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ORIGINAL ARTICLE

Outcomes of random start versus clomiphene citrate and gonadotropin cycles in occult premature ovarian insufficiency patients, refusing oocyte donation: a retrospective cohort study

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ABSTRACT

The aim of this study is to present the clinical outcomes of a random start, a spontaneous folliculogenesis protocol versus Clomiphene Citrate and Gonadotropin treatment in women with occult premature ovarian insufficiency. Women underwent treatment between 1 February 2009, and 30 May 2016. 41 women were treated with the random start protocol while 48 cases received ovarian stimulation with clomiphene and gonadotropins. All included cases met the criteria of 4 months of oligo-ovulation, follicular-stimulating hormone levels over 30 IU/L and anti-Mullerian hormone levels below 0.30 ng/mL. The random start protocol involved following the subjects for up to 6 months until spontaneous folliculogenesis occurred. The mean number of oocytes collected, mature oocytes, fertilized oocytes, and grade II embryos were significantly higher in the random start protocol ($p < .05$). The doses of gonadotropin administration and hCG were significantly lower in the random start protocol ($p < .05$). The clinical pregnancy and live birth rates were significantly higher in the random start protocol ($p < .05$). Likely stimulation is of little benefit in women with occult premature ovarian insufficiency. Observation while waiting for spontaneous folliculogenesis results in better outcomes, and less oocyte collections.

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Introduction

Premature ovarian insufficiency (POI) comprises 10–28% and 4–18% of all cases of primary and secondary amenorrhea, respectively [1,2]. Occult POI (OPOI) is a clinical entity with impaired ovarian function, regular or oligo-ovulation, elevated serum follicle-stimulating hormone (FSH) levels, low serum anti-Mullerian hormone (AMH) levels, and impaired fertility [1–7]. Premature ovarian failure (POF) – also known as POI – differs from OPOI, in that with OPOI, ovulations occur and serum FSH levels tend to be lower. While in POI ovulations have generally ceased, they may return spontaneously; however, no treatment has been found to induce these ovulations [8]. Most OPOI cases are idiopathic, although genetic defects comprise an important proportion of OPOI cases. Such genetic causes include X-chromosomal abnormalities, fragile X carrier status, and ESR1, HK3, and BRSK1 gene variations [9–14]. An autosomal mutation of the inhibin alpha subunit is also associated with OPOI [15]. Autoimmunity involving many endocrine organs – including the ovary and thyroid – are involved in OPOI etiology [16–18]. Environmental exposure, endocrine disruptors, and drug-induced ovarian harms have toxicities with regards to ovarian function and can also cause OPOI [19]. It should also be noted that OPOI is the state that precedes POF or POI, and that many of these factors ultimately lead to POI.

There are three possible mechanisms underlying POI pathophysiology – namely, premature follicular activation, the blocking of follicular maturation, and accelerated apoptosis of antral follicles [20]. OPOI may relate to the accelerated consumption of ovarian follicles, or derive from follicles resistant to endogenous maturation. Fertility problems are common among women with OPOI, and current care options include oocyte or embryo donation, or minimal-stimulation *in vitro* fertilization (IVF) with very low pregnancy rates [21]. Many patients will not accept oocyte or embryo donation as a first-line infertility treatment; many OPOI patients seek other treatment choices.

Considering that spontaneous conceptions occasionally occur among OPOI cases and that follicular waves happen throughout the menstrual cycle, one care option is a random start protocol, to commence when small antral follicles counts are greatest and spontaneous folliculogenesis is occurring. Another care option is the administration of clomiphene citrate (CC) to increase endogenous FSH levels, since high-dose exogenous FSH is ineffective in improving OPOI patient outcomes. When using CC, low-dose exogenous FSH can be prescribed.

The objective of this study was to determine rates of conception among OPOI patients who used minimal stimulation IVF protocols; furthermore, this study compares the outcomes of these two treatment modalities.

Materials and methods

A total of 313 OPOI cases were drawn from archived files of an IVF center located in northeastern Turkey; these women had been treated between 1 February 2009 and 30 May 2016. Institutional review board study approval was obtained.

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Cases of surgery-induced secondary ovarian insufficiency were excluded, leaving a total of 238 cases for evaluation. None of the OPOI cases had uncontrolled thyroid or other systemic diseases, uterine anomalies, or fibroids larger than 1.5 cm in maximum diameter, unresected uterine polyps, or abnormal karyotypes. All cases satisfied the following OPOI criteria: basal serum FSH levels >30 IU/L, more than four months of oligo-ovulation, and serum AMH levels <0.30 ng/mL [2]. Oligo-ovulation was determined by the presence of cycles less frequent than 35 days, or by serum progesterone levels seven days before an expected menses failing to detect ovulation during two cycles. An additional 15 cases with severe oligoasthenoteratozoospermia and seven cases with azoospermia were excluded from the study. Sixty-three cases were not treated with one of the two protocols under investigation and so were excluded, as were another 27 OPOI patients who had elected to undergo oocyte donation. Finally, also excluded were three cases with uterine septums, 30 cases with systemic disease (diabetes mellitus, familial Mediterranean fever, rheumatoid arthritis, and systemic lupus erythematosus), and four cases with karyotype abnormalities.

Of the remaining 89 cases, 41 cases were treated using the random start follow-up protocol (Group 1) and 48 cases were treated with CC plus low-dose gonadotropins (Group 2). Those with follicular cysts early in the follicular phase, as well as patients with severe ovarian dysfunction (i.e. no follicles observed in the basal evaluation), were enrolled in the random start group; others were included in the CC plus gonadotropin group. Figure 1 is a flow chart of this study's selection process.

For each study patient, body mass index (BMI), antral follicle count (AFC), AMH, basal FSH, luteinizing hormone (LH), prolactin (PRL), estradiol, progesterone and thyroxine (T4), and thyroid-stimulating hormone (TSH) values were recorded. Follicle cysts found during the early menstrual period were recorded. Human chorionic gonadotropin (HCG) day estradiol and progesterone values were recorded.

Random start follow-up consisted of follicle aspiration whenever they spontaneously developed during the menstrual cycle. Patients with follicles or follicular cysts were included in the random start group, and patients in that group were considered more difficult than those in the CC + Gn group; thus, a long course without stimulation was preferred for those cases. Patients presented themselves on day 2–3 of a spontaneous menstrual cycle, for transvaginal ultrasound evaluation. If mature follicles were seen at that time (which is common among OPOI cases), then a single dose of follitropin alpha (Gonal-f; Merck Serono, Rockland, MA) 225 IU was subcutaneously administered, and that evening 10,000 IU urinary human chorionic gonadotropin (Pregnyl; Schering-Plough, Kenilworth, NJ) was administered intramuscularly, 35 h before oocyte collection. If no mature follicles (15–20 mm in diameter) were present, then serial

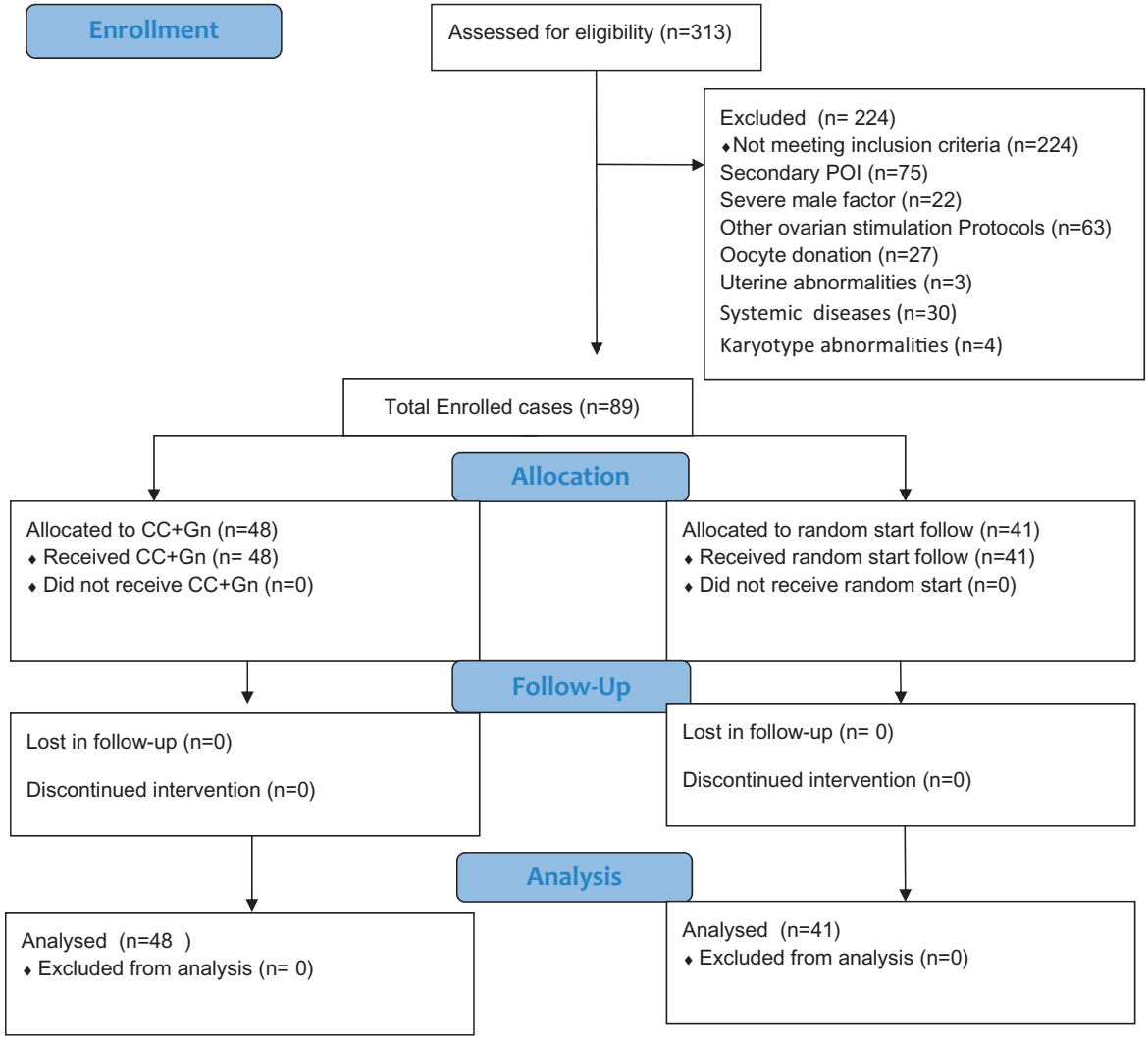

Figure 1. Flow chart of selection process.

ultrasounds were performed at five to seven-day intervals, for up to six months. Patients with aspirated follicles or no early follicular cysts were followed at seven-day intervals, to follow for three to six months any growing follicle independent of the menstrual day. Any mature follicles detected were stimulated with a single dose of Gonal-f 225 IU. On the same day, HCG was administered, and oocytes were retrieved 35 h later. Fertilized oocytes were vitrified on day 3, until at least two viable embryos were obtained for each case before embryo transfer (ET).

All patients in the CC + Gn group were evaluated at day 2–3 of the menstrual cycle. If mature follicles were not present, the twice-daily administration of CC 150 mg over five days was commenced. Follitropin alpha (Gonal-f) 150 IU SC was commenced on day 6, until a 17-mm follicle developed; at that point, HCG was administered and oocytes were retrieved 35 h after HCG injection. Cases were followed for up to six months to obtain at least two viable embryos for transfer. Fertilized oocytes were vitrified.

When two embryos were obtained, the vitrified embryo was thawed and a fresh and a vitrified embryo were transferred in the second collection cycle, assuming the endometrium was ready for transfer. A receptive endometrium was trilameter, not bleeding, and at least 8 mm in maximum anterior–posterior width. In cases where the endometrium was not eligible for ET, the embryo was vitrified and transferred in a hormone-supported vitrified ET cycle. In both cases, estradiol valerate 2 mg was orally administered three times daily, together with micronized progesterone 200 mg vaginally administered three times daily, were provided for luteal support.

Basal hormonal evaluation and AFC were recorded, and estradiol and progesterone values were recorded on the HCG day. Also, the number of treatment cycles, oocyte pick-ups, gonadotropins used, HCG doses used, oocytes retrieved, and embryos transferred, as well as data on oocyte maturations, fertilization rates, embryo qualities, endometrial thickness at ET, positive BHCG test results, biochemical pregnancies, spontaneous abortions, clinical pregnancy, and live births were recorded.

Statistical method

The Shapiro–Wilk test was used to assess whether the variables were normally distributed; based on those findings, the variables were reported as mean ± standard deviation or median (minimum–maximum) values. In line with the normality test results, an independent sample *t*-test or Mann–Whitney *U*-test was used to compare the two study groups. Pearson's chi-square and Fisher's exact tests were used to compare categorical variables. Binary logistic regression analysis was performed to determine the independent risk factors that affect preference for the CC + Gn protocol. SPSS v21 software (IBM Corp., Armonk, NY) was used to undertake statistical analysis, and any p values less than or equal to .05 was considered statistically significant.

Results

Table 1 lists the baseline characteristics of the patient population. The two groups were comparable in terms of age, BMI, infertility duration, ovarian reserve markers, prolactin, and thyroid function. Basal serum estradiol levels were significantly higher in the random start group, and basal serum prolactin levels were significantly higher in the CC + Gn group ($p < .001$ and $p = .006$, respectively).

Table 2 presents the results of ovarian stimulation, together with embryological characteristics. The mean number of oocytes collected, mature oocytes, fertilized oocytes, and grade II embryos were significantly higher in the random start group ($p < .001$, $p = .027$, $p = .010$, and $p = .008$, respectively). There was a significant decrease in the total dose of gonadotropins and HCG doses in the random start group, compared to the CC + Gn group (respectively, 450 IU and 2275 IU, $p < .001$; 31875 IU and 26829 IU, $p = .005$). The higher HCG dose equates to more collections being executed in the CC + Gn group, to obtain two viable embryos for transfer. There was no difference between the two groups in terms of the mean maximum endometrial thickness at the time of ET (9.85 mm and 10.16 mm; $p = .354$).

In the CC + Gn group, 14 of 48 patients (29.2%) underwent a fresh and a vitrified ET, while another 34 (70.8%) underwent only a vitrified ET; in the random start group, these numbers were 19 of 41 patients (46.3%) and 22 (53.7%). Positive BHCG test results, biochemical pregnancy rates, and early spontaneous abortion rates were similar between the CC + Gn and random start groups (respectively, 29.2% and 46.3%, $p = .095$; 10.4% and 12.2%, $p = 1.00$; and 10.4% and 12.2%, $p = 1.00$). The implantation rate (sac formation/ET) was higher in the random start group ($p = .029$). Clinical pregnancy and live birth rates were significantly higher in the random start group (clinical pregnancy: 22% vs. 6.3%, $p = .03$; live births: 22% vs. 6.3%, $p = .0$). These data are summarized in Table 3.

It should be noted that no multiple pregnancies or congenital malformations were observed in either study group. Logistic regression analysis was performed, and it was found that one-unit increase in the estrogen level reduce the preference of CC + Gn treatment by 4%. The results of logistic regression analysis are presented in Table 4.

Table 1. Baseline characteristics and serum hormone levels of participants.

	Random start group ($n = 41$)	CC + Gonadotropin group ($n = 48$)	p Value
Age (years)	29.93 ± 5.26	30.02 ± 4.94	.776[a]
BMI (kg/m^2)	28.15 ± 3.59	27.70 ± 3.80	.571[b]
Infertility duration (years)	3 (1–10)	4 (1–8)	.576[a]
AMH (ng/mL)	0.14 ± 0.05	0.14 ± 0.05	.889[b]
Basal LH (mIU/mL)	15.19 (13.45–24.21)	15.87 (13.24–42.47)	.268[a]
Basal FSH (mIU/mL)	41.34 (36.55–61.27)	(37.13–61.78)	.108[a]
Basal progesterone (ng/mL)	2.71 (1.23–4.44)	2.78 (1.10–5.13)	.684[b]
Basal estrogen (pg/mL)	250 (43.29–420)	25.18 (13.13 to290)	<.001[a]
Basal prolactin (ng/mL)	22.16 (13.87–31.33)	25.89 (13.99–34.81)	.006[a]
Basal TSH (uIU/mL)	1.84 (1.12–2.90)	1.87 (1.36–2.90)	.938[a]
Basal T4 (ng/dL)	1.32 (1.10–1.90)	1.31 (1.10–1.80)	.938[a]

Numerical data presented as mean (SD) or median (25th to 75th percentile).
[a]Mann–Whitney *U* test.
[b]Independent samples *t* test.

Table 2. Stimulation results and embryological characteristics of Random start follow up versus CC + Gonadotropin treatment.

	Random start group ($n = 41$)	CC + Gonadotropin group ($n = 48$)	p Value
Total number of oocytes collected	2.88 ± 0.95 3 (1 to 5)	2.19 ± 0.702 2 (1 to 4)	.001[a]
Number of OPU	3 (2 to 5)	3 (2 to 5)	.005[a]
Total Gn dose used	450 (450:1250) 601.22 ± 188.66	2775 (350:3500) 2704.17 ± 653.29	<.001[a]
Total hCG dose used	30,000 (20,000:50,000) 31,875 ± 8667.93	30,000 (20,000:50,000) 26,829 ± 7886.39	.005[a]
Number of MII oocytes	2 (1:3) 1.77 ± 0.69	2 (1:4) 2.10 ± 0.66	.027[a]
Number of MI oocytes	0 (0:1) 0.31 ± 0.47	0 (0:2) 0.42 ± 0.55	.404[a]
Number of GV oocytes	0 (0:1) 0.21 ± 0.41	0 (0:1) 0.39 ± 0.49	.061[a]
Number of oocytes fertilized	1.50 (1:3) 1.54 ± 0.58	2 (1:3) 1.90 ± 0.66	.010[a]
Embryo Grade I	0 (0:2) 0.52 ± 0.68	1 (0:2) 0.63 ± 0.70	.400[a]
Embryo Grade II	(0:2) 0.50 ± 0.62	1 (0:2) 0.90 ± 0.74	.008[a]
Embryo Grade III	0.50 (0:2) 0.52 ± 0.55	0 (0:2) 0.34 ± 0.53	.095[a]
Endometrial thickness at ET	9 (8.10:12.30) 9.85 ± 1.22	10.10 (8:13.50) 10.16 ± 1.42	.354[a]

[a]Mann–Whitney *U* test.

Table 3. Outcomes for random start follow up versus CC + Gonadotropin treatment.

Fresh + frozen ET	19 (46.30%)	14 (29.20%)	0.095[b]
Frozen ET	22 (53.70%)	34 (70.80%)	0.095[b]
Implantation rate	9 (22%)	3 (6.20%)	0.031[b]
total number of oocytes injected by ICSI	2 (1:4) 2.39 ± 0.74	2 (1:3) 2 ± 0.55	0.008[a]
Positive BhCG test	19 (46.30%)	14 (29.20%)	0.095[b]
Biochemical pregnancy	5 (12.20%)	5 (10.40%)	1.00[c]
Early spontaneous abortion	5 (12.20%)	5 (10.40%)	1.00[c]
Clinical pregnancy	9 (22%)	3 (6.30%)	0.031[b]
Live birth	9 (22%)	3 (6.30%)	0.031[b]
Number of embryo/s transferred	2 (0:2) 1.74 ± 0.50	1.50 (1:2) 1.50 ± 0.51	0.019[a]

[a]Mann–Whitney *U* test.
[b]Chi-Square test.
[c]Fisher's exact test.

Table 4. Logistic regression analysis.

Factor	Wald	OR (95%CI)	p Value
Estrogen, pg/mL	14.53	0.96 (0.94:0.98)	<.001
Prolactin, ng/mL	1.03	1.11 (0.91:1.35)	.311
Number of OPU	0.04	0.85 (0.18:4.14)	.840
Number of MII oocytes	0.31	2.28 (0.13:41.63)	.577
Number of oocytes fertilized	0.20	4.13 (0.01:2237.06)	.659
Implantation rate *(ref.cat: non implanted)*	0.13	0.53 (0.02:17.93)	.720
Total number of oocytes injected by ICSI	0.19	0.56 (0.04:7.53)	.663
Number of embryo transferred	0.01	0.68 (0.01:447.24)	.906

Logistic regression model was found statistically significant ($p < .001$). OR: Odds ratio.

Discussion

POI was first introduced in the medical literature by Fuller Albright in 1942, by emphasizing that insufficiency (rather than abnormal gonadotropin secretion) is an end-stage primary ovarian functional defect [3]. POI is defined as amenorrhea of more than four months accompanied by increased serum FSH levels >40 IU/L with low estrogenic status (i.e. <50 pg/mL) in patients younger than 40 years. OPOI, the stage preceding POI, is defined as ovarian function deviation that derives from premature exhaustion of the primordial follicles, with some menstrual competency and abnormal ovarian reserve test results [4]. Another term used in the context of ovarian dysfunction is 'ovarian aging,' which is taken to the extreme in OPOI. POF is a menopausal state, and the end stage of ovarian aging [22,23]. Apart from subfertility and infertility, POI brings the risk of cardiovascular disease, osteoporosis, neuropsychiatric deprivations, and diminished sexual desire [24].

The best pregnancy treatment strategy in OPOI patients, outside of oocyte donation, has not been determined. Women with POF or POI may experience a spontaneous resumption of ovarian function; in fact, spontaneous pregnancies occur in 5–10% of women with idiopathic POI. The possible mechanism underlying this spontaneous resolution is partial ovarian tissue damage caused by autoimmune problems: if the impact of pathological mechanisms can be lessened, the remaining healthy areas of the ovary can resume normal function. Antiovarian antibodies have been found in 18–59% of POF patients [25].

This study compares two very different follicle-collection protocols. One protocol involved essentially no stimulation, and relied upon the spontaneous development of follicles; the second used stimulation with high-dose endogenous FSH (i.e. CC 300 mg daily) followed by exogenous gonadotropin administration. The outcomes thereof were very different, and two explanations can be offered for this difference. One is that among OPOI cases, spontaneous folliculogenesis generates more competent oocytes than dose-stimulated folliculogenesis; this would make sense, given the likelihood that spontaneous folliculogenesis may occur in concurrence with improvements in the blocking factors of ovarian antibody titers. A second possibility is that high-dose CC has a negative effect on the endometrial lining: no case had a thin lining during a fresh-cycle transfer, for otherwise, a vitrified transfer would have been performed. However, it is possible that undetected endometrial factors were present. Nevertheless, this

study's results are intriguing, as few studies compare the ideal stimulation protocol for women with OPOI.

Ovarian follicular dynamics during the menstrual cycle have not been wholly elucidated. Baerwald et al. reviewed more than 200 studies via PubMed search and investigated antral folliculogenesis via histological, endocrinological, and ultrasonographic techniques. Three different mechanisms of antral follicle recruitment were noted: continuous recruitment throughout the menstrual cycle; late luteal and early follicular recruitment, which aligns with classical knowledge; and the recruitment of two or three cohorts or follicular waves in each cycle. Accumulated evidence indicates that multiple follicular waves develop during human menstrual cycles, as seen in many other mammals. Understanding the paracrine and endocrine mechanisms of waves may have some clinical implications for ovarian stimulations [20]. It is possible that the unstimulated random start protocol benefitted from folliculogenesis, based on a spontaneous follicular wave. Among the theories described, follicular waves are very important to understanding intermittent follicular developments during impaired menstrual cycles in POI cases. A 'wave of follicular development' is defined as the synchronous growth of antral follicles at regular intervals, which may be documented through transvaginal ultrasound. Successful luteal-phase oocyte retrievals were reported in *in vitro* maturation as a fertility preservation option [26]. Luteal-phase ovarian stimulation has been studied in cases with routine oocyte pick-up in the same cycle, by Zhang et al.; poor-responding patients reported the pick-up of more oocytes, as well as better embryo quality and good clinical outcomes [27]. Ongoing pregnancy from two waves of follicles during the follicular phase of the same cycle is reported by Bentow et al. [28]. Additionally, in one POI case, early follicular-aspirated oocytes were fertilized, and a vitrified–thawed embryo was transferred in the same cycle, resulting in a healthy live birth [29]. Hatirnaz et al. sought to leverage follicular waves in the impaired menstrual cycles of POI patients, and four of 14 vitrified and same-cycle fresh ETs in POI cases resulted in healthy live births (unpublished data). There are no obvious criteria for discriminating POI from POF, and so following follicles in the impaired menstrual cycles of POI cases in order to obtain oocytes can prompt clinicians to undertake random start follicle follow-up – something that may begin early in the menstrual cycle, with early follicles seen in ultrasound or through follow-ups at 7–10-day intervals [30,31]. These follicular wave follow-ups were obtained through sequential ultrasound examinations of interovulatory intervals. With this mode of treatment, two strategies are applied: a mechanical strategy, where any follicle or follicle-like cyst seen during the menstrual cycle is aspirated and found oocytes are fertilized and vitrified, and an ovarian stimulation strategy that uses gonadotropins, CC, or an aromatase inhibitor (i.e. letrozole). Synchronous endometrial development in such cycle management may derive suboptimal outcomes; thus, the use of fresh ET is not recommended. Embryos were vitrified, and in trilaminar endometrium observed cases, only fresh embryos were transferred with vitrified ones; otherwise, embryos were transferred as vitrified–thawed ETs.

Conclusions

In conclusion, ovarian stimulation in OPOI patients incurs cost while offering no benefit in terms of embryo quantity or quality. The use of serial ultrasounds for many months – until a follicle development is witnessed – can result in fewer oocyte collections higher live birth rates than the use of stimulation.

This study is one of the few to compare stimulation protocols among OPOI patients. Nonetheless, an inherent weakness is that its retrospective nature may have created undetected bias in one of the two study groups. Further research is recommended to validate these results.

Disclosure statement

No potential conflict of interest was reported by the authors.

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