Turner Syndrome: Meta-Analysis

ELIZABETH DABROWSKI, MD
PEDIATRIC ENDOCRINOLOGY FELLOW
ANN AND ROBERT H. LURIE CHILDREN’S HOSPITAL OF CHICAGO
I have nothing to disclose
Objectives

1. Introduce new data on spontaneous thelarche (breast development) and menarche in Turner Syndrome
2. Discuss significance of Y-chromosome mosaicism in Turner Syndrome
3. Discuss future directions in Turner Syndrome research
Turner Syndrome

- Short stature
- Characteristic facial features
- Fold of skin
- Constriction of aorta
- Poor breast development
- Elbow deformity
- Rudimentary ovaries
- Gonadal streak (underdeveloped gonadal structures)
- No menstruation

Spontaneous Thelarche and Menarche
Premature Ovarian Insufficiency

- In utero, there is a normal number of ovarian follicles
  - Undergo rapid agenesis, as early as 18 weeks gestation

- Despite POI, about 38% of patient undergo spontaneous thelarche and 15% spontaneous menarche
  - Studies report that girls with mosaic phenotypes are more likely to have spontaneous thelarche, menarche and possibly pregnancy
  - However, rates are given regarding TS patients in general, no one has looked at rates by various genotypes in detail

References:
Fertility in Turner Syndrome

- 2% spontaneous pregnancy
- 2% assisted pregnancy
- Correlating genotype with chances of spontaneous puberty may impact timing of fertility preservation
Y chromosome mosaicism

- 8-10% of phenotypic female diagnosed with TS have Y-chromosome mosaicism
- Currently, gonadectomy is recommended secondary to the risk of malignancy
- Timing of gonadectomy is traditionally done at diagnosis
  - Rationale is that these girls will not have endogenous estrogen production and gonads will be non-functional, so remove risk
  - Risk of malignancy/pre-malignant lesions is unclear in the literature (studies cite 2.2-43%)

Rates of pubertal Development in TS girls at Lurie Children’s Hospital

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Spontaneous thelarche</th>
<th>Spontaneous menarche (of those with thelarche)</th>
<th>Spontaneous menarche</th>
<th>Secondary Amenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 XO</td>
<td>5/15 (33%)</td>
<td>3/4 (75%)</td>
<td>3/15 (20%)</td>
<td>1/3</td>
</tr>
<tr>
<td>45 XO, 46XX variants</td>
<td>16/22 (72%)</td>
<td>9/12 (75%)</td>
<td>9/19 (47%)</td>
<td>2/9</td>
</tr>
<tr>
<td>45 XO, 47XXX</td>
<td>8/8 (100%)</td>
<td>5/6 (83%)</td>
<td>5/6 (83%)</td>
<td>0/5</td>
</tr>
<tr>
<td>Other</td>
<td>12/17 (71%)</td>
<td>6/10 (60%)</td>
<td>6/12 (50%)</td>
<td>3/6</td>
</tr>
<tr>
<td>Total</td>
<td>41/62 (66%)</td>
<td>23/32 (75%)</td>
<td>23/52 (44%)</td>
<td>6/23 (26%)</td>
</tr>
</tbody>
</table>

Current literature: 38% 15%
Meta-Analysis: Methods

- The study was registered with Prospero International Prospective Registrar of Systematic Reviews.
- MEDLINE via PubMed, Embase, and the Cochrane Database of Controlled Trials were searched
- No search limits or filters were used
- Reference lists of included studies and book chapters were screened for inclusion by 2 independent reviewers
- Inclusion criteria: genetic diagnosis of TS, pubertal staging by physician
- Exclusion criteria: case series, reports, patients on HRT, data based on recall
861 articles resulted

652 excluded

211 duplicates
100 case reports
57 not in English
284 not relevant

209 reviewed further

36 included

7 added from references

Total of 43 articles
## Results

**Table 2. Event Rates of spontaneous thelarche – Total and by karyotype**

<table>
<thead>
<tr>
<th>Group</th>
<th>N Patients</th>
<th>N Studies</th>
<th>Event Rate</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>45XO</td>
<td>105-680</td>
<td>16</td>
<td>0.132</td>
<td>0.087</td>
<td>0.197</td>
</tr>
<tr>
<td>45XO/46XX</td>
<td>8</td>
<td>8</td>
<td>0.629</td>
<td>0.532</td>
<td>0.717</td>
</tr>
<tr>
<td>45XO/47XXX</td>
<td>19/20</td>
<td>3</td>
<td>0.881</td>
<td>0.62</td>
<td>0.971</td>
</tr>
<tr>
<td>46XX with abnormalities of the second X</td>
<td>11</td>
<td>11</td>
<td>0.621</td>
<td>0.484</td>
<td>0.741</td>
</tr>
<tr>
<td>45XO/46XX with structural abnormalities of the second X</td>
<td>12</td>
<td>12</td>
<td>0.306</td>
<td>0.242</td>
<td>0.378</td>
</tr>
<tr>
<td>Y Chromosome Material</td>
<td>5</td>
<td>5</td>
<td>0.411</td>
<td>0.192</td>
<td>0.673</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>13</td>
<td>0.379</td>
<td>0.25</td>
<td>0.529</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,704</strong></td>
<td><strong>29</strong></td>
<td><strong>0.320</strong></td>
<td><strong>0.263</strong></td>
<td><strong>0.383</strong></td>
</tr>
<tr>
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<td>Upper Limit</td>
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<td>--------------------------------------------</td>
<td>------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>45XO</td>
<td>71/950</td>
<td>23</td>
<td>0.091</td>
<td>0.073</td>
<td>0.113</td>
</tr>
<tr>
<td>45XO/46XX</td>
<td>13</td>
<td>0.393</td>
<td>0.269</td>
<td>0.532</td>
<td></td>
</tr>
<tr>
<td>45XO/47XXX</td>
<td>26/40</td>
<td>4</td>
<td>0.662</td>
<td>0.493</td>
<td>0.798</td>
</tr>
<tr>
<td>46XX with abnormalities of the second X</td>
<td>16</td>
<td>0.355</td>
<td>0.242</td>
<td>0.486</td>
<td></td>
</tr>
<tr>
<td>45XO/46XX with structural abnormalities of the second X</td>
<td>14</td>
<td>0.137</td>
<td>0.103</td>
<td>0.178</td>
<td></td>
</tr>
<tr>
<td>Y Chromosome Material</td>
<td>5</td>
<td>0.191</td>
<td>0.68</td>
<td>0.433</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>0.33</td>
<td>0.224</td>
<td>0.456</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2,890</td>
<td>34</td>
<td>0.208</td>
<td>0.193</td>
<td>0.224</td>
</tr>
</tbody>
</table>

Table 3. Event Rates of spontaneous menarche – Total and by karyotype
## XO/XY Significance

### Event Rates of spontaneous thelarche

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</thead>
<tbody>
<tr>
<td>Y Chromosome Material</td>
<td>7/18</td>
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### Event Rates of spontaneous menarche

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</tbody>
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Conclusions

rates of spontaneous thelarche and menarche are greater than previously anticipated when patient are evaluated by individual genotype

- Highest rates of thelarche in 45,XO/47, XXX (88.1%)
- Lowest rates in 45,XO monosomy (13.2%)
- Highest rates of menarche in 45,XO/47, XXX (66.2%)
- Lowest rates in 45, XO monosomy (9.1%)
Future Directions

- Other studies show that in adult women predictors of ongoing fertility are:
  - Mosaic genotype
  - Spontaneous thelarche
  - Spontaneous menarche
  - Normal FSH levels
  - Normal AMH levels

- However, there are no clear predictors of fertility in pre-pubertal TS patients.

Future Directions

- This could be important, as with advances in oncofertility research, younger patients are undergoing fertility preservation.
- These techniques are being extrapolated to other populations at risk of ovarian failure and some centers have IRB protocols in place for TS fertility preservation in adolescents.
- Establishing clear parameters for gonadectomy in patients with Y-chromosome mosaicism.
- Considering fertility preservation in these patients as well.