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Association between the number of *in vitro* fertilization cycles and age at menopause

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ABSTRACT

Objective: To assess the association of the number of *in-vitro* fertilization (IVF) cycles and the age at menopause. **Methods:** A total of 65 women who underwent IVF treatment in the years 1992–1995 were included and a questionnaire was performed. **Results:** Thirty-two women had spontaneously become menopausal until follow-up evaluation. Women who had undergone ≥ 6 IVF-cycles had entered menopause significantly earlier than those who had undergone ≤ 5 cycles [(46.9 \pm 1.8) years, $n=11$ vs. (49.9 \pm 2.9) years, $n=21$; $P=0.03$]. **Conclusions:** Our data demonstrate a link between increasing number of IVF cycles and ovarian aging. A direct influence of IVF stimulation, the quality of oocytes at the time of IVF as well as genetic factors might contribute to this phenomenon.

1. Introduction

Infertility is considered as a public health issue affecting nearly every sixth couple in the Western world, and thus the use of assisted reproductive technologies is getting more and more common these days[1]. Although we are quite familiar with short-term complications of *in-vitro* fertilization (IVF) treatment, only little is known about long-term side effects except for the risk of gynecologic cancer[2]. We have been wondering for a long time whether IVF has a long-lasting effect on the ovarian function via its massive ovarian stimulation by supraphysiological hormonal doses. Thus, we aimed to assess the association of number of IVF cycles and the age at menopause in this study.

2. Materials and methods

Of a total of 187 women who underwent at least one IVF treatment cycle at the Medical University of Vienna,

Austria, Department of Gynecologic Endocrinology and Reproductive Medicine, in the years 1992–1995, 65 were willing to answer a questionnaire on general and female health issues. Of these, 32 had spontaneously become menopausal until follow-up evaluation. Menopause was defined as amenorrhea >6 months and presence of other menopause-related symptoms including hot flashes and vaginal dryness. After the approval by the medical ethics company, all patients included in this study signed a declaration of consent.

Variables are described by mean \pm SD. ANOVA and Fisher's exact test have been applied to compare subjects' characteristics between groups and differences in age at menopause. $P<0.05$ were considered statistically significant. Statistical analysis was performed by SPSS 15.0 (SPSS Inc., 1989–2006). The survey is described to be a retrospective case series with a long term follow up.

3. Results

Patients were (36.7 \pm 3.9) years at the time of their last IVF stimulation (IVF cycles at other departments included); a mean of (12.3 \pm 2.7) years had passed between their last IVF stimulation and the follow-up evaluation.

The patients had undergone a mean number of (4.8 \pm 4.6)

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IVF cycles (range 1–15 cycles). The mean age of onset of menopause was (48.8±2.9) years. Women who had undergone six or more IVF cycles were found to have entered menopause significantly earlier than those who had undergone five or less IVF cycles [(46.9±1.8) years, $n=11$ vs. (49.9±2.9) years, $n=21$; $P=0.03$]. There were no differences in age of menarche, age of last IVF stimulation cycle, incidence of ovarian hyperstimulation syndrome, and the number of resulting pregnancies and life births between two groups (data not shown).

4. Discussion

Our data demonstrate an association between number of IVF cycles and age at menopause. This could be of clinical interest, since age at menopause likely affects a woman's subsequent morbidity and mortality.

It remains unclear whether the observed effect is due to a direct influence of the hormonal stimulation on ovarian function. Anti Mullerian hormone (AMH) is considered the most accurate and stable marker for fertility and possible menopause despite several limitations^[3]. Notably, decreased serum AMH levels have been found after IVF stimulation procedures with the nadir on the day of human chorionic gonadotropin administration. On the 14th day after oocyte retrieval, the initial AMH levels had not yet been reached^[4]. This might be a clue that IVF could influence the ovarian reserve. However, it has been presumed that this could also be due to a negative effect of exogenous follicle stimulating hormone (FSH) on AMH production^[5]. To the best of our knowledge, literature lacks data on the impact of IVF stimulation on AMH levels in the long-term.

One might also speculate that a genetic background was responsible for the phenomenon of younger age at menopause in women having undergone five or more IVF cycles. For example, variations of the follicle stimulating hormone receptor (FSHR) have been shown to be associated with both female infertility and the response to ovarian stimulation^[6,7]. Although evidence does not support an influence of FSH receptor polymorphisms and age at natural menopause, mutations in the FSHR have been identified in women with premature ovarian failure^[6,8].

There is a third possible explanation. Repeated poor response to in IVF is known to be associated with an early occurrence of the menopausal transition^[9–11]. It has been suggested that a remaining low quantity of oocytes which is reflected by less number of retrieved oocytes at first IVF treatment was an important predictor of the risk of an early natural menopause. Notably, the quality of oocytes was reported to have no effect on this risk^[9]. In accordance to these results, the younger age at menopause found in women with more than 5 IVF cycles might be due both (i) to the remaining low quantity of oocytes, which attribute to higher number of IVF cycles in order to achieve pregnancy or (ii) directly to the number of IVF cycles. Due to the small sample size our data cannot provide an approach to answering this question.

Our study suffers from several limitations. Since the vast majority of these patients had undergone IVF treatment at different institutions and could not exactly remember the medications used for stimulation, there is a lack

of information on what IVF protocols had been used. Furthermore, the assessment of long-term outcome after IVF treatment is extremely difficult, since many patients are not willing to undergo such evaluations for emotional reasons. Moreover, many have moved and cannot be contacted anymore.

To the best of our knowledge, we are the first to directly focus on IVF and age at menopause and demonstrate a significant association. Further studies are needed to prove our data and to shed some light on the pathophysiologic mechanisms.

Conflict of interest statement

We declare that we have no conflict of interest.

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