained infertility is not clear

• Recent multicenter RCT – lifestyle pre-treatment vs immediate fertility treatment; control group had higher pregnancy and live births; had to conclude lack of benefit and higher pregnancy loss in intervention group

• Very low calorie restriction decreases IVF efficacy

• Morbid obese women undergoing bariatric surgery improves timing of ovulation and sexual function; also shorter duration of gestation and SGA babies
OWL PCOS trial/PPCOS II-Benefit of Delayed Fertility Therapy With Preconception Weight Loss Over Immediate Therapy in Obese Women With PCOS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PPCOSII/ clomiphene</th>
<th>OWL-PCOS OCP</th>
<th>OWL-PCOS Lifestyle</th>
<th>OWL-PCOS combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation rate</td>
<td>44.7%</td>
<td>46.1%</td>
<td>60.3%</td>
<td>67.1%</td>
</tr>
<tr>
<td>Relative Rate compared to PPCOSII</td>
<td>1.0 (0.8 –1.3) p=.96</td>
<td>1.4 (1.1–1.7) p =0.003</td>
<td>1.4 (1.2–1.8) p=.001</td>
<td></td>
</tr>
<tr>
<td>Live birth/patient</td>
<td>10.4%</td>
<td>10.2%</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>Relative Rate compared to PPCOSII</td>
<td>0.8 (0.3–2.3) p=.73</td>
<td>2.5 (1.4–4.6) p=.004</td>
<td>2.4 (1.3– 4.4) p=.01</td>
<td></td>
</tr>
</tbody>
</table>
Ovulation Induction in PCOS-1\textsuperscript{st} line

• Aromatase inhibitors (letrozole) and SERMs (clomiphene) with or without metformin – first line treatment in PCOS
• Current meta-analyses suggest women with PCOS are 50% more likely to have a live birth with letrozole compared clomiphene
• No statistically significant difference found in ovulation rates, miscarriage or multiple pregnancy rates
• Congenital anomalies rates between letrozole and clomiphene are similar
• Letrozole may also have less side effects (headaches, cramping, fatigue, dizziness, fewer hot flashes); lesser anti-estrogenic effect on the endometrium
Letrozole vs CC -

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with CC with or without adjuncts</td>
<td>Risk with letrozole with or without adjuncts</td>
<td>OR 1.68 (1.42 to 1.99)</td>
<td>2954 (13 RCTs)</td>
<td>Moderate*</td>
</tr>
<tr>
<td>Live birth rate</td>
<td>214 per 1000 (279 to 352)</td>
<td>314 per 1000 (279 to 352)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian hyperstimulation syndrome rate</td>
<td>5 per 1000 (5 to 5)</td>
<td>5 per 1000 (5 to 5)</td>
<td>RD 0.00 (−0.01 to 0.00)</td>
<td>2536 (12 RCTs)</td>
<td>High</td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>264 per 1000 (330 to 390)</td>
<td>359 per 1000 (330 to 390)</td>
<td>OR 1.56 (1.37 to 1.78)</td>
<td>4629 (25 RCTs)</td>
<td>Moderate*</td>
</tr>
<tr>
<td>Miscarriage rate by pregnancies</td>
<td>201 per 1000 (150 to 240)</td>
<td>191 per 1000 (150 to 240)</td>
<td>OR 0.94 (0.70 to 1.26)</td>
<td>1210 (18 RCTs)</td>
<td>High</td>
</tr>
<tr>
<td>Multiple pregnancy rate</td>
<td>17 per 1000 (7 to 21)</td>
<td>13 per 1000 (7 to 21)</td>
<td>OR 0.69 (0.41 to 1.16)</td>
<td>3579 (17 RCTs)</td>
<td>High</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the mean risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CIs: Confidence interval; RD: Risk difference; OR: Odds ratio.

Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD010287.
Ovulation induction in PCOS - 2\textsuperscript{nd} and 3\textsuperscript{rd} line

• Recombinant gonadotropins traditionally used as second line therapy
• Higher pregnancy rate than clomiphene but also higher adverse events such as ovarian hyperstimulation syndrome and multiple pregnancy
• In experienced hands, produce excellent pregnancy outcomes with a low multiple pregnancy rate
• IVF is 3\textsuperscript{rd} line treatment of infertility in PCOS
Case 3

- Added metformin, increased to 1500 mg
- Successful weight loss and improved cyclicity
- Not pregnant after 6 months
Case 3 – pregnant!