



# Impact of IVF on the Timing and Symptoms of Menopause

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**Background:** Age-related loss of female fertility is characterized by a decline in both the quantity and quality of ovarian follicles. Symptoms of ovarian stimulation, which is part of the process of in vitro fertilization (IVF), vary among women. This study was conducted to analyze the differences in menopausal timing and symptoms in women who had undergone IVF compared to those who had natural pregnancies.

**Methodology:** In this cross-sectional study, menopausal women were categorized into two groups: those who had undergone IVF ( $n = 50$ ) and those who had not ( $n = 50$ ). Clinical data were obtained from the participants' medical records, and patient interviews were conducted using the menopause rating scale (MRS) questionnaires.

**Results:** The IVF had no significant impact on psychological or somatic symptoms in either group ( $p > 0.05$ ). However, it affected urogenital symptoms ( $p < 0.05$ ). Additionally, there was a significant difference in the age of onset of menopause between the groups ( $p < 0.05$ ).

**Conclusion:** There is a significant correlation between IVF treatment, urogenital symptoms in menopause, and the age of onset of menopause.

**Keywords:** in vitro fertilization, menopause, infertility, psychological symptoms, urogenital

## Introduction

Infertility refers to the inability of a couple to achieve pregnancy after at least 12 months of regular sexual intercourse without the use of contraception.<sup>1</sup> Cause of female infertility are divided into three groups, namely, ovulation, tubal and pelvic, and uterine disorders. Ovulation disorders, which are often accompanied by menstrual disorders, have an incidence of 30%.<sup>2</sup> Couples who experience infertility often undergo a lengthy evaluation and treatment process, which can be physically and psychologically burdensome.<sup>3</sup> One of these treatments is in vitro fertilization (IVF).

One of the key steps of IVF is ovarian stimulation, a procedure that is performed to produce and generate as many mature eggs as possible in order to increase the odds of conception. Ovarian stimulation is performed using exogenous gonadotropin preparations or by increasing endogenous gonadotropin secretion through the administration of ovulation-inducing drugs.<sup>4</sup>

The follicular utilization program through recruitment, growth, and atresia are set in the mid-to-late stages of follicular development by pituitary gonadotropins.<sup>5</sup> Antral follicle count is a biomarker of reproductive age,<sup>6</sup> thus, the number of oocytes harvested per cycle of IVF treatment is a predictor of the time of onset of menopause, although its precision is low.<sup>7,8</sup> Follicles cannot be produced or changed, and menopause occurs when the numbers of follicles have reduced to a very low threshold of about 1.000; therefore, ovarian stimulation may accelerate

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the time of onset of menopause.<sup>9</sup> Although the side effects are much less severe than cancer, the potential impact of gonadotropin therapy cannot be ignored because early menopause restricts reproductive potential, affects sexual health, and increases the risk of cardiovascular and metabolic disorders.<sup>10,11</sup>

Many patients who underwent IVF in the 2000s and early 2010s have now reached menopausal age. To the best of our knowledge, the long-term effect of IVF on the onset and symptoms of menopause have not been well-studied. Data in Indonesia stated that by 2020, the population of menopausal women aged 40–65 years will increase by 29,021,128 (11.4%) from 7,998,543 (5.5%) in 1980.<sup>12</sup> This demonstrates the magnitude of the problem. Therefore, the aim of this study was to analyze the differences in menopausal timing and symptoms in women who had undergone IVF compared to those of women who had natural pregnancies.

## Methods

This research was conducted from August 2020 to August 2021 at the Cipto Mangunkusumo National Referral Hospital (RSCM) Jakarta.

This cross-sectional study compared menopausal women who had undergone IVF (the IVF group) with those who had never undergone IVF (the non-IVF group). The required total sample size was calculated using Slovin's formula to be between 96 and 100 patients; therefore, we included 50 participants in each group. Participants were recruited among patients who had undergone IVF at Yasmin Clinic, RSCM, between January 2010 and December 2015. Participants were considered eligible upon meeting the following criteria: 1) women over 45 years of age who had experienced menopause or had complaints of menopausal symptoms and had never undergone IVF; and 2) women who had undergone IVF using antagonist protocol. The IVF group comprised women who had undergone IVF. The exclusion criteria included women who had malignancies, women who did not use the antagonist protocol, and women who were unwilling to participate in the study.

Sampling was carried out using the medical records of female patients belonging to both groups. From the medical records, we obtained phone number of the patients. The tool used for obtaining data was a questionnaire: Patients in both groups, comprising those who underwent and those who did not undergo IVF, were interviewed by phone and the results were written by the interviewer. The questionnaire was divided into two parts. Briefly, the first part addressed menstrual and

reproductive history, infertility treatment, medical history, and lifestyle factors. The second part contained the menopause rating scale (MRS; obtained from <http://www.menopause-rating-scale.info/>) that focused on menopausal and perimenopausal symptoms. The questions had been translated to Indonesian as per international standards.<sup>12</sup> The symptoms investigated were psychological, somatic, and urogenital. Menopause was conventionally defined as 12 or more months of continuous amenorrhea with no apparent cause other than age. In a few cases, further clarification was required, and patients were contacted again by phone.

This study was approved by the ethics committee of the faculty of medicine, University of Indonesia (Study number: KET-1165/UN2.F1/ETIK/PPM.00.02/2020). Informed consent was obtained from all patients. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis was conducted using SPSS version 23.0 (IBM, Armonk, NY, USA). Demographic data were presented as mean  $\pm$  standard deviation. The comparison between the two groups was investigated using a nonparametric Mann–Whitney test. A p-value of  $<0.05$  was considered significant.

## Results

The participants' demographic characteristics are shown in Table 1. There were significant differences in age, number of children, menarche, previous medical history, marital status, and education between both groups ( $p < 0.05$ ). There were also data the age of IVF, number of IVF cycle, and smoking history.

Based on the MRS questionnaire, there was no significant impact on psychological and somatic symptoms in either group ( $p > 0.05$ ). Psychological symptoms such as depressive mood, irritability, anxiety and physical and mental exhaustion; somatic symptoms such as hot flushes, coronary discomfort, sleeping problems and muscle and joint problems. Nonetheless, there was a significant impact on urogenital symptoms in both groups (mean 44.33 vs 56.67,  $p < 0.05$ ; see Table 2). Urogenital symptoms such as sexual problems, bladder problems, and vaginal dryness. Additionally, there was a statistically significant difference in the age of onset of menopause between the IVF and the non-IVF groups (mean 49.84 vs 50.66, respectively,  $p < 0.05$ ).

Multivariate analysis demonstrated that none of the characteristic variables were independently associated with the severity of menopausal symptoms ( $p > 0.05$ ; see

**Table 1** Characteristics of IVF and Non-IVF Patients

Characteristics	IVF (n = 50)	Non-IVF (n = 50)	p-value
Age (mean $\pm$ SD)	51.02 $\pm$ 2.42	52.76 $\pm$ 2.37	0.000*
Age of IVF	41.26 $\pm$ 2.32		
Number of IVF cycle	2 (1–7)		
Number of children	0.78 (0–2)	2.72 (1–6)	0.000**
Menarche (mean $\pm$ SD)	13 $\pm$ 0.94	12.32 $\pm$ 1.23	0.003*
Onset age of menopause	49.84	50.66	0.004
Smoking history			0.461***
Yes	5 (5%)	3 (3%)	
No	45 (45%)	47 (47%)	
Previous surgical history			0.011***
Yes	18 (18%)	7 (7%)	
No	32 (32%)	43 (43%)	
Education			0.000***
Senior high school	–	15 (15%)	
Diploma	42 (42%)	17 (17%)	
Magister	4 (4%)	14 (14%)	
Doctor	4 (4%)	4 (4%)	

Notes: \*Independent Samples t-test, \*\*Mann–Whitney test, \*\*\*Chi-square.

**Table 2** Comparison Between IVF and Non-IVF Patients

Variable	IVF (n = 50)*	Non-IVF (n = 50)	p**
Somatic symptoms	51.59	49.41	0.701
Psycho symptoms	48.04	52.96	0.386
Urogenital symptoms	44.33	56.67	0.030

Note: \*Mean, \*\*Mann–Whitney test.

Table 3). Therefore, the differences in the baseline characteristics of both groups were negligible.

## Discussion

The ovaries age over time and eventually lose their function, as menopause marks the definite end of a woman's reproductive life. The ovarian aging concept of reproduction assumes that the age-related loss of female fertility is determined by a decrease in the quantity and quality of ovarian follicles. The number of ovarian follicles in women with regular menstrual cycles (premenopausal) are ten times higher than those of perimenopausal women of the same age, whereas follicles are almost absent in postmenopausal women.

In this study, although IVF significantly impacted earlier menopausal age, we also found that there was a relationship between urogenital symptoms of menopause and IVF. Early

menopausal symptoms occur before the age of 46; thus, women experiencing these symptoms might be at risk of early ovarian aging.<sup>13</sup> Women who respond poorly to controlled ovarian hyperstimulation during IVF treatment, as indicated by low numbers of retrieved oocytes, have impaired ovarian reserve and are at risk of early menopause compared to women who have a normal response.<sup>14</sup> This theoretical effect could result from accelerating the small follicle recruitment process or by increasing the rate of oocyte elimination or atresia.

Elder et al found no evidence that ovarian stimulation advances menopausal age in patients who had received fertility treatment.<sup>7</sup> No significant adverse association was found in the study between the numbers of oocytes harvested and early menopausal symptoms, possibly because more aggressive stimulation protocols were used in an attempt to produce larger oocyte harvest. Women should be informed that all procedures involved in the process of IVF treatment are generally safe and do not place women at risk of premature ovarian failure.

A study by Heijnen et al revealed that the administration of gonadotropins for fertility treatment did not appear to have a long-term impact on ovarian aging or the timing or symptoms of menopause. Based on a study by Boer et al, the association between the number of retrieved oocytes at the first IVF treatment and early menopausal transition was weak, although significant. Their results showed that women with a low oocyte counts taken at first IVF treatment had an increased risk of achieving menopausal transition or natural menopause within a decade after the first IVF treatment.<sup>8</sup> In the future, milder treatment strategies should be offered to patients undergoing IVF to prevent the risk of developing short-term or long-term side effects.<sup>15</sup>

Urogenital symptoms of menopause include various menopausal symptoms and signs that are associated with physical changes in the vulva, vagina, and lower urinary tract. These symptoms are related to postmenopausal reduction in the level of circulating estrogen. After menopause, the number of estrogen receptors continues to decrease; however, they never disappear completely. Although these problems are not life threatening, they may have an impact on a woman's quality of life.<sup>16</sup> For example, the prevalence of women with endometriosis decreases with age since the age of menopause is variable and ovarian activity can be increased in the first year after menopause.<sup>17</sup> A retrospective cohort study in the United Kingdom showed that women with poor ovarian response to gonadotrophins stimulation (three oocytes) are

**Table 3** Multivariate Analysis of Symptoms of IVF and Non-IVF Patients

Variable	Unstandardized $\beta$ Coefficient (95% CI)	p-value*
<b>Somatic Symptoms</b>		
Age	0.133 (0.005–0.261)	0.042
Number of children	–0.161 (–0.435–0.113)	0.247
Menarche	0.081 (–0.215–0.378)	0.587
Previous surgical history	–0.032 (–0.769–0.705)	0.932
Education	–0.061 (–0.468–0.346)	0.767
<b>Psycho Symptoms</b>		
Age	0.119 (–0.032–0.269)	0.120
Number of children	0.000 (–0.322–0.323)	0.998
Menarche	–0.35 (–0.384–0.313)	0.841
Previous surgical history	0.322 (–0.544–1.189)	0.462
Education	–0.449 (–0.928–0.030)	0.066
<b>Urogenital Symptoms</b>		
Age	0.072 (–0.047–0.192)	0.232
Number of children	0.082 (–0.174–0.338)	0.525
Menarche	0.041 (–0.236–0.318)	0.769
Previous surgical history	–0.223 (–0.911–0.466)	0.525
Education	0.072 (–0.309–0.452)	0.708

Note: \*Data analysis using linear regression, significant  $p < 0.05$ .

more likely to experience early menopause than those with a good response (6–15 oocytes).

The limitation of this study is that there is a recall bias. Contacting women at least 10 years after their IVF treatment has been impossible in some cases.<sup>18</sup> However, to the best of our knowledge, this is the first study to research this topic in Indonesia. Further research to investigate the underlying pathophysiological process is needed.

## Conclusion

There was a significant correlation between IVF treatment and urogenital symptoms in menopause. Furthermore, the age of onset of menopause in IVF patients was found to be earlier. However, the differences are not clinically significant and require further research.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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