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Research Article

Prediction of Ovarian Response in Women with Premature Ovarian Insufficiency Stimulated By Gonadotrophins Using Day-3 Serum Estradiol: A Retrospective Study

Abstract

Objective: The aim of this study was to evaluate the potential predictive value of day-3 serum estradiol for follicle growth, ovulation, and pregnancy rate in women with premature ovarian insufficiency.

Patients and Methods: This was a retrospective study which was carried out in International Fertility Centre Kingdom Saudi Arabia. The study included 80 consented women with desired fertility who were treated and monitored between the years of 2013-2016 into this study. The clinical, endocrinologic, chromosomal, and immunologic characters of these women were gathered. The main outcome values were follicle growth, ovulation, and pregnancy rate.

Results: In the current study, it was found that women with follicle growth, ovulation, and pregnancy rates were not significantly different as a function of parity, iatrogenic history, age of disease onset, follicle stimulating hormone (FSH) level at the time of diagnosis. The serum E2 levels on days 3 of withdrawal bleeding (Day 3 E2) were significantly higher in the cycles with successful follicle growth and ovulation than unsuccessful cycles ($P < 0.05$). Receiver-operator characteristic curve (ROC) analysis revealed the cutoff value of the Day 3 E2 to be 25 pg/mL for follicular growth, ovulation and spontaneous pregnancy.

Conclusion: In this study we found that those cycles with a Day 1-5 E2 ≥ 25 pg/mL have a higher rate of follicle growth and ovulation in patients with POI.

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 estrogens 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), hyperandrogeneism, 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:

- o Lupus anticoagulant antibodies.
- o Karyotyping.
- o Anticardiolipin antibodies.
- o Semen analysis from their husbands.
- o 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 chlormadinone acetate and 0.05 mg mestranol [Lutedion®, 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:

- o Power of the significance tests =80%
- o Confidence level=95%
- o Alfa error= 5%
- o Catchment area population is included, the total number of candidates were 80 to fulfill these criteria.

Statistical methodology

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

- Spearman correlation test was used to rank variables versus each other positively or inversely.
- ROC (receiver operator characteristic curve) was used to find out the best cut of value of certain predictor and its validity parameters as follows.
- Sensitivity = true ve +/true +ve + false –ve = ability of the test to detect +ve cases
- Specificity = true -ve/true-ve+ false +ve = ability of the test to exclude negative cases
- PPV (positive predictive value) = true+/true+ve +false +ve = % of true +ve cases to all positive
- NPV = true-/true-ve + false –ve = % of the true –ve to all negative cases
- Accuracy = true –ve +true +ve / all cases
- P value
  - P value >0.05 insignificant
  - P<0.05 significant
  - P<0.01 highly significant

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 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.

Table 1: Clinical and hormonal backgrounds of POI women (n = 80).

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

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

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

Character	Follicular growth			Ovulation			Pregnancy		
	Yes (N=19)	No (n=61)	P-value	Yes (n=10)	No (n= 70)	P-value	Yes (n=4)	No (n=76)	P-value
Presumed age of POI onset (years)	31.8± 4.1	32.1± 3.2	0.7400	32.2± 1.1	33.4± 3.6	0.3006	32.4± 1.2	32.5± 2.6	0.9395
Age of menarche (years)	12.4± 1.2	12.1± 2.3	0.5878	11.9± 3.2	12.5± 2.2	0.4499	11.8± 2.9	12.2± 3.2	0.8075
Age at the initial visit (years)	33.2± 1.2	34.2± 3.7	0.2517	32.9± 4.5	35.5± 4.2	0.0733	32.4± 2.7	35.2± 3.2	0.0903
Duration of ovarian dysfunction (years)	3.1± 1.2	3.2± 1.1	0.7358	3.6± 1.8	3.3± 2.4	0.7054	3.2± 1.3	3.9± 3.2	0.6659
Serum E2 at the initial diagnosis (pg/mL)	27.1± 4.3	22.2± 6.2	< 0.05	30.2± 4.2	21.3± 5.1	<0.05	30.4± 4.3	21.2± 7.2	<0.05
Serum FSH at the initial diagnosis (mIU/mL)	40.2± 3.2	41.5± 6.7	0.4178	40.1± 2.8	42.2± 4.6	0.1648	39.2± 3.8	42.4± 5.2	0.2297
Pregnancy history	5	10	0.333	4	11	0.0656	4	11	0.0656
Delivery history	3	9	0.912	4	8	0.179	4	8	0.179
Iatrogenic history	3	8	0.767	2	9	0.539	2	9	0.539

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

Character	Follicular growth			Ovulation			Pregnancy		
	Yes	No	P -value	Yes	No	P –value	Yes	No	P –value
Age during the cycle (years)	32.2±1.1	32.5±2.4	0.6003	32.2±4.1	34.1±3.1	0.0859	29.9±2.1	31.2±5.8	0.6580
Day 3 E2 (Pg/ml)	27.2±3.4	24.9±3.1	0.0072*	27.6±2.1	24.2±1.1	<0.05	28.1±2.5	23.2±6.1	<0.05
Day 1-3 FSH (U/L)	37.1±4.1	42.2±5.7	0.0005*	31.2±4.8	44.2±4.5	<0.05	30.9±2.1	46.2±5.9	<0.05

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

Character	Follicular growth	P –value	Ovulation	P -value	Pregnancy	P – value
Day-3 E2 < 25 Pg/ml (n= 58)	5	< .05. (sig)	2	< .05. (sig)	1	< .05. (sig)
Day 3 E2 ≥ 25 Pg/ml (n= 22)	14		8		3	

follicle is growing; a high level FSH might strongly and immediately stimulate E2 release from the dominant follicle; and serum E2 might reach a high level on cycle days 1-5, that is an indicator of a dominant follicle and the subsequently intermittent ovarian activity.

A shorter POI might also be considered a favorable possible factor for ovulation. The POI also had an inverse relationship with follicular growth and pregnancy, although a significant difference was not demonstrated, presumably due to small sample size. There are various case reports in the literature involving POI women who spontaneously and unexpectedly got pregnant [6,8,14-25], but very few had demonstrated statistical analysis of this population due to the rarity of POI. Bidet et al. [26], demonstrated predictive factors for spontaneous recovery of ovarian function in POI women. Retrospective and prospective studies were done, and included 358 consecutive POI women. Multivariate analysis demonstrated that a family history of POI, amenorrhea, the follicular growth on ultrasound, and inhibin B and E2 values were significantly predictive of resumption of ovulation [26]. Interestingly, serum E2, but not serum FSH, is of value as a predictive factor for follicular growth, as demonstrated in the multivariate analysis [26], and the current study. In contrast, it had been reported that POI women with a FSH level < 15 mIU/mL before stimulation might ovulate in response to exogenous gonadotropins [27]. These results collectively demonstrate that each woman might have an optimal value of serum FSH for follicular growth in each cycle.

Anti-müllerian hormone (AMH) is a widely accepted biomarker for ovarian response [28-30], but is not reliable for predicting follicular growth in POI women [31-33], because most POI women have undetectable AMH values.

Bidet et al. [26] also demonstrated that during 1- 423 months of followup (58.8 ± 57 months [mean ± SD]) of 358 women with idiopathic POI, 86 women (24%) had features indicating recovery of ovarian function, and 21 spontaneous gestations (16 births and 5 miscarriages) happened in 15 women (4.4%). It was demonstrated in the current study that during the follow-up of 80 women with idiopathic POI, 19 POI women (23.75%) had follicle development. Ovulation was noticed in 10 women (14.3%). Four (5%) women got pregnant and all gave birth to healthy babies. Although these two studies could not be directly compared, it is possible that the high rates of spontaneous recovery of ovarian function and pregnancies obtained in the current study may be, at least in part, due to the close and continuous monitoring of the growth of follicles to detect very scarce ovulations. The fundamental dogma for the ovaries is now changing due to the developing novel concept of oogonial stem cells (OSCs); OSCs had been lately reported in many studies [34-36]. Isolation and expansion of OSCs from POI women may be the cornerstone to a new strategy for fertility management. Kawamura et al. [37], established the concept of in vitro activation (IVA) of mere primordial follicles in mouse ovaries; 13 women with POI were managed using this method, and 1 woman gave birth to a healthy baby. These unique methods might be able to offer a new fertility management for women with POI in the future.

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.

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