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Aberdeen Maternity Hospital
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Aberdeen, UK

Declared no potential conflict of interest
Genetic aetiology of poor and hyper responders

Sesh Sunkara
Background

- Poor and hyper responders: two ends of the spectrum of response to ovarian stimulation
- Challenge to controlled ovarian stimulation (COS)
- Implications for IVF outcomes
- Long term consequences – health implications
Poor ovarian response

- Depletion of ovarian follicle pool
  - Insufficient initial follicle number
  - Accelerated follicle loss

- Ovarian follicle dysfunction
  - Signalling defect
  - Enzyme deficiency
  - Autoimmunity

De Vos et al., LANCET. 2010
POR: aetiology

- Advanced age
- Genetic conditions
  - Chromosomal anomalies
  - Gene mutations
- Acquired conditions
  - Endometriomas
  - Chemo/ radiotherapy
  - Ovarian surgery

De Vos et al., LANCET. 2010
Chromosomal abnormalities
- Numerical: Turner syndrome
- Structural: macrodeletions (Xq; Xp)

Genetic variations
- FMR1
- FSH receptor mutation
- LH β polypeptide mutation

De Vos et al., LANCET. 2010
Chromosomal abnormalities

- Higher incidence among subfertile women vs general population
  - 1.5% - 3.3% vs 0.16% (Schreurs et al., Fertil Steril 2000; van der Ven et al., Hum Reprod 2000)

- Only small to moderate reproductive risk

- X chromosome loss - significant correlation with female age (Guttenbach et al., Am J Hum Genet 1995)
Sex chromosome aneuploidy

- Low level sex chromosome mosaicism
  - Twice more common among subfertile women – 9.6% vs 4.8% (Morel et al., Hum Reprod 2002)

- Impact of X chromosome mosaicism on IVF outcome?

- Congenital vs acquired age related mosaicism
Low-level sex chromosome mosaicism in female partners of couples undergoing ICSI therapy does not significantly affect treatment outcome

B. Sonntag¹, D. Meschede², V. Ullmann¹, P. Gassner³, J. Horst², E. Nieschlag³ and H. M. Behre¹,⁴

<table>
<thead>
<tr>
<th>Measures of ovarian response</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.3±0.95</td>
<td>33.6±0.80</td>
</tr>
<tr>
<td>Follicles &gt;17 mm (n)a</td>
<td>4.74 ± 0.36</td>
<td>4.49 ± 0.38</td>
</tr>
<tr>
<td>Oestradiol (pmol/l)a</td>
<td>7365.5 ± 848.6</td>
<td>6066.2 ± 906.6</td>
</tr>
<tr>
<td>Days of stimulation</td>
<td>11.74 ± 0.52</td>
<td>12.00 ± 0.53</td>
</tr>
<tr>
<td>Total FSH dosageb</td>
<td>52.71 ± 4.84</td>
<td>67.47 ± 10.24</td>
</tr>
<tr>
<td>Oocytes retrieved (n)</td>
<td>11.77 ± 1.28</td>
<td>10.43 ± 0.91</td>
</tr>
<tr>
<td>MII oocytes (n)</td>
<td>9.35 ± 1.20</td>
<td>7.46 ± 0.60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertilization rate (%)</td>
<td>55.9</td>
<td>51.6</td>
</tr>
<tr>
<td>Embryos transferred (n)</td>
<td>2.67 ± 0.12</td>
<td>2.57 ± 0.12</td>
</tr>
<tr>
<td>CES</td>
<td>30.90 ± 2.21</td>
<td>27.26 ± 1.72</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>12.5</td>
<td>17.8</td>
</tr>
<tr>
<td>Pregnancy rate (%)³</td>
<td>23.3</td>
<td>28.6</td>
</tr>
<tr>
<td>Abortion rate (%)</td>
<td>14.3</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Group I = 38 ICSI cycles in women with low level sex chromosome mosaicism
Group II = 38 ICSI cycles in control group without chromosomal abnormality
Does 45,X/46,XX mosaicism with 6–28% of aneuploidy affect the outcomes of IVF or ICSI?

L. Homer a,b,c,d,*, F. Morel b,c,d,e, F. Gallon e, M.-T. Le Martelot a, V. Amice e, V. Kerlan b,f, M. De Braekeleer b,c,d,e

Ovarian response and outcomes in the 45,X/46,XX (4%), 45,X/46,XX (6–28%) and 46,XX groups.

<table>
<thead>
<tr>
<th></th>
<th>45,X/46,XX 4% (n = 25 cycles)</th>
<th>45,X/46,XX 6–28% (n = 126 cycles)</th>
<th>46,XX (n = 128 cycles)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at oocyte retrieval (years)</td>
<td>35.2 ± 3.5</td>
<td>34.6 ± 3.9</td>
<td>34.9 ± 3.5</td>
<td>0.09</td>
</tr>
<tr>
<td>IVF with ICSI</td>
<td>70.0</td>
<td>77.0</td>
<td>75.9</td>
<td>0.72</td>
</tr>
<tr>
<td>Cancellation of cycle</td>
<td>12.0</td>
<td>11.9</td>
<td>10.2</td>
<td>0.89</td>
</tr>
<tr>
<td>Days of stimulation</td>
<td>12.5 ± 1.4</td>
<td>12.4 ± 2.1</td>
<td>12.7 ± 2.0</td>
<td>0.42</td>
</tr>
<tr>
<td>Total dose of follicle-stimulating hormone (UI)</td>
<td>2780 ± 978</td>
<td>2405 ± 961</td>
<td>2592 ± 941</td>
<td>0.11</td>
</tr>
<tr>
<td>Oestradiol (pg/ml)</td>
<td>2546 ± 909</td>
<td>2260 ± 909</td>
<td>2304 ± 995</td>
<td>0.47</td>
</tr>
<tr>
<td>Retrieved oocytes</td>
<td>7.9 ± 5.5</td>
<td>8.9 ± 5.5</td>
<td>8.5 ± 4.7</td>
<td>0.56</td>
</tr>
<tr>
<td>Atretic oocytes</td>
<td>1.0 ± 1.7</td>
<td>1.0 ± 1.3</td>
<td>1.1 ± 1.4</td>
<td>0.95</td>
</tr>
<tr>
<td>Metaphase II oocytes</td>
<td>6.2 ± 5.1</td>
<td>7.4 ± 4.7</td>
<td>6.9 ± 4.2</td>
<td>0.49</td>
</tr>
<tr>
<td>Embryos</td>
<td>2.7 ± 2.5</td>
<td>3.9 ± 3.7</td>
<td>2.9 ± 2.6</td>
<td>0.07</td>
</tr>
<tr>
<td>IVF fertilization rate</td>
<td>50.0</td>
<td>55.1</td>
<td>57.2</td>
<td>0.43</td>
</tr>
<tr>
<td>ICSI fertilization rate</td>
<td>92.9</td>
<td>90.8</td>
<td>89.2</td>
<td>0.77</td>
</tr>
<tr>
<td>Transferred embryos</td>
<td>1.6 ± 1.2</td>
<td>2.0 ± 1.1</td>
<td>1.8 ± 1.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Pregnancy/cycle</td>
<td>19.8</td>
<td>17.4</td>
<td>18.7</td>
<td>0.87</td>
</tr>
<tr>
<td>Pregnancy/transfer</td>
<td>22.7</td>
<td>23.7</td>
<td>26.4</td>
<td>0.67</td>
</tr>
</tbody>
</table>
Turner syndrome

- Incidence: 1/2500 newborn girls
  - Ovarian dysgenesis
  - 45% 45,X0 karyotype

- Premature ovarian insufficiency with 45,X0 karyotype

- Variable phenotype with mosaics related to proportion/location of affected cells
  - Spectrum of POR to POI

Danodille et al., Eur J Endocrinol 2012
Oocyte Cryopreservation for Fertility Preservation in Postpubertal Female Children at Risk for Premature Ovarian Failure Due to Accelerated Follicle Loss in Turner Syndrome or Cancer Treatments

K. Oktay MD 1,2.*, G. Bedoschi MD 1,2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>13</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>Turner syndrome</td>
<td>Turner syndrome</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Serum FSH (mU/ml)</td>
<td>5.7</td>
<td>5.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Serum LH (mU/ml)</td>
<td>3.9</td>
<td>9.5</td>
<td>5.3</td>
</tr>
<tr>
<td>Serum estradiol (ng/ml)</td>
<td>15.1</td>
<td>65.2</td>
<td>33.5</td>
</tr>
<tr>
<td>Serum AMH (ng/ml)</td>
<td>1.59</td>
<td>0.9/1.7*</td>
<td>0.76</td>
</tr>
<tr>
<td>Serum Inhibin B (pg/ml)</td>
<td>54.8</td>
<td>&lt;30.0</td>
<td>47.2</td>
</tr>
<tr>
<td>Antral follicle count</td>
<td>6</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Antagonist</th>
<th>Antagonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total gonadotropin stimulation dose</td>
<td>2475 IU rFSH + 150 IU rLH</td>
<td>1800 IU rFSH + 450 hMG/3750 IU rFSH + 2100 hMG</td>
<td>2025 IU hFSH + 75 IU rLH</td>
</tr>
<tr>
<td>Duration of ovarian stimulation</td>
<td>11</td>
<td>10/14</td>
<td>10</td>
</tr>
<tr>
<td>Peak E2 levels on the day of trigger (ng/ml)</td>
<td>1548</td>
<td>2275/2029</td>
<td>1613</td>
</tr>
<tr>
<td>Trigger medication and dose</td>
<td>3300 IU hCG</td>
<td>Lupron 1 mg/Lupron 1 mg</td>
<td>250mcg rhCG</td>
</tr>
<tr>
<td>Total number of oocytes retrieved</td>
<td>19</td>
<td>11/7</td>
<td>16</td>
</tr>
<tr>
<td>Number of mature oocytes cryopreserved</td>
<td>9 + 1 (IVM)</td>
<td>8/4</td>
<td>7 + 5 (IVM)</td>
</tr>
</tbody>
</table>

* Case 2 underwent 2 oocyte cryopreservation cycles.
**X chromosome regions for ovarian function**

Portnoi et al., *Hum Reprod* 2006

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**Dual colour (red and green) FISH showing one normal X chromosome (FISH) showing two normal X chromosomes and one deleted X chromosome**

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Whole X chromosome painting showing one normal X and one deleted X chromosome

Whole X chromosome (green) and chromosome 1 (red) painting showing the (X;1) translocation
X chromosome abnormalities and ovarian insufficiency

- X numerical abnormalities: 52%
- X structural abnormalities: 29%
- X-autosomal translocation: 14%
- XY cell line: 5%

Summary of frequency of chromosomal abnormalities in different population studies of POF:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Frequency of CA (%)</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>12.1</td>
<td>Chinese</td>
</tr>
<tr>
<td>Baronchelli et al. (2011)</td>
<td>10.0</td>
<td>Italian</td>
</tr>
<tr>
<td>Lakhal et al. (2010)</td>
<td>10.8</td>
<td>Tunisian</td>
</tr>
<tr>
<td>Ceylaner et al. (2010)</td>
<td>25.3</td>
<td>Turkish</td>
</tr>
<tr>
<td>Janse et al. (2010)</td>
<td>12.9</td>
<td>Dutch</td>
</tr>
<tr>
<td>Portnoi et al. (2006)</td>
<td>8.8</td>
<td>French</td>
</tr>
<tr>
<td>Zhang et al. (2003)</td>
<td>12.5</td>
<td>Chinese (Chongqing)</td>
</tr>
<tr>
<td>Devi and Benn. (1999)</td>
<td>13.3</td>
<td>English</td>
</tr>
<tr>
<td>Davison et al. (1998)</td>
<td>2.5</td>
<td>English</td>
</tr>
<tr>
<td>Castillo et al. (1992)</td>
<td>32.0</td>
<td>English</td>
</tr>
<tr>
<td>Rebar and Connolly (1990)</td>
<td>25.4</td>
<td>American</td>
</tr>
</tbody>
</table>

Jiao et al., Hum Reprod 2012
Genes linked to ovarian function

**Known human X chromosome-located functionally relevant genes**
- Basic helix-loop-helix protein (BHLHB9)
- **Bone morphogenetic protein 15 (BMP15)**
- Homologue of the *Drosophila* dachshund gene (DACH2)
- Second human homologue of the *Drosophila* diaphanous gene (DIAPH2)
- **Fragile X mental retardation syndrome (FMR1)**
- X-linked mental retardation, associated with fragile site FRAXE (FMR2)
- Premature ovarian failure 1B (POF1B)
- X-inactivation-specific transcript (XIST)
- X-prolyl aminopeptidase 2 (XPNPEP2)

**Known human autosomal functionally relevant genes**
- Autoimmune regulator (AIRE)
- Deleted in azoospermia-like (DAZL)
- Homologue of yeast disrupted meiotic cDNA 1 (DMC1)
- Eukaryotic translation initiation factor 5B (eIF5B)
- Oestrogen receptor 1 (ESR1)
- Homologue of murine factor in germline α (FIGLA)
- Forkhead transcription factor (FOXL2)
- Forkhead box 01A (FOXO1A)
- Forkhead box 03A (FOXO3A)
- β chain of follicle-stimulating hormone (FSHB)
- **Follicle-stimulating-hormone receptor (FSHR)**
- Galactose-1-phosphate uridylyltransferase (GALT)
- Growth-differentiation factor 9 (GDF9)
- G protein-coupled receptor 3 (GPR3)
- Type II 3-β-hydroxysteroid dehydrogenase deficiency (HSD3B2)
- Inhibin alpha (INHA)
- Luteinising hormone, β polypeptide (LHB)
- LIM homeobox gene 8 (LHX8)
- Homologue of Escherichia coli MutS, 5 (MSH5)
- Homologue of *Drosophila* Nanos3 (NANOS3)
- Homologue of murine newborn ovary homeobox (NOBOX)
- Homologue of murine noggin (NOG)
- Nuclear receptor subfamily 5, group A, member 1 (NR5A1)
- Progesterone receptor membrane component 1 (PGRMC1)
- DNA polymerase γ (POLG)
- Transforming growth factor-β receptor, type 3 (TGFBRIII)
- Y box-binding protein 2 (YBX2)

*De Vos et al., LANCET. 2010*
FMR1 gene

- **FMR1** (fragile X mental retardation 1) gene located on the long (q) arm of the X chromosome at position 27.3

- Codes for fragile X mental retardation protein (**FMRP**)

- **FMRP** essential for cognitive development and female reproductive function
**FMR1 gene**

- **FMR1 gene** contains a DNA segment CGG trinucleotide

- Four categories based on CGG repeat length
  - Normal: *FMR1* CGG repeat length < 45
  - Intermediate or “gray zone”: 45 – 54 repeats
  - Premutation: 55 – 199 repeats
  - Full mutation: ≥ 200 CGG repeats
FMR1 gene CGG repeats and ovarian reserve

Scattergram and correlation between FSH levels and CGG repeats in allele-2. FSH levels correlated significantly ($P<.01$) with CGG triple repeats on allele-2: $\text{FSH} = (-15.4 \pm 16.0) + (n \text{ CGG count}/5) \times (5.96 \pm 2.20)$. The graph does not show FSH levels $>20 \text{ mIU/mL}$. ◆ denotes POA; + denotes repeat aborters; ▼ denotes POF.

Scattergram of lowest AMH levels in correlation to repeats in allele-2. The AMH levels of $\geq 1.0 \text{ ng/mL}$ were significantly ($P<.04$) associated with increases in CGG triple repeats above 32. ◆ denotes POA; + denotes repeat aborters; ▼ denotes POF.

Gleicher et al., Fertil Steril 2009
FMR1 gene CGG repeats and ovarian function

Table II  Prevalence of the FMR1 premutation and intermediate allele in women with POI and in controls.

<table>
<thead>
<tr>
<th></th>
<th>Women with POI</th>
<th>Controls</th>
<th>$\chi^2$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premutation (55–200 repeats)</td>
<td>7/535 (1.3%)</td>
<td>1/521 (0.19%)</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Intermediate (45–54 repeats)</td>
<td>17/535 (3.2%)</td>
<td>7/521 (1.3%)</td>
<td>0.046</td>
<td></td>
</tr>
</tbody>
</table>

POI, primary ovarian insufficiency.

aSubjects with positive family history or an abnormal karyotype known to cause infertility are not included.

Karimov et al., Hum Reprod 2011

- FMR1 premutation identified in 0.8 – 13% of women with POI (Conway et al., Hum Reprod 1998; Murray et al., J Med Genet 1998; Gersak et al., Hum Reprod 2003; Bussani et al., Eur J Obstet Gynecol Reprod Biol 2004)
# FMR1 premutation and ovarian insufficiency

Tosh et al., *Arch Gynecol Obstet* 2014

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
<th>Ev/Case</th>
<th>Ev/Ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chatterjee et al</td>
<td>0.876 (0.017, 44.715)</td>
<td>0/80</td>
<td>0/70</td>
</tr>
<tr>
<td>Ishizuka et al</td>
<td>3.893 (0.185, 82.024)</td>
<td>2/128</td>
<td>0/98</td>
</tr>
<tr>
<td>Lai et al</td>
<td>15.895 (0.905, 279.246)</td>
<td>7/392</td>
<td>0/408</td>
</tr>
<tr>
<td>Present study</td>
<td>1.258 (0.025, 63.609)</td>
<td>0/286</td>
<td>0/360</td>
</tr>
<tr>
<td><strong>Subgroup Asian (I^2=0%, P=0.616)</strong></td>
<td><strong>3.909 (0.737, 20.741)</strong></td>
<td><strong>9/886</strong></td>
<td><strong>0/936</strong></td>
</tr>
<tr>
<td>Bussani et al</td>
<td>4.694 (0.233, 94.373)</td>
<td>3/45</td>
<td>0/28</td>
</tr>
<tr>
<td>Bodega et al</td>
<td>45.595 (2.733, 760.749)</td>
<td>19/190</td>
<td>0/200</td>
</tr>
<tr>
<td>Barasoain et al</td>
<td>4.333 (0.079, 236.480)</td>
<td>0/7</td>
<td>0/32</td>
</tr>
<tr>
<td>Murray et al</td>
<td>5.473 (1.724, 17.376)</td>
<td>5/254</td>
<td>7/1915</td>
</tr>
<tr>
<td><strong>Subgroup European (I^2=0%, P=0.573)</strong></td>
<td><strong>6.854 (2.582, 18.194)</strong></td>
<td><strong>27/496</strong></td>
<td><strong>7/2175</strong></td>
</tr>
<tr>
<td>Bretherick et al</td>
<td>2.033 (0.096, 43.249)</td>
<td>2/106</td>
<td>0/42</td>
</tr>
<tr>
<td>Kenneson et al</td>
<td>1.070 (0.043, 26.879)</td>
<td>0/33</td>
<td>1/108</td>
</tr>
<tr>
<td>Costa et al</td>
<td>17.545 (0.885, 347.736)</td>
<td>3/41</td>
<td>0/96</td>
</tr>
<tr>
<td><strong>Subgroup Other (I^2=0%, P=0.415)</strong></td>
<td><strong>3.597 (0.606, 21.346)</strong></td>
<td><strong>5/180</strong></td>
<td><strong>1/246</strong></td>
</tr>
<tr>
<td>Overall (I^2=0%, P=0.804)</td>
<td>5.419 (2.530, 11.606)</td>
<td>41/1562</td>
<td>8/3357</td>
</tr>
</tbody>
</table>

**Odds Ratio (log scale)**
Mutation in the Follicle-Stimulating Hormone Receptor Gene Causes Hereditary Hypergonadotrophic Ovarian Failure

Kristiina Aittomäki, José Luis Dieguez Lucena, Pirjo Pakarinen, Pertti Sistonen, Juha Tapanainen, Jörg Gromoll, Riitta Kaskikari, Eeva-Marja Sankila, Heikki Lehväslaiho, Armando Reyes Engel, Eberhard Nieschlag, Ilpo Huhtaniemi, and Albert de la Chapelle

Influence of follicle-stimulating hormone receptor (FSHR) Ser680Asn polymorphism on ovarian function and in-vitro fertilization outcome: A meta-analysis

Yao Yao \textsuperscript{a,b}, Cai-hong Ma \textsuperscript{c}, Hui-lin Tang \textsuperscript{a}, Yong-fang Hu \textsuperscript{a,*}

\textbf{Background:} A common follicle-stimulating hormone (FSH) receptor (or FSHR) polymorphism Ser680Asn (rs6166) was found to be associated with altered ovarian response in women undergoing in-vitro fertilization. To further investigate such an association, a meta-analysis was conducted.

\textbf{Methods:} A PubMed literature search was conducted to identify all cohort studies investigating such a relationship. The following parameters—basal FSH levels, total FSH doses, oocytes retrieved, and pregnancy rates—were used to evaluate the ovarian function, its response to exogenous FSH and in-vitro fertilization and intracytoplasmic sperm injection outcome.

\textbf{Results:} A total of 1421 cases were collected from eight studies. Of them, a significantly lower basal FSH level was observed in patients harboring Asn/Asn (NN) genotype than those carrying the Ser/Ser (SS) genotype both in Asian (WMD: $-2.57$ mIU/ml, 95% CI: $-2.96$ to $-2.19$, \(P<0.0001\)) and Caucasian retrospective groups (WMD: $-1.86$ mIU/ml, 95% CI: $-2.07$ to $-1.66$, \(P<0.0001\)) with no heterogeneity. Moreover, carriers of the SS tended to require greater FSH doses than NN (WMD: $-268.82$ IU, 95% CI: $-561.28$ to $23.63$, \(P=0.07\)).

Other parameters, such as oocytes retrieved and pregnancy rate, were not significantly different between the groups.

\textbf{Conclusion:} Carriers of the SS variant have slightly higher basal FSH levels, tending to require higher doses of exogenous FSH for stimulation.
Genetic Polymorphisms Influence the Ovarian Response to rFSH Stimulation in Patients Undergoing In Vitro Fertilization Programs with ICSI

Radia Boudjenah¹,²*, Denise Molina-Gomes¹,², Antoine Torre¹,², Marianne Bergere¹,², Marc Bailly¹,², Florence Boitrelle¹,², Stéphane Taieb², Robert Wainer¹,², Mohamed Benahmed³, Philippe de Mazancourt², Jacqueline Selva¹,², François Vialard¹,²*

PLoS ONE June 2012

Figure 1. Poor and high response risks, according to FSHR⁶⁶⁰ polymorphism genotypes.

Overall study Population

Homogeneous Subgroup

Overall study population

Homogeneous Subgroup

1: FSH Asn/Asn or/and AMH Ile/Ile
2: FSHR Ser/Ser and AMH Ser/Ser
Genetics of PCOS

- Complex polygenic trait
- Several genes in the multiple biochemical pathways implicated
  - Genes involved in ovarian steroidogenic hormones
  - Genes involved in steroid hormone effects
  - Gonadotrophin release and action genes
  - Insulin secretion and action genes
  - Adipose tissue metabolism genes
- Pro-inflammatory cytokine/ cytokine receptor genes
Interaction of genetics and environment

ETHNICITY

ENVIRONMENTAL FACTORS
- obesity
- sedentary life
- nutrition
- intrauterine affliction

PCOS PHENOTYPE

PREDISPOSING / PROTECTIVE GENES

Genes related to insulin resistance

Genes related to the biosynthesis and the action of androgens

Genes encoding inflammatory cytokines

Insuline resistance and impaired glucose tolerance

Hyperandrogenism

Inflammation

Deligeoroglou et al., Gynecol Endocrinol 2009
Genes involved in steroid biosynthesis

Qin et al., JCEM 2006, Jin et al., BMC Med Genet 2012
Genes involved in steroid hormone effect

Higher frequency of AR gene polymorphism in PCOS (Hickey et al., JCEM 2002)
- Correlation between increased serum testosterone and AR gene polymorphism

Positive correlation between SHBG gene polymorphism and PCOS (Ferk et al., Hum Reprod 2007)
- Decreased SHBG concentrations contribute to increased androgen output to tissues
Genes related to insulin secretion and action

- Insulin gene on chromosome 11
- Insulin receptor gene on chromosome 19
- Insulin receptor substrate (IRS) -1 gene (Ruan et al., Endocr J 2012)
- IRS – 2 gene
- Insulin growth factor (IGF) – 1 gene
- IGF – 2 gene (Millan et al., JCEM 2004)
Genetic basis of PCOS

- PCOS genes still await clearer unfolding

- Difficulties with genetic studies in PCOS
  - Different diagnostic criteria
  - Varied phenotypes
  - Inadequate understanding of the pathophysiology
  - Small sample size
  - Failure to attempt replication of findings
  - Lack of an animal model
Functional genetic polymorphisms and female reproductive disorders: Part I: polycystic ovary syndrome and ovarian response

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BACKGROUND: The identification of polymorphisms associated with a disease can help to elucidate its pathogenesis, and this knowledge can be used to improve prognosis for women with a particular disorder, such as polycystic ovary syndrome (PCOS). Since an altered response to ovarian stimulation is also a characteristic of the disease, further knowledge about its aetiology could help in defining the parameters that determine the response of an individual to ovarian stimulation. METHODS: PubMed and EMBASE databases were systematically searched for gene association studies published until the end of August 2007, using search criteria relevant to PCOS and ovarian response to stimulation. Data from additional papers identified through hand searches were also included; 139 publications were reviewed. RESULTS: Several genes involved in ovarian function and metabolism are associated with increased susceptibility to PCOS, but none is strong enough to correlate alone with susceptibility to the disease, or response to therapy. A single-nucleotide polymorphism in exon 10 of the FSH receptor (FSHR) gene, FSHR p.N680S, was consistently identified as having a significant association with ovarian response to FSH. CONCLUSIONS: No consistent association between gene polymorphism and PCOS could be identified. The FSHR gene may play a significant role in the success of ovarian stimulation, and can be used as a marker to predict differences in FSHR function and ovarian response to FSH. Genotyping the FSHR p.N680S polymorphism may provide a means of identifying a population of poor responders before in vitro fertilization procedures are initiated.
Genome wide association studies

- Significant copy number variations (CNVs) among women with POI (Aboura et al., JCEM 2009)

- Strong association between PCOS and 3 loci: 2p16.3, 2p21 and 9q33.3 (Chen et al., Nat Genet 2011)
Conclusion

- Underlying genetics determining
  - Ovarian reserve
  - Ovarian response to stimulation
  - POR and POI
  - Hyper response and susceptibility to OHSS
- Further elucidation with advances in genetic evaluation
- Incorporation of pharmacogenomics into individualised fertility management
Thank you
Thank you
Thank you
Thank you