Introduction

The view of deficient ovarian reserve had gained general acceptance in infertility practice. In in vitro fertilization (IVF), the linking of poor ovarian response due to deficient ovarian reserve with cycle cancellation and a significant decrease in success rates is well defined [1,2]. Proper identification of women who are at risk for poor response can help gynecologists to individualize counseling and allow women to decide whether to undergo a needed infertility management. Accurate evaluation of ovarian response potential before women enter an IVF program is, so, of an outstanding importance.

It is well known that reproductive aging is linked to both a quantitative and a qualitative decrease of the primordial follicle count. As women age, their ovarian reserve declines, and the rates of both spontaneous and treatment-induced pregnancies decrease. But, for individual predictions of ovarian response and IVF success, chronological age only is of limited importance. Basal FSH was the first used endocrine marker of ovarian response that had better potential than age alone for predicting diminished ovarian function and decreased success rates after IVF [3]. However related to this phenomenon, FSH and age appeared to be independent prognostic indicators of assisted reproduction success rate [4].

Recently, many biomarkers of ovarian reserve are suggested. Basal Estradiol (E2) is a natural estrogen produced by follicular granulosa cells. Estradiol levels (<20 or >80 pg/ml) on day 3 might indicate poor responder; if E2 level is high then even if FSH is normal we cannot predict that ovarian reserve is quite normal [5-7]. This was an outstanding finding, as increased E2 values might be able to stop FSH into the normal level in women who have substantially decreased ovarian reserve and eventually may lead to false-negative FSH test results. Also, basal inhibin B has been advocated as an endocrine prognostic indicator for assisted reproduction success, although reports were conflicting [8-10].

Many articles have been published lately on the usefulness of ovarian sonar characters in predicting diminished ovarian potential during hormone induction. The antral follicle count (AFC) as well as the volume of the ovary seemed to be indicative of diminished response in assisted reproduction [11-13].

In this retrospective study we investigated the relationship between clinical, endocrinologic, chromosomal, and immunologic parameters and intermittent ovarian activity, including follicle growth, ovulation, and pregnancy rate, of 80 POI women with desired fertility.
Patients and Methods

The study includes 80 women with premature ovarian insufficiency enrolled consecutively from International Fertility Centre Kingdom Saudi Arabia and studied retrospectively.

Inclusion criteria were

1. The age was between 18-40 years old.
2. Women with premature ovarian insufficiency. POI was defined as at least 3 months of amenorrhea, 2 serum FSH readings > 40 mIU/mL.
3. None of the patients had male factor infertility or a history of pelvic radiotherapy.

Exclusion criteria were

1. Known or definitive causes explaining infertility like: history of maternal hyperprolactinemia, luteal insufficiency (detected due to repeatedly decreased luteal progesterone level), hyperandrogenism, polycystic ovary syndrome or hypersecretion of luteinizing hormone (LH) and insulin resistance.
2. Acquired (antiphospholipid syndrome) or hereditary thrombophilic disorders.
3. Different forms of uterine malformation had been ruled out by ultrasound and hysteroscopy.
4. Karyotype abnormalities (as Turner syndrome).

Women were subjected to the following procedures

a) Full history: presumed age at the onset of POI; age at menarche; age at the initial visit; personal history of autoimmunity; history of pregnancy and/or delivery; iatrogenic history, including chemotherapy or surgery on the ovary; hormonal evaluation, including determination of E2 and FSH; and systematic screening for thyroid autoimmunity. The onset of POI was presumed based on irregular menstruation or amenorrhea.

b) Detailed examination (general, abdominal and local)

c) Investigations have been collected from the cases which include mainly:
   - Lupus anticoagulant antibodies.
   - Karyotyping.
   - Anticardiolipin antibodies.
   - Semen analysis from their husbands.
   - Radiological examination in the form of pelvic ultrasonography and hysterosalpingography.

d) Pelvic ultrasound screening included the presence or absence of follicles. Follicle growth was defined as the presence of follicle(s) of any size in the ovary with a serum E2 > 25 pg/mL, or the presence of a follicle(s) in which the mean diameter was > 14 mm with or without an E2 measurement. Ovulation was defined as the disappearance of the follicle(s) and/or formation of a corpus luteum after confirmation of follicle growth with or without administration of human chorionic gonadotropin. Patients with POI desiring pregnancy with their own oocytes provided a semen specimen from their partner for analysis and underwent hysterosalpingography to rule out other causes of infertility. They were then most often treated with cyclic hormone therapy (cyclic EPT) using estrogen (conjugated equine estrogen [CEE], 1.25 - 2.5 mg [Premarin, 2 - 4 tablets]/day for 7- 28 days, representing an absolute time period) followed by estrogen in combination with progestin (0.5 mg norgestrel and 0.05 mg ethinylestradiol [Planovar, 1 tablet] or 2.00 mg chloromadinone acetate and 0.05 mg mestranol [Lutetion, 1 tablet]/day for 10 -12 days, representing an absolute time period), or in some occasions, human menopausal gonadotropins with or without estrogen or gonadotropin-releasing hormone agonist. Basal serum levels of FSH and E2 were measured on cycle days 1-5 after withdrawal bleeding. While receiving cyclic EPT, follicle size and number, and ovulation were closely monitored biweekly or twice a month.

e) Hormone measurements: Blood was collected, and serum was immediately separated by centrifugation for 6 min at room temperature. Serum E2 and FSH were measured by electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland). The intra- and inter-assay coefficients of variation were 1.07-3.5% and 2.03-2.55% for E2 and 0.73-1.24% and 2.10-2.40% for FSH at all ranges, respectively. The detection limits for E2 and FSH were 5 pg/mL and 0.1 mIU/mL, respectively.

f) Sample size calculation: On line statistical calculator was used for sample size calculation guided by:
   - Power of the significance tests =80%
   - Confidence level=95%
   - Alfa error= 5%
   - Catchment area population is included, the total number of candidates were 80 to fulfill these criteria.

Statistical methodology

- Analysis of data was done by IBM computer using SPSS (statistical program for social science version 12 ) as follows
- Description of quantitative variables as mean, SD and range
- Description of qualitative variables as number and percentage
- Chi-square test was used to compare qualitative variables
- Unpaired t-test was used to compare two groups as regard quantitative variable in parametric data (SD<50%mean)
- Mann Whitney U test was used instead of unpaired t-test in non-parametric data (SD>50%mean)

The mean presumed age of onset of POI in patients with
34.8 ± 3.1
12.5 ± 1.1
3.6 ± 0.2
11
25.6 ± 1.9
Number (%)
None of the other clinical
32.2± 4.2
41.3 ± 8.2
During the follow-up, some patients exhibited intermittent ovarian
activity; 19 POI patients (23.75%) had follicle growth. Ovulation
was observed in 10 patients (14.3%). Four (5%) patients conceived
and all gave birth to healthy babies. The relationship between each
parameter and intermittent ovarian activities is demonstrated in
Table 2. The mean presumed age of onset of POI in patients with
follicle growth was not significantly different from that of patients
without follicle development (31.8 ± 4.1 years vs. 32.1 ± 3.2 years, P
= 0.74). The median DOD in ovulatory patients was not significantly
shorter than that in an ovulatory patients (P = 0.7054; Table 2). The
DOD in patients with follicle growth and pregnancy was also not
comparatively shorter than that in patients without follicle growth
and pregnancy (P= 0.7358; Table 2). None of the other clinical
parameters were significantly different between patients with and
without intermittent ovarian activity, as well as laboratory factors,
including FSH levels at the time of diagnosis. But serum E2 was
significantly higher in patients with intermittent ovarian activity than
those without.

There was a slight correlation between the incidence of ovulation
and pregnancy, although the trend was not significant (R = 0.76, P
= 0.07). For further assessment, Day3 E2 and Day 1-3 FSH averaged
27.2 ± 3.4 pg/mL and 37.1 ± 4.1 mIU/mL, respectively in those with
follicular growth. The average age at the time the treatment cycle was
32.2 ± 1.1 years. Comparison of the mean value of each parameter
between cycles with and without intermittent ovarian activity is
shown in Table 3.

Evaluating intermittent ovarian activity, follicle development
was observed in 19 women. Ovulation was confirmed in 10 women.
Pregnancy occurred in 4 women. Day 3 E2 were significantly higher
in women with successful follicle growth and ovulation than cycles
without ovarian activity (P < 0.05). ROC curve analysis on prediction
of follicle growth and ovulation revealed that an optimal cut-off value
of 25 pg/mL for Day 3 E2 had sensitivities of 75.1% and 71.1%, and
specificities of 81.9 and 80.4 %, respectively.

To address the relationship between Day 3 E2 and intermittent
ovarian activity, the patients were divided into two groups based on
the Day 3 E2 (< 25 pg/mL and ≥ 25 pg/mL). Patients with Day 3 E2 ≥
25 pg/mL were more likely to have follicle growth and ovulation than
patients with Day 3 E2 < 25 pg/mL (P < 0.05; Table 4).

Discussion

In the current study we looked for a possible factor that might
predict intermittent ovulation in premature ovarian insufficiency
(POI) women. The results assumed that the cycle in which Day 3
E2 was higher than 25pg/mL had a higher rate of follicular growth
and ovulation in women with premature ovarian insufficiency. The
accurate mechanism underlying the linkage between resuming
ovarian function and high E2 values in cycles with follicular growth
or ovulation on cycle day 3 remains to be elucidated; but, a possible
mechanism is that: hormone replacement therapy containing estrogen
and progesterone down-regulates FSH release through a negative
feedback; subsequent stoppage of hormonal supplementation leads
to the release of the negative feedback, and thereafter, increases
FSH release, which consequently, might stimulate the follicular
development and its E2 release when a FSH-responsive competent

Results

At baseline, the mean presumed age of onset of POI for these
80 patients was 32.2 ± 4.2 years. All of our patients presented with
secondary amenorrhea; the mean age of menarche was 12.5 ± 1.1
years. The mean age at the initial visit was 34.8 ± 3.1 years. The
duration of ovarian dysfunction (DOD), defined as the period from
the onset of POI to the initial visit, was an average of 3.6 ± 0.2 years.
15 patients had a history of pregnancy and 12 delivered term babies.
11 patients had an iatrogenic history, 8 patients had histories of
thyroid diseases, and three patients had histories of surgery on the
ovary. The clinical and hormonal backgrounds of the POI patients
are listed in Table 1.

As anticipated, the mean FSH level at the time of initial diagnosis
was high (41.3 ± 8.2 mIU/mL).

Outcomes of POI patients for intermittent ovarian activity
during the follow-up, some patients exhibited intermittent ovarian

during secondary amenorrhea; the mean age of menarche was 12.5 ± 1.1
years. The mean age at the initial visit was 34.8 ± 3.1 years. The
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Outcomes of POI patients for intermittent ovarian activity
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Table 1: Clinical and hormonal backgrounds of POI women (n = 80).

<table>
<thead>
<tr>
<th>Character</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumed age of POI onset (years)</td>
<td>32.2± 4.2</td>
</tr>
<tr>
<td>Age of menarche (years)</td>
<td>12.5 ± 1.1</td>
</tr>
<tr>
<td>Age at the initial visit (years)</td>
<td>34.8 ± 3.1</td>
</tr>
<tr>
<td>Duration of ovarian dysfunction (years)</td>
<td>3.6 ± 0.2</td>
</tr>
<tr>
<td>Serum E2 at the initial diagnosis (pg/mL)</td>
<td>25.6 ± 1.9</td>
</tr>
<tr>
<td>Serum FSH at the initial diagnosis (mIU/mL)</td>
<td>41.3 ± 8.2</td>
</tr>
<tr>
<td>Pregnancy history</td>
<td>15</td>
</tr>
<tr>
<td>Delivery history</td>
<td>12</td>
</tr>
<tr>
<td>Iatrogenic history</td>
<td>11</td>
</tr>
</tbody>
</table>

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Table 2: Relationship between clinical and hormonal parameters and resumption of ovarian function in POI patients.

<table>
<thead>
<tr>
<th>Character</th>
<th>Follicular growth</th>
<th>Ovulation</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (N=19)</td>
<td>No (n=61)</td>
<td>P-value</td>
</tr>
<tr>
<td>Presumed age of POI onset (years)</td>
<td>31.8± 4.1</td>
<td>32.1± 3.2</td>
<td>0.7400</td>
</tr>
<tr>
<td>Age of menarche (years)</td>
<td>12.1± 1.5</td>
<td>12.1± 2.3</td>
<td>0.5878</td>
</tr>
<tr>
<td>Age at the initial visit (years)</td>
<td>33.2± 1.2</td>
<td>34.2± 3.7</td>
<td>0.2517</td>
</tr>
<tr>
<td>Duration of ovarian dysfunction (years)</td>
<td>3.1± 1.2</td>
<td>3.2± 1.1</td>
<td>0.7358</td>
</tr>
<tr>
<td>Serum E2 at the initial diagnosis (pg/mL)</td>
<td>27.1± 4.3</td>
<td>22.2± 6.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Serum FSH at the initial diagnosis (mIU/mL)</td>
<td>40.2± 3.2</td>
<td>41.5± 6.7</td>
<td>0.4178</td>
</tr>
<tr>
<td>Pregnancy history</td>
<td>5</td>
<td>10</td>
<td>0.333</td>
</tr>
<tr>
<td>Delivery history</td>
<td>3</td>
<td>9</td>
<td>0.912</td>
</tr>
<tr>
<td>Iatrogenic history</td>
<td>3</td>
<td>8</td>
<td>0.767</td>
</tr>
</tbody>
</table>

Table 3: Cycle-based analysis for prediction of intermittent ovarian activation.

<table>
<thead>
<tr>
<th>Character</th>
<th>Follicular growth</th>
<th>Ovulation</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (N=19)</td>
<td>No (n=61)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age during the cycle (years)</td>
<td>32.2± 1.1</td>
<td>32.5± 2.4</td>
<td>0.6003</td>
</tr>
<tr>
<td>Day 3 E2 (pg/ml)</td>
<td>27.2± 3.4</td>
<td>24.9± 3.1</td>
<td>0.0072*</td>
</tr>
<tr>
<td>Day 1-3 FSH (U/L)</td>
<td>37.1± 4.1</td>
<td>42.2± 5.7</td>
<td>0.0005*</td>
</tr>
</tbody>
</table>

Table 4: Relationship between Day 1-5 E2 and intermittent ovarian activity.

<table>
<thead>
<tr>
<th>Character</th>
<th>Follicular growth</th>
<th>Ovulation</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (N=19)</td>
<td>No (n=61)</td>
<td>P-value</td>
</tr>
<tr>
<td>Day 3 E2 &lt; 25 pg/ml (n = 58)</td>
<td>5</td>
<td>2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Day 3 FSH ≥ 25 pg/ml (n = 14)</td>
<td>14</td>
<td>8</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Conclusion

In the current study, the value of Day 3 E2 for predicting intermittent ovulation was suggested. To shorten the duration of POI, it is of value to educate women to seek assessment when they have irregular menses or amenorrhea. However, Day 3 E2 had less statistically significant power due to the small sample size in POI women and further study in a large scale will be needed, the results are helpful for treating POI women who have a strong desire to get pregnant.
References


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