Idiopathic primary ovarian insufficiency: a study of serial hormonal profiles to assess ovarian follicular activity

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BACKGROUND: Ovarian follicular activity in serial hormone profiles has been reported in up to 86% of patients with primary ovarian insufficiency (POI). In most of these studies, patients had a short duration of amenorrhea or irregular menstrual cycles which could influence the occurrence of spontaneous follicular activity. The aim was to study the incidence of follicular activity in serial hormonal profiles of women with spontaneous POI and amenorrhea of 1 year duration.

METHODS: This observational study involved 20 patients with spontaneous POI, amenorrhea of >1 year duration and normal karyotype. Serum measurements of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone, free T3, free T4, thyroid-stimulating hormone and anti-thyroperoxidase antibodies, taken in the absence of estrogen replacement, were followed by weekly measurements of serum E2, FSH, LH and progesterone for 1 month then monthly measurements for 2 months. Increases in serum E2 >184 pmol/l and serum progesterone >10 nmol/l were taken as evidence of follicular activity and ovulation, respectively.

RESULTS: A rise in serum E2 >184 pmol/l was noted in 2/18 subjects [11.1%; 95% confidence interval (CI): 1.4–34.7%]. Though the corresponding serum FSH levels showed a decline, the values remained >40 IU/l. None of the subjects had serum progesterone levels >10 nmol/l, return of menses or pregnancy.

CONCLUSION: Endogenous ovarian follicular function is intermittently present in only 11.1% of Asian Indian women with POI. However, the 95% CI (1.4–34.7%) was large due to a small sample size.

Key words: primary ovarian insufficiency / premature ovarian failure / estradiol / follicular activity / remission

Introduction

Primary ovarian insufficiency (POI) is the syndrome consisting of primary or secondary amenorrhea and hypergonadotrophic hypogonadism in women <40 years of age (de Moraes-Ruehsen and Jones, 1967; Welt, 2008; Rebar, 2009). It is diagnosed on the basis of two measurements of serum follicle-stimulating hormone (FSH) >40 IU/l taken 4–6 weeks apart (Conway, 2000; Nelson, 2009). Studies of serial hormone profile in patients with POI have reported spontaneous follicular activity in up to 86% (Rebar et al., 1982; Boyers et al., 1988; Nelson et al., 1994; Taylor et al., 1996; Welt et al., 2005). Spontaneous clinical remission has also been reported in 5–10% of spontaneous POI patients (van Kasteren and Schoemaker, 1999; Goswami and Conway, 2005; Nelson, 2009).

In one of our previous studies, we observed 52 patients with POI over 2 years period (Goswami et al., 2003). Thyroid autoimmunity was found to be common (24%) with a prevalence rate similar to that reported by other investigators (Goswami et al., 2006). However, in our clinical practice we have not observed occurrence of spontaneous remission or pregnancy in any of the patients except in one who had associated hypoparathyroidism. Past studies reporting a high incidence of ovarian follicular activity in POI included patients with irregular menses and a short duration of amenorrhea (Rebar et al., 1982; Taylor et al., 1996; Welt et al., 2005). The variability in the incidence of spontaneous follicular activity in POI could be influenced by duration of amenorrhea. In the present study we report the incidence of follicular activity on serial hormonal profile in patients with POI presenting with amenorrhea of more than 1 year duration.
Methods

The study subjects included all the patients with spontaneous POI attending the Gynec-Endocrinology clinic at the Maulana Azad Medical College and Lok Nayak Hospital, New Delhi during 2008–2009. The inclusion criteria were (i) age < 40 years, (ii) amenorrhea of > 1 year duration and (iii) serum FSH ≥ 40 IU/l on at least two occasions 4–6 weeks apart. Patients with iatrogenic ovarian insufficiency or abnormal karyotype and those who expressed their inability for regular weekly follow-up during the study protocol were excluded. Of the 27 patients with POI attending the clinic, 5 did not give consent for the study, 1 had ovarian insufficiency following bilateral ovarian surgery and 1 had isochromosome X. The 20 eligible patients with spontaneous POI were included in the study. The enrollment scheme for the study subjects is given in Fig. 1. Written consent was obtained from each of the subjects recruited for the study.

A detailed history was taken from all the patients including age, duration of amenorrhea, pattern of preceding menstrual cycles, past pregnancies, associated thyroid or other autoimmune disease, symptoms (hot flushes, genitourinary complaints), smoking, any pelvic surgery, any family history of POI or early menopause (i.e. at age < 45) and details of past hormonal treatments. Patients with secondary amenorrhea were also asked about their age at menarche. An examination involved height and weight measurements for body mass index (BMI) and a general systemic and pelvic examination.

Baseline investigations were carried out at presentation. Those who were on hormone replacement were asked to stop use for 2 months for baseline investigations (n = 10). They were given the telephone numbers of first and second authors (D.G. and A.A.) and were asked to report any symptom due to estrogen withdrawal. Studies in the past have used a wash-out period varying from 1 week to 3 months (Rohr et al., 1999; Christin-Maire et al., 2003; Anderson et al., 2004) and the peak incidence of vasomotor symptoms after discontinuation of hormonal replacement was reported at about 8 weeks (Gordon et al., 2004).

The baseline investigation (Sample 1) in all subjects included fasting serum FSH, LH, E2, progesterone, free T3, free T4, thyroid-stimulating hormone (TSH) and anti-thyroperoxidase (anti-TPO) antibodies. Ultrasound evaluation of the ovaries was done on a Phillips HD11 machine within a week of baseline blood sampling. It was performed by trained radiologists at our institution who were aware of the diagnosis. One of the authors (A.A.) was present during the ultrasound scans. The number and size of ovarian follicles were noted for both ovaries and the 2D ovarian volume was calculated using the prolate ellipsoid formula, i.e. length × width × height × 0.523 (Sample et al., 1977). The lower size limit for definition of a follicle was 5 mm.

After initial assessment, subjects were asked to report for weekly follow-ups in the first month (Samples 2, 3 and 4) and then every month for the next 2 months (Samples 5 and 6). Blood samples were drawn in a fasting state at each visit for serum FSH, LH, E2 and progesterone.

After 3 months of serial blood sampling, patients were put on oral conjugated equine estrogen of 0.625 mg (Premarin, Wyeth) from Days 1 to 25 and medroxy progesterone acetate 10 mg (Meprate, Serum international) from Days 16 to 25. Thirteen subjects who were sexually active and desirous of pregnancy were followed up for a further 9 months to note occurrence of pregnancy.

The ethical committee of Maulana Azad Medical College and associated Lok Nayak Hospital approved the study protocol.

Definitions

Patients were considered to have evidence of ovarian follicular activity if there was a rise of serum E2 > 184 pmol/l (50 pg/ml, conversion factor of 3.671) in any of the six samples. Serum E2 levels of < 184 pmol/l are typical of women with absent or non-functioning follicles since most of the E2 is produced by the granulosa cells surrounding the developing oocyte (Baird and Fraser, 1974; Rebar, 2009). Hence, this cutoff was used as the indicator of follicular activity.

Presence of serum progesterone > 10 nmol/l (3 ng/ml, conversion factor of 3.18) in any of the six samples was taken as the presumptive evidence of ovulation since plasma concentrations of progesterone in the follicular phase rarely exceed 10 nmol/l (Israel et al., 1972; Li and Cooke, 1991).

Hypothyroidism was diagnosed if serum TSH was at least 5 mU/ml along with anti-TPO antibodies > 34 IU/ml or if serum TSH was at least 10 mU/ml with normal anti-TPO antibodies (Goswami et al., 2006).

Biochemical assessment

All hormonal assays were done on fasting blood samples to minimize inter-individual variation (Esche et al., 2007). The serum samples drawn for hormone estimations and anti-TPO antibodies were stored at −20°C and assayed together to minimize inter-assay variations. All the assays were performed using chemiluminescence immunoassay (Roche diagnostic elecsys immunoassay system, Germany) in the department of biochemistry of our institution (author A.S.). The inter- and intra-assay variations for serum FSH, LH, E2 and progesterone were 5.3 and 1.8%, 5.25 and 1.8%, 6.2 and 5.7% and 5.4 and 2.4%, respectively.
### Table I Baseline characteristics of the study subjects.

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age (years)</th>
<th>Amenorrhea and duration (years)</th>
<th>Menarche (years)</th>
<th>Hypothyroid</th>
<th>Past estrogen replacement</th>
<th>BMI (kg/m²)</th>
<th>Serum FSH (IU/l)</th>
<th>Serum LH (IU/l)</th>
<th>Serum E2 (pmol/l)</th>
<th>Serum Progesterone (nmol/l)</th>
<th>Right ovary volume (ml)</th>
<th>Left ovary volume (ml)</th>
<th>Folliclesa</th>
<th>Folliclesb</th>
</tr>
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<tr>
<td>1</td>
<td>28</td>
<td>Secondary (1.5)</td>
<td>15</td>
<td>No</td>
<td>No</td>
<td>22.7</td>
<td>126.00</td>
<td>55.97</td>
<td>84.47</td>
<td>1.68</td>
<td>2.6</td>
<td>1.2</td>
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<td>Few</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>Secondary (5)</td>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>24.0</td>
<td>141.50</td>
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<td>&lt;18.36</td>
<td>0.84</td>
<td>0.9</td>
<td>1.0</td>
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<td>Absent</td>
</tr>
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<td>3</td>
<td>34</td>
<td>Secondary (3)</td>
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<td>No</td>
<td>24.6</td>
<td>187.00</td>
<td>99.00</td>
<td>57.38</td>
<td>0.99</td>
<td>1.6</td>
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<td>Few</td>
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<tr>
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<td>36</td>
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<td>21.9</td>
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<td>Yes</td>
<td>28.8</td>
<td>91.39</td>
<td>40.36</td>
<td>24.49</td>
<td>0.53</td>
<td>1.6</td>
<td>1.3</td>
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<tr>
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<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>21.2</td>
<td>121.50</td>
<td>42.21</td>
<td>&lt;18.36</td>
<td>1.52</td>
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<td>0.5</td>
<td>Absent</td>
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<tr>
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<td>No</td>
<td>24.9</td>
<td>118.50</td>
<td>43.8</td>
<td>23.16</td>
<td>0.76</td>
<td>1.5</td>
<td>3.0</td>
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<td>Few</td>
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<td>11</td>
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<td>31.0</td>
<td>71.02</td>
<td>57.79</td>
<td>50.37</td>
<td>1.27</td>
<td>1.4</td>
<td>1.6</td>
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<td>Few</td>
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<tr>
<td>9</td>
<td>31</td>
<td>Secondary (2)</td>
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<td>No</td>
<td>No</td>
<td>22.5</td>
<td>178.00</td>
<td>77.08</td>
<td>38.69</td>
<td>0.79</td>
<td>1.6</td>
<td>1.0</td>
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<td>Few</td>
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<td>10</td>
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<td>15</td>
<td>No</td>
<td>No</td>
<td>24.8</td>
<td>79.00</td>
<td>41.2</td>
<td>&lt;18.36</td>
<td>0.32</td>
<td>1.1</td>
<td>2.1</td>
<td>Few</td>
<td>Few</td>
</tr>
<tr>
<td>11</td>
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<td>Secondary (1)</td>
<td>16</td>
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<td>Yes</td>
<td>23.6</td>
<td>84.56</td>
<td>55.78</td>
<td>18.69</td>
<td>1.49</td>
<td>0.6</td>
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<td>Few</td>
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<tr>
<td>12</td>
<td>20</td>
<td>Primary</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>21.6</td>
<td>61.26</td>
<td>30.09</td>
<td>&lt;18.36</td>
<td>1.23</td>
<td>0.6</td>
<td>0.6</td>
<td>Multiple</td>
<td>Multiple</td>
</tr>
<tr>
<td>13</td>
<td><strong>20</strong></td>
<td>Primary</td>
<td><strong>NA</strong></td>
<td><strong>No</strong></td>
<td><strong>Yes</strong></td>
<td>20.8</td>
<td><strong>54.75</strong></td>
<td><strong>33.42</strong></td>
<td><strong>172.79</strong></td>
<td><strong>1.76</strong></td>
<td><strong>0.5</strong></td>
<td><strong>0.7</strong></td>
<td>Few</td>
<td>Multiple</td>
</tr>
<tr>
<td>14</td>
<td>38</td>
<td>Secondary (2)</td>
<td>14</td>
<td>Yes</td>
<td>No</td>
<td>26.5</td>
<td>85.34</td>
<td>44.93</td>
<td>34.07</td>
<td>0.66</td>
<td>1.0</td>
<td>1.8</td>
<td>Multiple</td>
<td>Few</td>
</tr>
<tr>
<td>15</td>
<td>32</td>
<td>Secondary (6)</td>
<td>16</td>
<td>No</td>
<td>No</td>
<td>20.1</td>
<td>132.00</td>
<td>62.41</td>
<td>&lt;18.36</td>
<td>0.52</td>
<td>0.6</td>
<td>0.5</td>
<td>Few</td>
<td>Few</td>
</tr>
<tr>
<td>16</td>
<td>38</td>
<td>Secondary (1.5)</td>
<td>14</td>
<td>No</td>
<td>No</td>
<td>22.8</td>
<td>75.47</td>
<td>48.94</td>
<td>&lt;18.36</td>
<td>1.14</td>
<td>0.9</td>
<td>1.0</td>
<td>Few</td>
<td>Few</td>
</tr>
<tr>
<td>17</td>
<td>38</td>
<td>Secondary (2)</td>
<td>12</td>
<td>Yes</td>
<td>Yes</td>
<td>27.5</td>
<td>83.76</td>
<td>61.79</td>
<td>37.22</td>
<td>1.05</td>
<td>0.7</td>
<td>0.8</td>
<td>Multiple</td>
<td>Multiple</td>
</tr>
<tr>
<td>18</td>
<td>36</td>
<td>Secondary (4)</td>
<td>15</td>
<td>Yes</td>
<td>No</td>
<td>25.5</td>
<td>128.10</td>
<td>63.35</td>
<td>20.34</td>
<td>1.19</td>
<td>3.5</td>
<td>3.2</td>
<td>Few</td>
<td>Few</td>
</tr>
</tbody>
</table>

Patients 1 and 13 (indicated in bold fonts) showed evidence of follicular activity on serial hormonal monitoring.

aFew, follicle count ≤ 5; multiple, follicle count > 5; all were < 10 mm in size.

bThese two patients failed to follow-up for serial blood sampling and were dropped from analysis.
Statistical analysis
SPSS (version 11.5) was used to analyze the data. The incidence of follicular activity was expressed as a proportion (%) along with the 95% confidence interval (CI).

Results

Patient characteristics
There were 20 patients recruited for the study (Table I): 16 patients presented with secondary amenorrhea and 4 had primary amenorrhea. The average age at presentation of the subjects with secondary amenorrhea was $34.7 \pm 4.2$ years and the age of those who presented with primary amenorrhea was $19.3 \pm 1.5$ years. The duration of secondary amenorrhea was $3.7 \pm 2.6$ years at the time of recruitment into the study protocol. The mean age of menarche in patients with secondary amenorrhea was $14.2 \pm 1.5$ years. Of the 16 patients with secondary amenorrhea, 10 had symptoms of hypoes-
trogenemia. None of the subjects had history of smoking. There were 13 patients, all with secondary amenorrhea, who were sexually active.

Table II Weekly mean serum FSH, LH, E2 and progesterone values (off estrogen treatment) in 18 patients with POI.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Serum FSH (IU/l)</th>
<th>Serum LH (IU/l)</th>
<th>Serum E2 (pmol/l)</th>
<th>Serum progesterone (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Baseline)</td>
<td>102.6 ± 31.8</td>
<td>53.2 ± 13.9</td>
<td>35.97 ± 38.18</td>
<td>1.27 ± 0.64</td>
</tr>
<tr>
<td>2</td>
<td>101.1 ± 32.1</td>
<td>52.6 ± 13.0</td>
<td>44.42 ± 60.57</td>
<td>0.95 ± 0.64</td>
</tr>
<tr>
<td>3</td>
<td>97.7 ± 35.4</td>
<td>52.0 ± 14.5</td>
<td>38.18 ± 48.82</td>
<td>0.95 ± 0.32</td>
</tr>
<tr>
<td>4</td>
<td>95.9 ± 33.6</td>
<td>49.7 ± 12.3</td>
<td>39.28 ± 52.13</td>
<td>0.95 ± 0.32</td>
</tr>
<tr>
<td>5</td>
<td>102.3 ± 36.3</td>
<td>50.9 ± 14.4</td>
<td>44.79 ± 54.69</td>
<td>0.95 ± 0.64</td>
</tr>
<tr>
<td>6</td>
<td>97.2 ± 37.9</td>
<td>51.6 ± 12.3</td>
<td>45.89 ± 75.25</td>
<td>0.95 ± 0.32</td>
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</tbody>
</table>

Figure 2 Serial hormonal levels of the 18 subjects completing the study.
and 8 of them reported at least one successful pregnancy in the past. Of the 16 subjects with secondary amenorrhea, 7 (43.5%) had hypothyroidism and were on thyroxin therapy. Three of them had raised levels of serum anti-TPO antibodies.

The baseline serum FSH and LH values were \( > 40 \text{ IU/l} \) in all except 2 women who had serum LH levels of 30 and 33 IU/l. None of the 10 subjects who had their hormone therapy discontinued prior to baseline hormonal study reported any estrogen withdrawal symptom.

On baseline ultrasonography (USG), a follicle count of five or less was labeled as a few follicles and was observed in 60% of the patients; 30% had more than five ovarian follicles (labeled as multiple follicles) in at least one ovary. All the follicles were \(< 10 \text{ mm} \) in size. Ovarian follicles were not visualized in 10% of the cases. The 2D ovarian volumes of all the cases are given in Table I.

### Serial hormonal profile

Of the 20 patients, 18 completed the study protocol including all serial samplings for 3 months. Two patients, one each with primary and secondary amenorrhea did not report for follow-up at the stipulated time of sampling and were, therefore, dropped from further analysis (Table I). The serial serum FSH, LH, E2 and progesterone levels of 18 subjects, taken at 6 points, are shown in Fig. 2 and Table II. Serum FSH remained \( > 40 \text{ IU/l} \) in all patients in all six serial samples. A rise in serum E2 \( > 184 \text{ pmol/l} \) was noted in 2/18 subjects (11.1%; 95% CI: 1.4–34.7%), in Patients 1 and 13. A careful analysis of individual values showed that Patients 1 and 13 showed the rise in serum E2 values \( > 184 \text{ pmol/l} \) in 3/6 and 2/6 samples, respectively.

Patient 1 showed a rise in serum E2 values in Samples 4, 5 and 6. The corresponding serum FSH values showed a decline (Fig. 3). This patient had presented with secondary amenorrhea for 18 months and had never received hormonal replacement. Her BMI was 22.7 kg/m\(^2\). Her thyroid function tests were normal and both of her ovaries had \(< 5 \text{ follicles} \) on baseline USG.

Patient 13 showed a rise in serum E2 values in Samples 2 and 3; the corresponding serum FSH levels were low (Fig. 3). This patient had primary amenorrhea and was on hormonal replacement, which was stopped for 2 months prior to baseline blood sampling as per the study protocol. Her BMI was 20.8 kg/m\(^2\). Her thyroid function tests were also normal and on baseline USG \(< 5 \text{ follicles} \) were noted in both the ovaries.

Thus in both these cases the rise in serum E2 was associated with a relative fall in serum FSH, but values remained \( > 40 \text{ IU/l} \). Their serum progesterone levels were \(< 3 \text{ nmol/l} \) in all six samples.

After the completion of the study protocol of serial hormone sampling, all of the 18 subjects were put on estrogen progesterone replacement. None of 13 patients who were sexually active conceived during the next 9 months of follow-up.

### Discussion

In the present study only 11.1% of the patients with POI and amenorrhea of \( \geq 1 \) year duration showed an increase in serum E2 levels suggestive of ovarian follicular activity on serial hormonal sampling. None of them conceived or showed evidence of ovulation during the period of study.

Previous studies have reported a high incidence of endogenous ovarian follicular activity (47–86%) and ovulation (16–49%) in POI (Randolph et al., 2004). Rebar et al. (1982) did daily blood sampling in 18 women with idiopathic POI and identified two patterns of hormonal profile. One was that of sustained high levels of FSH, FSH/LH ratio \( \geq 1 \) and low E2. The other was that of increased serum E2 with appropriate feedback response of gonadotrophins (decrease in serum FSH and FSH/LH ratio \(< 1 \)). They recommended that patients with the latter type of hormonal pattern on weekly hormonal assays may be considered for ovulation induction.

Boyers et al. (1988) reported elevated serum E2 levels in 22% of cases with idiopathic POI on serial hormonal assays, but none of them responded to high-dose hMG for ovulation induction. Recently Hubayter et al. (2010) studied 97 patients with POI and reported the presence of antral follicles (size \( \geq 3 \text{ mm} \)) on ultrasound in 73%. However, these follicles failed to respond to FSH stimulation even when their size was \( \geq 8 \text{ mm} \).

Nelson et al. (1994) did weekly hormonal sampling and USG in 57 Caucasians and Afro-Americans women with POI and observed raised serum E2 levels suggestive of follicular activity and raised progesterone levels suggestive of ovulation in 49 and 16% of the subjects, respectively. Serum concentrations of E2 have been reported to be 20% lower in Asian women than in Caucasian and Afro-American women over the entire midlife age range (Randolph et al., 2004). There is no study reporting on fluctuations in serum E2 levels in Asian Indian women with POI.

Taylor et al. (1996) conducted a 12-week crossover trial of estradiol treatment with serial hormonal and USG monitoring in 31 patients with POI. Follicular activity was reported in 78% of the subjects.
<table>
<thead>
<tr>
<th>S. no.</th>
<th>Reference</th>
<th>n*b</th>
<th>Clinical characteristics</th>
<th>Abnormal karyotype</th>
<th>Autoimmune association</th>
<th>Sampling-serum FSH, LH, E2, progesterone</th>
<th>Remission parameters</th>
<th>Ovulation parameters</th>
<th>Pregnancy</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily × 1 months</td>
<td>Follicular activity</td>
<td>Ovulation parameters</td>
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<td>18 (4,14)</td>
<td>Irregular menses or amenorrhea</td>
<td>None</td>
<td>7 thyroid</td>
<td>E2 &gt;50 pg/ml (184 pmol/l)</td>
<td>50%</td>
<td>27%</td>
<td>1</td>
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<tr>
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<td>Boyers et al., 1988</td>
<td>19 (0,19)</td>
<td>8– pelvis surgery 1–chemotherapy</td>
<td>I</td>
<td>None</td>
<td>Weekly × 5 wks (off HRT × 6 weeks)</td>
<td>47%</td>
<td>None</td>
<td>1</td>
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<td>3</td>
<td>Nelson et al., 1994</td>
<td>65 (3,62)</td>
<td>Amenorrhea Median 2.8 year (9 months–11 year)</td>
<td>None</td>
<td>27 (21 thyroid)</td>
<td>Weekly × 2–6 months + USG</td>
<td>49%</td>
<td>16%</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Taylor et al., 1996</td>
<td>31 (1,30)</td>
<td>Amenorrhea ≤ 1 year in 23 subjects</td>
<td>8/18 tested</td>
<td>21 (11 thyroid)</td>
<td>Weekly × 12weeks + USG (6 weeks on and 6 weeks off estradiol)</td>
<td>78%</td>
<td>46%c</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Welt et al., 2005</td>
<td>49 (37 from study no. 4)</td>
<td>As in study no. 4</td>
<td>9/25 tested</td>
<td>25 (12 thyroid)</td>
<td>As in study no.4</td>
<td>86%</td>
<td>49%</td>
<td>As in study no.4</td>
</tr>
<tr>
<td>6</td>
<td>Present study</td>
<td>18 (4,14)</td>
<td>Amenorrhea &gt;1 year</td>
<td>None</td>
<td>7 thyroid</td>
<td>Weekly × 1 month → monthly × 2 months (off HRT × 2 months)</td>
<td>11% (95% CI: 1.4–34.7%)</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*aFigures in bracket indicate number of patients with primary and secondary amenorrhea, respectively.
*b100% in subjects with amenorrhea <3 months and 26% in those with >3 months amenorrhea.
The ovulation rate was 100% in subjects with amenorrhea <3 months and 26% in those with >3 months amenorrhea. Welt et al. (2005) studied 49 women with POI (including 37 from Taylor’s study) and reported similar findings (Table III).

Bidet et al. (2008) observed five pregnancies in a cohort of 302 women with POI all of which occurred less than a year after the diagnosis of POI. They proposed that a short duration of amenorrhea and presence of cycle-to-cycle variability of serum FSH and E2 may be the potential predictors of ovarian functions in POI.

Most of the studies reporting a high incidence of spontaneous follicular activity in POI have included subjects with irregular menses or shorter durations of amenorrhea (Table III). The current study included a homogenous group of Asian Indian women with POI and amenorrhea of >1 year duration. The clinical presentation of the study subjects was similar to that reported in other studies (Conway et al., 1996; Bachelot et al., 2009). It is possible that with an increasing duration of amenorrhea there is a progressive decline in ovarian activity in POI. This could be the reason for the low incidence of follicular activity observed in the current study. This observation has implications when counseling newly diagnosed cases of POI regarding the prognosis for fertility.

The limitations of this study include a small sample size leading to a wide CI. The upper limit of a 95% CI is 34.7%, which indicates that even in the worst of circumstances these patients may have ovarian function intermittently. It would require about 420 cases of POI to estimate the incidence of follicular activity in this condition with an absolute error margin of 3% in a two-sided 95% CI. This may not be feasible in a single center within a reasonable time frame. The other limitations of the study are that single gene disorders that relate to POI were not studied and serial ultrasound monitoring to elicit ovarian follicular dynamics concomitant with serial hormonal assessment was not undertaken. Ultrasound assessment was done by different sonologists so inter-observer variability in observations cannot be excluded. The strength of the study lies in the fact that the studied population was a homogenous group of subjects comprising a cohort of Asian Indian women with POI and amenorrhea of >1 year duration.

In conclusion, endogenous ovarian follicular function is intermittently present in only 11.1% of Asian Indian women with POI. However, the 95% CI (1.4–34.7%) was large due to a small sample size.

Authors’ roles

D.G., as the chief investigator, planned the study design, recruited the patients and followed them up. She also analyzed the data and wrote the manuscript. A.A. collected the clinical data, did serial blood samplings and followed up the patients. She compiled the data and helped in its analysis. A.S. from the department of Biochemistry provided the hormonal assay results. S.B. reviewed the manuscript.

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