POI: Clinical Management Challenges: Optimizing Hormone Therapy in Adult Turner’s Syndrome

Wendy Wolfman MD
Professor Department of Ob/Gyn University of Toronto
Director Menopause and POI Clinics
Mt Sinai Hospital Toronto Canada
North American Menopause Society Orlando USA
Oct 6, 2016

Objectives

• To review etiology of inadequate endogenous hormones in Turner’s syndrome
• To discuss impact of hormonal depletion on patients with Turner’s syndrome
• To formulate optimal hormone therapy replacements for women with Turner’s syndrome
• To discuss controversial issues in replacement

Turner’s Syndrome

• Initially a clinical diagnosis with characteristic physical features with evidence of complete or partial absence of second X with or without mosaicism.
• Broad phenotypic spectrum and good quality of life in general

Bondy et al. J Clin Endocrinol Metab 2007

Oocyte Destruction in Utero - Determined by Karyotype

• Incidence-1/2500 pregnancies, < 1% 45X survive pregnancy
• Normally X is inactivated in somatic cells during late blastocyst but 15-25% genes on short arm are still expressed
• In 45X accelerated atresia by 15-20 wk - few follicles in fibrous streak at birth
• Chromosomal types determine any residual oocytes
  • 50% 45X
  • 20-30% mosaics
  • about 20% one normal X and structurally abnormal X

Davenport M J Clin Endocrinol Metab 2010
Levitsky Curr Op in Endo, Diab and Ob 2015
Diagnosis

1. Short stature (5’) and 2. Delayed puberty 60-90%
2. Phenotypes - Edema hands, feet, Webbed neck, low post, hairline, Rotated ears, small mandible, cubitus valgus, short 4th metacarpal, high arched palate, widely spaced nipples or hypoplastic breasts, multiple naevi
3. Cardiac anomalies - coarctation, bicuspid aortic valve, dilated aortic root
4. Renal anomalies - horseshoe kidney, double or cleft renal pelvis
5. Autoimmune - Increased Hashimoto’s thyroiditis, hypothyroidism, liver function abnormalities, coeliac disease, IBD
6. Metabolic - diabetes, hypertension and metabolic syndrome
7. Hearing problems, sensorineural loss
8. Learning issues, autism ADHD

Etiology of Hormonal Insufficiency

1. Gonadal failure from haploinsufficiency of multiple X genes
2. Candidates - USP9X involved in protein degradation and BMP (bone morphogenetic protein 15), type of growth factor expressed in oocytes
3. Exact reason not known
4. Short stature due to homeobox-containing gene (SHOX); found on short arm of X in pseudoautosomal region

What hormones are missing and need to be optimized?

<table>
<thead>
<tr>
<th>Missing hormone</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>Short stature</td>
</tr>
<tr>
<td>Estrogen-produced by oocytes</td>
<td>No or delayed puberty</td>
</tr>
<tr>
<td>Progesterone-after ovulation</td>
<td>No secondary sexual characteristics</td>
</tr>
<tr>
<td>Testosterone-50% from ovary</td>
<td>No growth spurt</td>
</tr>
<tr>
<td></td>
<td>Small uterus</td>
</tr>
<tr>
<td></td>
<td>Emotional +cognitive changes</td>
</tr>
<tr>
<td></td>
<td>Infertility</td>
</tr>
<tr>
<td></td>
<td>?Sexual issues?</td>
</tr>
</tbody>
</table>

How many go through puberty?

1. 70-80% have no spontaneous pubertal development
2. 90% primary amenorrhea
3. Correlates with karyotype-50% 45X
4. 20-30% mosaics
5. About 20% one normal X and structurally abnormal X
6. Study with TS in 522–puberty less with 45X (9%)
7. 84 (16%) attained puberty with menses of these 36% regular for 9 years -14% secondary amenorrhea within 1.6-2 years after menarche
Modern Day Turner’s in Multi-disciplinary Clinic

- Interdisciplinary clinic with endocrinology, gynaecology and cardiology, possible ENT, psychiatry and cognitive support
- GH, step-wise estrogen maybe oxandrolone to induce puberty
- 2 groups (most with primary amenorrhoea) fewer menstruating
  - Group 1-need optimal HT
  - Group 2-need to follow if and when HT needed
  - discussion about protecting future fertility (freezing eggs or embryos)
  - If menses sporadic and low AMH could initiate sequential HT
  - MAY NEED CONTRACEPTION

Importance of Adequate Hormones pre and post Puberty

- Attainment of height, body habitus and BMD maintenance
- Brain development-Cognitive function and mood- nonverbal learning
- CVR function
- Secondary Sexual Development close to peers
- Emotional development and Sexuality-excessive shyness, social anxiety, delayed sexual debut, decreased marriage rate
- Uterine growth-size of uterus for future fertility-prolonged doses of E
- Liver function-improved with E
- Glucose control

Effects of E Deficiency on Brain Development

- Sex steroids affect neuromodulators, alter synapse function, attention, learning, memory, motor function and cell survival
- Adolescence critical for higher cognitive functions, social and emotional behavior-increases white matter and decreases cortical gray matter
- E alters cognition and mood in women-verbal working memory better during E dominant phase of menses
- Early replaced TS better verbal and nonverbal memory, faster more accurate performances on timed spatial and motor tasks.

BMD in Turner’s

- TS-reduced BMD and increased fracture risk with HT-? Inadequate doses?
- Multifactorial-SHOX haploinsufficiency, reduced androgen, low vit D, high PTH and abn GH/IGF-1 axis
- In POI treated with long-term estrogen from adolescence, BMD maintained at LS compared to untreated-+ increased bone formation
- ESRM-healthy lifestyle, weight-bearing exercise, no smoking, normal body weight to optimize bones
- calcium, vitamin D and estrogen replacement
Androgen insufficiency

- A, DHT, free T and total T reduced, DHEAS normal
- Study in 14 TS adults with methyl T-increased BMD at spine and femoral area increased LBM, decreased chol HDL and TG, increased lean body mass
- If T is added as adults need to monitor—long term safety and virilization side effects
- Improvement in energy, sexuality bone and cognition—possible not proven

Hormone therapies during reproductive life

- When to start—usually age 12 at low dose and titrate up—adult dose by 15
  no OCP to start as it affects breast development (tubular)
- Route—Transdermal estrogens versus oral estrogens
- Type of progestin? Progesterone or synthetic
- Endometrial protection considering many years of hormone therapy
- Sequential versus daily
- Restarting hormones after delivery—right away

Evidence that HRT superior to OCP

- 1. Bone—improved LS after 12 mo HRT versus OCP and bone formation
- 2. Uterus—better uterine lining 4.8 versus 3 mm—differences between Turner’s and other POI patients I
- 3. CVR-BP and lipids—lower syst and diast BP with transdermal HT—also differences in lipids with OCP’s
- 4. Less androgen suppression—increase in SHBG and free T with OCP
- 5. Breast—some physiological differences on stimulation between progestins

How do you optimize patient response and compliance?

- 1. acknowledge effects and risks of early menopause
- 2. Reassure that this therapy is necessary and not risky
- 3. rule out contraindications (very few)
- 4. how old is the patient?
- 5. decide on patient’s preferred option
- 6. Younger women need higher doses
- 7. does patient have a drug plan?
  • INDIVIDUALIZE THERAPY
Menopausal Issues Similar

**Symptoms**
- Vasomotor Symptoms
- Sleep disturbances
- Mood changes and depression
- Joint aches
- Vaginal Dryness
- Sexual Issues-Dyspareunia, Decreased Libido
- Irregular Bleeding

**Other Issues**
- Cardiovascular Aging
- Osteoporosis
- Metabolic issues, BP
- Diabetes and Cirrhosis
- Earlier neurological problems
  - Dementia
  - Strokes
  - Parkinson’s
- Earlier death-50% excess-CVR

---

**Why transdermal route in Menopausal aged Women?**
- Is this data relevant for young women?

- **Systemic Review and Meta-analysis**—low confidence
  - 15 observational studies oral HT versus transdermal therapy- 3-20 yrs, 22,489 on oral 5671 on transdermal
  - Oral ET increased risk of first VTE (RR 1.63 CI 1.4-1.9 ) DVT 2.09 CI 1.35-3.23) and possibly stroke RR 1.24 CI 1.03-1.48)
  - But not MI (RR 1.17 CI 0.80-1.71)
  - No increase in TG or CRP

- Bergendal+ Simon Menopause 2016-support findings

---

**What is the Best Replacement?**
- Depends on patient and compliance-Individualize
  - younger patients tend to prefer OCP’s, older HT
  - Average estrogen level during menstrual cycle 382 pmol/L-be physiologic-try and match
  - Prefer transdermal therapies with 100μgm estradiol patches or 2 mg estrace-Higher doses
  - 12 days sequential (300 mg P) versus daily progestin-however optimal dose for daily P unknown with higher doses of E-
  - May be benefit to adding T and local estrogens vaginally

---

**Controversies re Optimal Hormone therapy**
- Does the patient want to menstruate?
- What to do in patient intolerant to progestins?
- 100 mg P may be inadequate for long term endometrial protection
- Are local therapies needed? (usually no symptoms with these dosages)
- Should we add testosterone?
- Body identical (physiological) therapies
- For how long?

---

References:
- Rebar R Obstet Gynecol 2009
- Kaunitz Obstet Gynecol 2015
- N Am Men Society 2012
- Stute P Climacteric 2016
- Sassarini Cl Endo and Metab 2015
- Stute P Climacteric 2016
- Sassarini Cl Endo and Metab 2015
### Spontaneous fertility
- Correlates with karyotype:
  - Fertility from 0.8% 45X to 69% 45X/47XXX
  - 45X does not rule out ovarian function-usually not persistent
- Gonadotropin levels and AMH may be useful for predicting future gonadal function and determining timing of estrogen replacement
- AMH < 2 pmol/L predictor of failure to enter puberty imminent POI
- Increased incidence of spontaneous abortion, stillborn congenital anomalies and aneuploidy in any pregnancies

---

### Fertility Options
- 90% primary amenorrhea, 2-5% conceive
- 10% may have small residual follicles at birth or early childhood
- Need long arm of X for maintaining fertility
- Cryopreservation of mature oocytes or ovarian tissue
- Pre pregnancy high risk multi-disciplinary and cardiac evaluation
- Embryo donation Gestational surrogacy
- Adoption

---

### ESHRE Guidelines 2016 for POI and Turner’s
- Untreated POI associated with reduced life expectancy, due to CVR disease
- "HRT has role in primary prevention of CVR disease and for bone protection and should be offered throughout normal reproductive lifespan"
- No increased risk of breast CA in this age group
- Patient preference for route and method should be considered
- Androgens have limited data-evaluate after 3-6 mo and limit to 24 mo
- Most alternative and complementary treatments have limited data and efficacy

---

### Consequences of untreated POI
- Reduced life expectancy
- Increased CVR disease
- Earlier Parkinson’s, dementia, Alzheimer’s
- Osteoporosis

---
Conclusion

- Turner's syndrome patients have many of the same issues of women with early menopause but are unique.
- Best estrogen replacement is currently an individual decision.
- More evidence accumulating that transdermal HT is preferable and should be prescribed until the average age of menopause or beyond.
- Adequate progestins need to be prescribed in patients using replacements for many years.