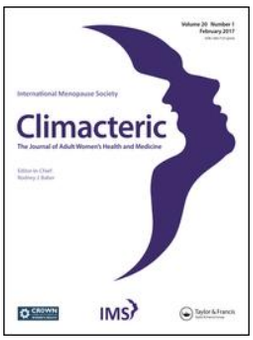

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ORIGINAL ARTICLE

# Effects of oral contraceptives on ovulation induction in *in vitro* fertilization patients with premature ovarian insufficiency

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**ABSTRACT**

**Objective:** To report a case series of *in vitro* fertilization patients with premature ovarian insufficiency, who were treated with oral contraceptives to reduce follicle stimulating hormone levels.

**Method:** This was a consecutive case series in a tertiary teaching hospital in China. Twenty-two women with refractory and idiopathic premature ovarian insufficiency were administered a drospirenone/ethinylestradiol oral contraceptive orally. The main outcome measures were the number of oocytes retrieved and the number of embryos frozen.

**Results:** There were total 106 oral contraceptive treatment cycles and 53 oocyte retrieval cycles in 20 patients (91%, 20/22; 2.4 cycles per woman, 53/22). The total number of oocytes retrieved was 48 in 17 patients (77%, 17/22; 2.2 oocytes per woman, 48/22), and the total number of embryos frozen was 33 in 16 patients (73%, 16/22; 1.5 embryos per woman, 33/22).

**Conclusion:** Oral contraception may be an effective method to induce ovulation for some patients with premature ovarian insufficiency.

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**KEYWORDS**
Oral contraceptives; premature ovarian insufficiency; premature ovarian failure; ovulation induction; infertility

## Introduction

Premature ovarian insufficiency (POI), or premature ovarian failure, is defined as a disease with the loss of ovarian function before age 40 years[1]. POI is mainly marked by amenorrhea or oligoamenorrhea with high gonadotropins and low estradiol levels[1]. Its prevalence is generally reported as 1% by age 40 years, and 0.1% by age 30 years but may be higher[2]. POI is associated with chromosomal and genetic disorders, iatrogenic injury or autoimmune diseases; however, the cause is unknown in the majority of patients[3]. The diagnosis of POI is based on (1) amenorrhea and/or oligoamenorrhea for at least 4 months, and (2) follicle stimulating hormone (FSH) > 25 IU/l on two occasions more than 4 weeks apart[1]. However, the diagnostic criteria are not definitive because ovarian activity in patients with POI is often intermittent, and there is a small possibility (5–10%) of spontaneous pregnancy after diagnosis[4–6]. It is generally accepted that there are no effective methods yet available to increase ovarian activity or improve reproductive outcome[1]. However, there is a hypothesis that supraphysiologic FSH levels could down-regulate FSH receptors in residual follicles, and that the suppression of FSH to the normal physiological range may up-regulate receptors, improve the responsiveness of residual follicles, and induce ovulation[7]. Many drugs, including oral contraceptives, hormone replacement therapy and gonadotropin releasing hormone agonists (GnRHa), have been proven to be effective in the suppression of the high levels of gonadotropins[7]. The use of oral contraceptives to induce ovulation was first reported as case reports in the late 1980s[8,9]. Brahma and Kallen[10] reported the first case of ovarian hyperstimulation after gonadotropin suppression with oral contraceptives. In the present study, we performed a retrospective analysis of the use of oral contraceptives for refractory and idiopathic POI in our department during the last 16 months.

## Materials and methods

### Patients

This was a retrospective case series of consecutive patients with refractory and idiopathic POI. In our study, refractory POI was defined as amenorrhea and/or oligoamenorrhea for at least 4 months, FSH >40 IU/l on two occasions more than 4 weeks apart, without visible antral follicle count on two occasions more than 4 weeks apart. Idiopathic POI was defined as cause unexplained. None of the patients had chromosomal/genetic disorders, iatrogenic injury or autoimmune diseases. Institutional Review Board Project No. 01/01/2016 was approved on 1 January 2016 by the Navy General Hospital Ethics Committee.

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Supplemental data can be accessed here.

### Treatments

To suppress FSH levels into the physiologic range (< 15 IU/l), Yasmin® (3 mg drospirenone +0.03 mg ethinylestradiol) was administered orally (dosage: one tablet/2 days, one tablet/1 day, or two tablets/1 day) for 1–3 weeks. The FSH level was maintained between 5 and 15 IU/l for 1–4 weeks. During this period, transvaginal ultrasounds and biochemical examinations were performed at 5–7-day intervals to find potential follicles. When the follicles were found, the Yasmin dose was halved or quartered to increase and keep the FSH levels at around 10–25 IU/l, with or without ovarian stimulation. When a follicle exceeded a mean diameter of 14–18 mm and serum estradiol was 150–250 pg/ml, 10 000 IU of human chorionic gonadotropin (hCG) or 250 μg of recombinant hCG was given, and a transvaginal oocyte retrieval followed 24–36 h later. After *in vitro* fertilization and intracytoplasmic sperm injection, all available embryos were frozen for frozen-thawed embryo transfer (FET). In the event of no follicle being found or no follicular growth, all drugs were withdrawn, and the patient was scheduled to receive oral contraceptives in the next treatment cycle (see Supplemental Table S1 for details of the treatments).

### Outcomes

We recorded the following outcomes: the number of oocytes retrieved, the number of embryos obtained, the number of embryos frozen, the number of clinical pregnancies (a gestational sac with fetal heart beat, confirmed by ultrasound), the number of live births, and adverse effects associated with the treatment (e.g. miscarriage, fetal abnormality, side-effects from oral contraceptives). Live birth was defined as delivery of one or more living infants after 20 completed weeks of gestation[11].

## Results

Patient characteristics and outcomes of treatment cycles are listed in Tables 1 and 2. No oral contraceptive-related adverse event was detected.

There were total 106 oral contraceptive treatment cycles in the 22 women (median 5, range 2–8). There were 53 oocyte retrieval cycles in 20 patients, but in two cases there was no follicular development. The total number of oocytes retrieved was 48 in 17 patients; the total number of 2-pronucleus was 34 in 16 patients. The normal fertilization rate was 70.8% (34/48). The total number of embryos frozen was 33 in 16 patients.

Preliminary results of FET, nine cases at the time of writing this paper, were as follows: one case, one FET with one embryo, pregnancy not achieved; one case, two FETs with three embryos, clinical pregnancy, singleton at $27^{+3}$ weeks; one case, one FET with one embryo, pregnancy not achieved; one case, one FET with two embryos, spontaneous abortion; one case, two FETs with three embryos, pregnancy not achieved; one case, one FET with two embryos, pregnancy not achieved; one case, one FET with one embryo, one live birth, Cesarean section at $38^{+6}$ weeks; one case, one FET with two embryos, clinical pregnancy, singleton at $12^{+5}$ weeks; one case, one FET with two embryos, clinical pregnancy, singleton at $11^{+3}$ weeks (see Table 3).

## Discussion

We have reported 22 consecutive patients with POI treated with oral contraceptives. All patients suffered infertility with relatively persistent high levels of FSH (77.74 ± 30.51 IU/l, range 40.2–134 IU/l), without any visible follicles on two occasions more than 4 weeks apart. We found that oral contraceptives could effectively reduce the supraphysiologic FSH level to the normal range within 3 weeks. In the total 106

Table 1. Characteristics and outcomes.

| Case number | Age (years) | Infertility type | Infertility length (years) | Body mass index (kg/m$^2$) | Basal FSH (IU/l) | Number of OC treatment cycles | Number of oocyte retrieval cycles | Number of oocytes retrieved | Normal fertilization rate (number of 2-pronucleus) | Number of embryos frozen |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 29 | Primary | 5 | 24.34 | 87 | 8 | 5 | 6 | 66.7% (4) | 4 |
| 2 | 26 | Primary | 3 | 18.3 | 116 | 3 | 3 | 0 | (0) | 0 |
| 3 | 34 | Primary | 8 | 20.1 | 68.1 | 8 | 4 | 5 | 60% (3) | 4 |
| 4 | 32 | Secondary | 1.5 | 27.4 | 40.2 | 2 | 1 | 1 | 100% (1) | 0 |
| 5 | 33 | Primary | 1 | 23.44 | 41.4 | 2 | 2 | 2 | 50% (1) | 2 |
| 6 | 36 | Secondary | 2 | 22.15 | 78.1 | 3 | 1 | 0 | (0) | 0 |
| 7 | 35 | Secondary | 2 | 18.07 | 54.3 | 7 | 2 | 2 | 100% (2) | 2 |
| 8 | 38 | Secondary | 1 | 20.28 | 84 | 3 | 1 | 1 | 100% (1) | 1 |
| 9 | 27 | Primary | 2 | 24.46 | 47.2 | 7 | 6 | 4 | 50% (2) | 3 |
| 10 | 30 | Primary | 6 | 25.95 | 81.8 | 3 | 1 | 0 | (0) | 0 |
| 11 | 36 | Primary | 7 | 23.62 | 49 | 3 | 2 | 1 | 100% (1) | 1 |
| 12 | 31 | Primary | 3 | 23.53 | 78 | 3 | 2 | 1 | (0) | 1 |
| 13 | 33 | Primary | 3 | 19.92 | 123.5 | 5 | 2 | 3 | 66.7% (2) | 2 |
| 14 | 31 | Secondary | 2 | 21.4 | 134 | 2 | 1 | 1 | 100% (1) | 1 |
| 15 | 29 | Primary | 6 | 26.56 | 80.9 | 5 | 0 | 0 | (0) | 0 |
| 16 | 29 | Primary | 3 | 24.4 | 100 | 5 | 0 | 0 | (0) | 0 |
| 17 | 25 | Primary | 2 | 20.82 | 127 | 7 | 3 | 4 | 50% (2) | 1 |
| 18 | 32 | Primary | 5 | 24.2 | 110 | 6 | 2 | 1 | 100% (1) | 1 |
| 19 | 34 | Primary | 4 | 24.65 | 47.2 | 8 | 4 | 3 | 100% (3) | 3 |
| 20 | 38 | Secondary | 2 | 24.83 | 79.7 | 6 | 3 | 4 | 100% (4) | 4 |
| 21 | 37 | Primary | 4 | 23.4 | 40.8 | 6 | 5 | 7 | 71.4% (5) | 2 |
| 22 | 36 | Primary | 6 | 20.5 | 42 | 4 | 3 | 2 | 50% (1) | 1 |

OC, oral contraceptives; FSH, follicle stimulating hormone.

Table 2. Number of treatment cycles, number of oocytes retrieved, and number of embryos frozen in the 22 cases.

| | *Total number* | *Number of cases* | *Percentage*[a] *(number of cases/22)* | *Per woman*[b] *(total number/22)* |
|---|---|---|---|---|
| OC treatment cycles | 106 | 22 | – | Median 5 and range 2–8 per woman |
| Oocyte retrieval cycles | 53 | 20 | 91% (20/22) | 2.4 cycles per woman, 53/22 |
| Oocytes retrieved | 48 | 17 | 77% (17/22) | 2.2 oocytes per woman, 48/22 |
| Embryos frozen | 33 | 16 | 73% (16/22) | 1.5 embryos per woman, 33/22 |

OC, oral contraceptives.
[a]Percentage: the percentages of POI patients who achieved oocyte retrieval cycles, oocytes retrieved, and embryos frozen; [b]per woman: the numbers of oocyte retrieval cycles, oocytes retrieved, and embryos frozen per POI patient.

Table 3. Preliminary results of frozen–thawed embryo transfer (FET) in nine cases[a].

| | *Case* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* |
| FET cycle[b] | 1C with 1E | 1C with 2E; 1C with 1E | 1C with 1E | 1C with 2E | 1C with 2E; 1C with 1E | 1C with 2E | 1C with 1E | 1C with 2E | 1C with 2E |
| Outcome | Pregnancy not achieved | Singleton at $27^{+3}$ weeks | Pregnancy not achieved | Spontaneous abortion | Pregnancy not achieved | Pregnancy not achieved | Singleton live birth, Cesarean section at $38^{+6}$ weeks | Singleton at $12^{+5}$ weeks | Singleton at $11^{+3}$ weeks |

[a]Preliminary results of FETs in nine cases at the time of writing this paper; [b]FET cycle: the number of FET cycles (C) with the number of embryos (E).

treatment cycles with oral contraceptives of the 22 patients, there were 53 oocyte retrieval cycles in 20 patients (91%, 20/22; 2.4 cycles per woman, 53/22); the total number of oocytes retrieved was 48 in 17 patients (77%, 17/22; 2.2 oocytes per woman, 48/22), and the total number of embryos frozen was 33 in 16 patients (73%, 16/22; 1.5 embryos per woman, 33/22). These results indicated that the use of oral contraceptives was a potential way temporarily to arouse ovarian activity in patients with POI.

It is typical of idiopathic POI patients that spontaneous ovulation may occur in 20% of patients, and spontaneous pregnancies in 5–10%[12,13]. Although it is generally accepted that there are no reliable interventions for infertility except oocyte donation for POI women, there has always been a hope that pituitary suppression could arouse ovarian activity. It was thought that prolonged supraphysiologic FSH levels could down-regulate FSH receptors in follicles, resulting in poor ovarian response to any endogenous or exogenous stimulation[14]. Pituitary suppression treatments, including oral contraceptives, estrogen, progestogen, androgen, and GnRHa, might restore the ovarian sensitivity in some patients[14]. Ovulation induction has been reported to occur even in women without follicles at ovarian biopsy[2]. In our study, the POI patients did not have any visible follicles; the treatment with oral contraceptives reduced FSH levels of all 22 patients within 3 weeks, and follicular reappearance and growth were observed in most women (91%, 20/22). We reduced the oral contraceptive dose to increase the FSH levels as endogenous stimulation, or gave gonadotropins as exogenous stimulation, and oocyte retrievals and embryos frozen were achieved in more than half of the patients. However, two cases failed to produce any follicles after five oral contraceptive treatment cycles per patient. The reason for this remains unknown but may represent a more advanced stage of POI.

This study has some important limitations. Although these patients satisfied the definition of idiopathic POI, their absolute ovarian reserves were unknown and probably ranged along a spectrum of activity[15]. We did not report live birth rates or fetal abnormality at this time. Secondary outcomes, such as clinical pregnancy rate, number of oocytes retrieved, and number of embryos obtained, were unable to prove that the use of oral contraceptives could improve reproductive endpoints. Further studies should be investigated as randomized controlled trials, despite the difficulties in ethical issues, recruiting patients, and quality control[16,17].

In conclusion, this case series showed that the use of oral contraceptives reduced FSH levels efficiently and consistently and induced ovulation in most of these patients with POI.

***Conflict of interest*** The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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## References

1. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, Webber L, Davies M, Anderson R, *et al*. ESHRE guideline: management of women with premature ovarian insufficiency. *Hum Reprod* 2016;31:926–37
2. Tartagni M, Cicinelli E, De Pergola G, De Salvia MA, Lavopa C, Loverro G. Effects of pretreatment with estrogens on ovarian stimulation with gonadotropins in women with premature ovarian failure: a randomized, placebo-controlled trial. *Fertil Steril* 2007;87:858–61
3. Kokcu A. Premature ovarian failure from current perspective. *Gynecol Endocrinol* 2010;26:555–62
4. Nelson LM, Covington SN, Rebar RW. An update: spontaneous premature ovarian failure is not an early menopause. *Fertil Steril* 2005;83:1327–32
5. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. *Fertil Steril* 2016;106:1588–99
6. Committee on Gynecologic Practice. Committee Opinion No. 698: Hormone Therapy in Primary Ovarian Insufficiency. *Obstet Gynecol* 2017;129:e134–41
7. Ben-Nagi J, Panay N. Premature ovarian insufficiency: how to improve reproductive outcome? *Climacteric* 2014;17:242–6

8. Alper MM, Jolly EE, Garner PR. Pregnancies after premature ovarian failure. *Obstet Gynecol* 1986;67(3 Suppl):59–62S
9. Check JH, Chase JS, Spence M. Pregnancy in premature ovarian failure after therapy with oral contraceptives despite resistance to previous human menopausal gonadotropin therapy. *Am J Obstet Gynecol* 1989;160:114–15
10. Brahma PK, Kallen CB. Ovarian hyperstimulation after a short course of an oral contraceptive in a patient with premature ovarian failure. *Fertil Steril* 2008;90:2004–7
11. Qian G, Xu X, Chen L, *et al*. The effect of maternal low flow oxygen administration during the second stage of labour on umbilical cord artery pH: a randomised controlled trial. *BJOG* 2017;124: 678–85
12. Nelson LM, Anasti JN, Kimzey LM, *et al*. Development of luteinized graafian follicles in patients with karyotypically normal spontaneous premature ovarian failure. *J Clin Endocrinol Metab* 1994; 79:1470–5
13. van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. *Hum Reprod Update* 1999;5:483–92
14. van Kasteren YM, Hoek A, Schoemaker J. Ovulation induction in premature ovarian failure: a placebo-controlled randomized trial combining pituitary suppression with gonadotropin stimulation. *Fertil Steril* 1995;64:273–8
15. Progetto Menopausa Italia Study Group. Premature ovarian failure: frequency and risk factors among women attending a network of menopause clinics in Italy. *BJOG* 2003;110:59–63
16. Zhang X, Wu Z, Zhao H, Li C, Wu J, Dai G. Conclusiveness of the cochrane reviews in palliative and supportive care for cancer. *Am J Hosp Palliat Care* 2017;34:53–6
17. Zhang X, Chuai Y, Nie W, Wang A, Dai G. Thrombopoietin receptor agonists for prevention and treatment of chemotherapy-induced thrombocytopenia in patients with solid tumours. *Cochrane Database Syst Rev* 2017;11:CD012035