“59 Year-old Woman with Osteoporosis”

Dr. Dickens does not have any relevant financial relationships with any commercial interests.
ENDORAMA:
59 Year-old Woman with Osteoporosis

Laura Dickens
February 9, 2017
Objectives

• Review the differential diagnosis and evaluation of primary amenorrhea
• Review the recommendations for estrogen replacement in females with hypogonadism and consequences of inadequate replacement.
• Discuss the effects of diet-induced weight loss on bone loss
Chief complaint

59 year old woman presents for evaluation of osteoporosis
HPI

• DEXA done for routine screening in 7/2015 showed osteoporosis
  – L1-L4 spinal T score -3.1
  – Total hip T score -1.7
• No history of fracture
• Adult height 5’5”, current height 5’5”
• Treated with Risedronate for about nine months, currently tolerating well with no adverse effects
Additional History

Past Medical History:
- Ovarian cancer (age 18) – treated with surgery and radiation
- Colon cancer x2 (age 35, 45) – treated with surgery x2, 5-FU and FOLFOX chemotherapy
- HTN
- Obesity *

Past Surgical History: Hysterectomy and BSO (age 18), sigmoid resection for colon cancer (age 35), right hemicolecetomy for second colon cancer (age 45)
Additional History

Family History: Hip fracture in her mother around age 80, no known diagnosis of osteoporosis. Breast cancer in paternal cousin, colon cancer in paternal cousin. No family history of kidney stones.

Social Hx: Married, three adopted children. No tobacco, rare ETOH, no drugs

Medications:
- Aspirin 81mg daily
- Vitamin D3 1000 IU daily
- Losartan 25mg daily
- Phentermine-topiramate (Qsymia) 7.5-46mg daily
- Risedronate 150mg once monthly
Physical exam

VITALS: Temp 37.1, BP 134/90, HR 70, BMI 27.7

**Constitutional:** She appears well-developed and well-nourished. No distress.

**HENT:** Normocephalic and atraumatic. EOM are normal. Pupils are equal, round, and reactive to light. No scleral icterus.

**Neck:** Normal range of motion. Neck supple. No thyromegaly present.

**Cardiovascular:** Normal rate and regular rhythm. No murmur heard.

**Pulmonary/Chest:** Breath sounds normal. No respiratory distress. She has no rales (clear to auscultation). Normally developed breasts.

**Abdominal:** Well healed midline vertical incision. Soft. Bowel sounds are normal. She exhibits no distension and no mass. There is no tenderness.

**Musculoskeletal:** Normal range of motion. She exhibits no edema and no tenderness. Kyphosis at the thoracolumbar junction

**Neurological:** She is alert. She has normal reflexes. No cranial nerve deficit. Coordination and gait are normal.

**Skin:** Skin is warm and dry. No rash noted. No erythema.

**Psychiatric:** She has a normal mood and affect. Her behavior is normal. Judgment normal.
<table>
<thead>
<tr>
<th>Value</th>
<th>138</th>
<th>99</th>
<th>16</th>
<th>92</th>
<th>Ca 9.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4</td>
<td>27</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

25OH vitamin D = 33
PTH 41
GGT 93 (H)
Red flags: Osteoporosis risk factors

1. Estrogen deficiency?
2. Weight loss
3. Parental history of hip fracture
Pubertal and Gynecologic History

- Normal female external genitalia
- Patient recalls breast and pubic hair development at around age 12, similar to peers
- Growth normal, ultimately adult height normal
- Never underwent menarche
- At age 17 was evaluated for primary amenorrhea, found to have an “ovarian cyst”, and surgical removal was recommended
Ovarian Cancer History

• After surgery she was told they found ovarian cancer and “underdeveloped female organs”. She was told the surgeons “removed everything”

• Transferred care to UCMC, underwent additional exploratory surgery and radiation treatment for ovarian cancer

• On estrogen for one year, stopped due to concern about cancer risk
Primary Amenorrhea

• Definition:
  – Failure to menstruate by age 15 with normal secondary sexual characteristics
  – Failure to menstruate within 5 years of breast development if that occurs before age 10
  – *Age 13 with absent secondary sexual characteristics and no menses

Image: https://www.endocrineweb.com/endocrinology/overview-ovaries
Differential Diagnosis of Primary Amenorrhea

Table 1. Major Causes of Amenorrhea

<table>
<thead>
<tr>
<th>Outflow tract</th>
<th>Pituitary</th>
<th>Hypothalamic</th>
<th>Other endocrine gland disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Autoimmune disease</td>
<td>Eating disorder</td>
<td>Adrenal disease</td>
</tr>
<tr>
<td>Complete androgen resistance</td>
<td>Cocaine</td>
<td>Functional (overall energy deficit)</td>
<td>Adult-onset adrenal hyperplasia</td>
</tr>
<tr>
<td>Imperforate hymen</td>
<td>Cushing syndrome</td>
<td>Gonadotropin deficiency</td>
<td>Androgen-secreting tumor</td>
</tr>
<tr>
<td>Müllerian agenesis</td>
<td>Empty sella syndrome</td>
<td>(e.g., Kallmann syndrome)</td>
<td>Chronic disease</td>
</tr>
<tr>
<td>Transverse vaginal septum</td>
<td>Hyperprolactinemia</td>
<td>Infection (e.g., meningitis,</td>
<td>Constitutional delay of puberty</td>
</tr>
<tr>
<td>Acquired</td>
<td>Infiltrative disease</td>
<td>tuberculosis, syphilis)</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Asherman syndrome</td>
<td>(e.g., sarcoidosis)</td>
<td>Malabsorption</td>
<td>Ovarian tumors (androgen producing)</td>
</tr>
<tr>
<td>(intrauterine synechiae)</td>
<td>Medications</td>
<td>Rapid weight loss</td>
<td>Polycystic ovary syndrome (multifactorial)</td>
</tr>
<tr>
<td>Cervical stenosis</td>
<td>Antidepressants</td>
<td>(any cause)</td>
<td>Thyroid disease</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
<td>Stress</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antihypertensives</td>
<td>Traumatic brain injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>Tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Opiates</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other pituitary or central</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>nervous system tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prolactinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sheehan syndrome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Primary ovarian insufficiency          |                               |                                   |                                          |
| Congenital                             |                               |                                   |                                          |
| Gonadal dysgenesis (other than Turner  |                               |                                   |                                          |
| syndrome)                              |                               |                                   |                                          |
| Turner syndrome or variant             |                               |                                   |                                          |
| Acquired                               |                               |                                   |                                          |
| Autoimmune destruction                 |                               |                                   |                                          |
| Chemotherapy or radiation              |                               |                                   |                                          |

Information from references 1, 2, and 4 through 11.
Primary Amenorrhea Evaluation

- Evaluation:
  - Physical exam – abnormal in 15% of primary amenorrhea
  - Labs – pregnancy test, prolactin, TSH, FSH
  - Ultrasound
• After being diagnosed with two separate colon cancers (age 35 and 45) patient was referred to the Cancer Risk Clinic for genetic testing
Differential: Phenotypic female with 46XY

- 46,XY gonadal dysgenesis
- Complete androgen insensitivity syndrome
- Defect in androgen synthesis

Source: Up To Date. Causes of primary amenorrhea.
How would you establish a diagnosis?
Additional Genetic Testing

**Human Genetics Report**

**46,XY DSD / Complete Gonadal Dysgenesis Sequencing Panel**

**RESULT:** c.331C>T (p.Gln111*) pathogenic sequence change identified in the SRY gene in the hemizygous state.

**INTERPRETATION:** This pathogenic sequence change is the likely cause of this patient's phenotype.

**SUGGESTIONS:**

Truncating sequence changes in SRY are typically de novo. For confirmed de novo sequence changes, the risk to this patient's father is less than 1% with each pregnancy, based on the theoretical risk of germline mosaicism.

The GenomeConnect patient registry collects de-identified genetic and health information to advance knowledge of genetic variants, and is available for this patient. To learn more about this research opportunity please visit genomeconnect.org.

Genetic counseling is recommended to explain the implications of this result. Please call our genetic counselor with any questions regarding these results.

**DETAILS:** DNA sequence analysis of the SRY gene demonstrated a sequence change, c.331C>T, which results in the creation of a premature stop codon at amino acid position 111, p.Gln111*. This pathogenic sequence change is predicted to result in an abnormal transcript, which may be degraded, or may lead to the production of a truncated SRY protein with potentially abnormal function. This sequence change has not been described in patients with SRY-related disorders, however different truncating sequence changes in the same protein domain of SRY have been described in patients with 46,XY Complete Gonadal Dysgenesis (Hawkins, 1982; Giuffrè, 2004). This pathogenic sequence change is the most likely cause of this patient's phenotype.

Sequencing of all other genes included in the 46,XY DSD/CGD Sequencing panel was completed, and was normal. A list of synonymous or benign sequence changes, if identified for this patient, is available upon request. Our interpretation is based on the current understanding of the genetics of disorders of sex development.
Embryonic Gonadal Development

3-7th week of pregnancy

Puberty

Oestrogens

Androgens

SECONDARY SEXUAL CHARACTERISTICS

Facial hair...

Breasts...

## Disorders/Differences of Sexual Differentiation

<table>
<thead>
<tr>
<th>Gene Involved in male development</th>
<th>Function</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHM</td>
<td>Signaling molecule</td>
<td>L0F: XY partial or complete gonadal dysgenesis</td>
</tr>
<tr>
<td>DHH</td>
<td></td>
<td>Hemagigosity: XY gonadal dysgenesis</td>
</tr>
<tr>
<td>DHH2</td>
<td></td>
<td>Deletion of 9q24 (including DHH2): XY gonadal dysgenesis (smoky), hypospadias</td>
</tr>
<tr>
<td>ARX</td>
<td>Chromatin remodeling</td>
<td>Dysembryonic testes, ambiguous genitalia</td>
</tr>
<tr>
<td>GATA4</td>
<td></td>
<td>Deletion of GATA4: embryonic lethality</td>
</tr>
<tr>
<td>MAP2K2</td>
<td>Kinase</td>
<td>XX premature ovary failure (POV)</td>
</tr>
<tr>
<td>NR0B2</td>
<td>Nuclear receptor</td>
<td>X0-1: fail to develop bi-potential gland</td>
</tr>
<tr>
<td>Wnt1</td>
<td></td>
<td>Duplications, congenital adrenal hyperplasia (CAH)</td>
</tr>
<tr>
<td>NGF</td>
<td>Reduction</td>
<td>Demyelination, WAG1, and Freeman syndrome</td>
</tr>
<tr>
<td>TSP1</td>
<td>Chromatin modifier</td>
<td>Dysembryonic testes and ambiguous genitalia</td>
</tr>
</tbody>
</table>

## Genes involved in female development

<table>
<thead>
<tr>
<th>Gene Involved in female development</th>
<th>Function</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOXD1</td>
<td>Signaling molecule</td>
<td>RunX-1: Premature ovary failure, RPES, and premature ovary failure (POV)</td>
</tr>
<tr>
<td>FSHb</td>
<td></td>
<td>Fshb-/-: subfertility (male-to-female sex reversal)</td>
</tr>
<tr>
<td>SRY</td>
<td></td>
<td>XX partial-to-male sex reversal, similar to Wolfian-/- and conditional Ovotestis knock-out</td>
</tr>
<tr>
<td>WNT7</td>
<td>Signaling molecule</td>
<td>Duplication of 1p (including WNT7 and RSP01) and 1p: XX gonadal dysgenesis (GOF)</td>
</tr>
<tr>
<td>WNT7</td>
<td></td>
<td>XX Mullerian duct agenesis, testosterone synthesis, and cokoid vesical formation</td>
</tr>
</tbody>
</table>

SRY gene

- Mammalian Y-chromosomal testis-determining gene
- Regulates Sox9 expression in Sertoli cell precursors to activate testis-specific genes and lead to testis determination

Timing and level of Sry and Sox9 are critical
XY Gonadal Dysgenesis – Swyer Syndrome

- Pure or complete gonadal dysgenesis
- Incidence of one in 80,000 births
- Genetics: 10–20% of women with Swyer syndrome have a deletion in the DNA-binding region of the SRY gene
- Clinical presentation: Typically presents with primary amenorrhea and delayed puberty. Phenotypically female with unambiguous female genitalia and normal Mullerian structures

Swyer Syndrome

- **Diagnosis**
  - Labs: LH, FSH, prolactin, TSH, SHBG, estradiol, testosterone, androstenedione
  - Peripheral blood karyotype
  - Sequencing of causative genes
  - Consider tumor markers: AFP, b-HCG, LDH, placental alk phos

- **Imaging:**
  - Transabdominal pelvis ultrasound

Swyer Syndrome

Treatment
- Bilateral gonadectomy at the time of diagnosis
  - Risk of gonadoblastoma (benign germ cell neoplasia) 15 - 35%
  - Can be precursor to germ cell malignancy, dysgerminoma most commonly
- Hormonal treatment – to be discussed
- Fertility? Possible with egg donation by anecdotal report
- Psychosocial support

Outstanding questions

1. How did normal breast development occur?
2. How should estrogen replacement have been managed?
Breast development?

- Case series of 8 patients with Swyer syndrome s/p gonadectomy
- Six patients (75%) had gonadal tumors: gonadoblastoma (3), dysgerminoma (1), gonadoblastoma + dysgerminoma (2)

Breast development?

- Three gonadoblastomas had hormonal activity:
  - 2 estrogen-producing -> associated with higher Tanner stage breast development
  - 1 testosterone-producing -> associated with clitoromegaly


<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Histology</th>
<th>FSH (mU/mL)</th>
<th>LH (mU/mL)</th>
<th>E₂ (pg/mL)</th>
<th>T (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>Gonadoblastoma</td>
<td>64.4</td>
<td>66.5</td>
<td>40.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>Gonadoblastoma</td>
<td>68.0</td>
<td>45.0</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>Gonadoblastoma</td>
<td>82.4</td>
<td>52.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>Gonadoblastoma + dysgerminoma</td>
<td>95.5</td>
<td>38.0</td>
<td>25.0</td>
<td>5.8</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>Gonadoblastoma + dysgerminoma</td>
<td>89.8</td>
<td>31.5</td>
<td>81.0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>Dysgerminoma</td>
<td>40.1</td>
<td>27.1</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>Dysgenetic gonads</td>
<td>72.2</td>
<td>48.5</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>Dysgenetic gonads</td>
<td>98.0</td>
<td>38.0</td>
<td>7.3</td>
<td></td>
</tr>
</tbody>
</table>

FSH indicates follicle-stimulating hormone; LH, luteinizing hormone.
Estrogen replacement?

• General recommendations for Swyer syndrome
  – Low dose estrogen to mimic normal puberty and breast development
  – Cyclic estrogen and progesterone throughout life until age 50
  – Estrogen therapy vital for bone mass

• What are the recommendations and evidence for other disorders with premature gonadal insufficiency (Turner’s syndrome)?

• Does the diagnosis of ovarian cancer change the approach?

Estrogen Therapy in Turner’s Syndrome

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Age-specific suggestions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–11</td>
<td>Monitor for spontaneous puberty by Tanner staging and FSH level</td>
<td>Low-dose estrogen treatment may not inhibit GH-enhanced growth in stature</td>
</tr>
<tr>
<td>12–13</td>
<td>If no spontaneous development and FSH elevated, begin low dose E2</td>
<td>Equivalent initial E2 doses: depot (im) E2, 0.2–0.4 mg/month; transdermal E2, 6.25 μg daily; micronized E2, 0.25 mg daily by mouth</td>
</tr>
<tr>
<td>12.5–15</td>
<td>Gradually increase E2 dose over about 2 yr (e.g., 14, 25, 37, 50, 75, 100, 200 μg daily via patch) to adult dose</td>
<td>Usual adult daily dose is 100–200 μg transdermal E2, 2–4 mg micronized E2, 20 μg EE2, 1.25–2.5 mg CEE</td>
</tr>
<tr>
<td>14–16</td>
<td>Begin cyclic progesterone treatment after 2 yr of estrogen or when breakthrough bleeding occurs</td>
<td>Oral micronized progesterone best option at present; usual adult dose is 200 mg/d for 20–30 of monthly cycle or 100–120 of 3-month cycle</td>
</tr>
<tr>
<td>14–30</td>
<td>Continue full doses at least until age 30 because normally estrogen levels are highest between age 15 and 30 yr</td>
<td>Some women may prefer using oral or transdermal contraceptive for HRT; monitor endometrial thickness</td>
</tr>
<tr>
<td>30–50</td>
<td>The lowest estrogen dose providing full protection vs. osteoporosis is 0.625 CEE or equivalent</td>
<td>Monitor osteoporosis risk factors, diet, exercise; obtain BMD and begin regular screening mammography by age 45 yr</td>
</tr>
<tr>
<td>&gt;50</td>
<td>Decision on estrogen use based on same considerations as for other postmenopausal women</td>
<td>New HRT options are appearing, and these recommendations may need updating in near future</td>
</tr>
</tbody>
</table>

CEE, Conjugated equine estrogens; E2, estradiol; EE2, ethinyl estradiol; HRT, hormone replacement treatment.

* The lowest-dose commercially available E2 transdermal patches deliver 14 and 25 μg daily; it is not established whether various means of dose fractionation (e.g., administering a quarter patch overnight or daily or administering whole patches for 7–10 d per month) are equivalent.

- BMD recommended at the initial visit in the adult clinic with follow up depending on results

Effect of (no) ERT in Turner’s Syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ERT ≥75% (n = 34)</th>
<th>ERT &lt;75% (n = 16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42 ± 1.4</td>
<td>42 ± 2.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>144.2 ± 1.1</td>
<td>145.2 ± 1.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54 (36–150)</td>
<td>61 (40–120)</td>
<td>0.23a</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 (18–47)</td>
<td>29 (20–54)</td>
<td>0.04a</td>
</tr>
<tr>
<td>Years ERT taken</td>
<td>25 ± 1.5</td>
<td>8 ± 1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Eating disorders, n (%)</td>
<td>5/34 (15)</td>
<td>1/16 (6)</td>
<td>0.37</td>
</tr>
<tr>
<td>DXA LS-AP BMD (g/cm²)</td>
<td>0.91 ± 0.02</td>
<td>0.75 ± 0.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DXA LS-AP Z-score</td>
<td>−0.9 ± 0.2</td>
<td>−1.9 ± 0.3</td>
<td>0.002</td>
</tr>
<tr>
<td>QCT LS BMD (mg/cm³)</td>
<td>137 ± 3.8</td>
<td>109 ± 6.8</td>
<td>0.0005</td>
</tr>
<tr>
<td>QCT LS Z-score</td>
<td>−0.6 ± 0.2</td>
<td>−2 ± 0.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diagnosis of osteoporosis, n (%)</td>
<td>0/34 (0)</td>
<td>6/16 (38)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

aRank-sum test.

bThe diagnosis of osteoporosis according to WHO criteria (T-score ≤ −2.5 SDs) is based on DXA data. DXA, however, is an areal method that tends to underestimate BMD in small people. Therefore, we corrected the measured areal BMD values for body surface area as previously described and then calculated T-scores using the corrected areal BMD and normative data from the manufacturer.
Estrogen Therapy in Ovarian Cancer Survivors

- RCT in 1999 randomized patients with invasive epithelial carcinoma to estrogen replacement (ERT) or no ERT
- Compliance was good
- No difference in disease free or overall survival

Estrogen Therapy in Ovarian Cancer Survivors

In summary

• Hindsight is 20/20
• Patient would have benefitted from ERT, or at least further discussion about risks and benefits
• BMD should have been evaluated sooner
Psychosocial impact of diagnosis

• Patient was informed of her diagnosis by a genetic counselor over the phone
• She had many questions...
  – Was I supposed to be a man?
  – What do I tell my husband?
• Counseling recommended

Any experiences with delayed diagnosis of DSD?
Back to the reason for her visit – Osteoporosis

Additional labs
• Estradiol <10
• Testosterone
  – Free = 1
  – Total = 12
• BSAP 21

Repeat DEXA
• L1-L4 spinal T score -2.7 (decreased 5.5% from 7/2015)
• Total hip T score -2.0 (decreased 6.8% from 7/2015)

Why is she still losing bone?
Bone Loss after Bariatric Surgery

- 23 patients who underwent RYGB followed for one year
- BMD, PTH, 25-OH vitamin D, osteocalcin, and urinary N-telopeptide
- Significant decreases in BMD
  - Femoral neck 9.2% decrease
  - Total hip 8.0% decrease
- Strong correlation between extent of weight loss

Diet-induced Weight Loss and Bone Loss

- 66 women
  - 47 weight loss (WL)
  - 19 weight maintenance (WM)
- WL group randomized to normal or high Ca intake (supp + MVI + diet)
- BMD at baseline and 6 months

Change in BMD with Weight Loss

Meta-Analysis: Diet-induced weight loss and BMD

- Meta-analysis of 38 publications which included healthy patients with BMI >25 undergoing dietary weight loss intervention
- Studies NOT included if involved exercise as the “primary means of eliciting weight loss” or weight loss meds
- Outcomes: BMD of total hip, lumbar spine, total body, bone turnover markers
Case Conclusion

- Switched from Risedronate to IV Zoledronic acid for more potent antiresorptive effect
- Continues follow up with weight loss clinic
- To our knowledge has not yet informed her husband about her diagnosis of 46, XY complete gonadal dysgenesis
Special Thanks

- Dr. Darrel Waggoner (Clinical Genetics)
- Jessica Stoll (Genetics Counselor)
Objectives

• Review the differential diagnosis and evaluation of primary amenorrhea
• Understand the physiology and presentation of disorders/differences of sexual development (DSD) and 46, XY Complete Gonadal Dysgenesis
• Review the recommendations for estrogen replacement in females with hypogonadism and consequences of inadequate replacement.
• Discuss the effects of diet-induced weight loss on bone loss
References


• Up To Date. Causes of primary amenorrhea.


