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Levent Gökgözoğlu[1, A–C], Mine İslimye[2, A, B], Hasan Onur Topçu[3, D–F], Utku Özcan[3, E, F]

The Effects of Total Abdominal Hysterectomy on Ovarian Function – Serial Changes in Serum Anti-Müllerian Hormone, FSH and Estradiol Levels

[1] Giresun Bulancak State Hospital, Giresun, Turkey
[2] Department of Obstetrics and Gynecology, Balıkesir Univesity, Balıkesir, Turkey
[3] Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Objectives. The aim of this study was to evaluate ovarian function with longitudinal changes in serum levels of anti-mullerian hormone (AMH), follicle stimulating hormone (FSH) and estradiol (E2) after total abdominal hysterectomy (TAH) with ovarian conservation.

Material and Methods. In this prospective longitudinal study, a total of 29 women, aged 39 to 48 years, suffering from uterine pathologies underwent TAH with ovarian conservation. Their serum AMH, FSH and E2 levels were measured at baseline, at the first month and the third month after TAH.

Results. There was a statistically significant decrease in AMH serum levels between the baseline and the first postoperative month; the values were 0.22 (0.16–1.49) ng/mL and 0.18 (0.04–0.52) ng/mL, respectively. However, significant differences were not seen for serum levels of FSH and E2 when baseline and one-month values were compared. In addition, no statistically significant differences were detected between the baseline and third-month serum AMH, FSH and E2 levels.

Conclusions. The study demonstrated that TAH affects ovarian function temporarily (**Adv Clin Exp Med 2014, 23, 5, 821–825**).

Key words: anti-mullerian hormone, hysterectomy, ovarian conservation.

Hysterectomy is one of the most frequent surgical procedures in women of reproductive age [1]. In women between 40 and 49 years old, if the cases do not have an ovarian pathology, the decision whether to perform a hysterectomy with bilateral oophorectomy or without oophorectomy is still a big problem for gynecologists.

More than half of all women who have hysterectomies are younger than 44 years old [2]. Hysterectomy with ovarian conservation may be performed on women in their early forties. Despite this protective approach, there are still concerns about the effects of hysterectomy on the ovaries. The effects of hysterectomy on the ovaries are open to dispute. Several studies have been published about the ovarian reserve after hysterectomy; among the effects reported were acute permanent decrease in the ovarian reserve [3], decreases in the ovarian reserve [4], and no change in the ovarian reserve [5].

Anti-mullerian hormone (AMH) is a constant and valuable marker in the evaluation of the ovarian reserve and it does not change with the menstrual cycle [6–8]. Follicle stimulating hormone (FSH) and estradiol (E2) are also important markers in the evaluation of the ovarian reserve.

The aim of this study was to investigate the effects of total abdominal hysterectomy (TAH) on the ovaries by assessing longitudinal changes of serum AMH, FSH and E2 levels.

Material and Methods

This prospective longitudinal study was conducted at Zekai Tahir Burak Women's Health Education and Research Hospital in Ankara, Turkey. This is a tertiary reference research hospital; the participants were mostly referred from outside medical centers. A total of 29 women between 39 and 48 years old and suffering from uterine pathologies were included in the study. TAH with bilateral ovarian and tubal conservation using surgical sutures was performed on these women for benign gynecologic diseases. The inclusion criteria for the study were regular (21–35 days) menstrual cycles; normal ovarian reserve, as indicated by basal FSH levels < 10 IU/L; no history of ovarian surgery or ovarian abnormalities; no history of infertility, ovulatory dysfunction or other endocrine disorders. The study was approved by the institution's ethics committee, and written informed consent was obtained from all the participants.

After taking a complete history, including an obstetrical and gynecological history, the patients were examined. The data were recorded including age, gravidity, parity, indication of hysterectomy, pre-operative FSH, E2, AMH levels on day 3 of the menstrual cycle, and post-operative levels of these hormones.

The baseline blood collection was performed in the morning of day 3 of the menstrual cycle before the surgery. All the operations were performed in the follicular phase of the menstrual cycle. After the hysterectomy, due to the absence of menstrual flow, the patients were instructed to recognize their early follicular phase by consulting their past menstrual diary and noting a rapid decrease of self-reported "fluid retention", indicated by a feeling of bloating, edema and/or nocturia during the expected menses [9]. The ovarian reserve was re-evaluated when the early follicular phase was confirmed by a serum progesterone (P) level < 1 ng/mL in conjunction with an ultrasound evaluation showing the absence of a dominant follicle > 10 mm in either of the ovaries.

After the blood collection, the serum was stored at –70°C until the measurement of the AMH levels. The serum levels of AMH were determined using a commercially available enzyme-linked immunosorbent assay kit (Diagnostic Systems Laboratories, Webster, TX USA). FSH and serum E2 were measured by electrochemiluminescence immunoassay (ECLIA, Roche). The statistical analysis was performed using SPSS software (version 11.5, SPSS, Chicago, IL USA). The continuous variables were analyzed by the Shapiro-Wilk test. Descriptive statistics for continuous variables were shown as mean with standard deviation or median, and categorical variables were given as case numbers and percentiles. The Friedman test was used to investigate the longitudinal significant change in serum FSH, estradiol and AMH levels. Where an important difference was detected, the Wilcoxon signed-rank test was performed. Spearman's correlation test was used to detect significant correlations between continuous variables. The Bonferroni correction was used to counteract Type 1 errors in the multiple comparisons, A p value < 0.05 was considered statistically significant.

Results

The characteristics and post-operative histopathology results of the cases are presented in Table 1. The mean age of the women in the study was 43.9 ± 2.5; there was only one woman aged 48 and she had no premenopausal symptoms. Table 2 shows the baseline, post-operative first month and third month's serum FSH (mIU/mL), E2 (pg/mL) and AMH (ng/mL) levels. There was no statistically significant difference between the baseline and follow-up serum FSH and E2 levels; however, the differences between the baseline and post-operative first month's serum AMH levels were statistically significant (p = 0.009).

The correlation coefficient and materiality levels of BMI and age in relation to the baseline, post-operative first and third month changes in serum FSH, E2 and AMH levels are shown in Table 3. There was no statistically significant correlation between age, BMI and the changes in serum levels of FSH, E2 and AMH. The Bonferroni correction was used and p < 0.017 was accepted as statistically significant.

Table 1. The demographic and clinical characteristics of the patients

Characteristics	**n = 29**
Age	43.9 ± 2.5 (39–48)
Gravidity	4 ± 3
Parity	3 ± 1
BMI (kg/m^2)	29.3 ± 6.3
Pathology[a]	
Adenomyosis	3 (10.3%)
Simple atypical hyperplasia	2 (6.8%)
Leiomyoma	22 (75.8%)
Leiomyoma + Adenomyosis	1 (3.4%)
Proliferative endometrium	1 (3.4%)

a – post-operative pathology results.

Table 2. Longitudinal changes in serum FSH, E_2 and AMH levels

	Baseline	First Month	Third Month	p [a]
FSH (mIU/mL)	6.0 (4.3–7.9)	6.6 (4.6–9.7)	5.2 (4.4–6.5)	0.485
E_2 (pg/mL)	107 (60–206.7)	102.4 (45.8–197.4)	127.8 (51.1–216.1)	0.519
AMH (ng/mL)	0.22 (0.16–1.49)[b]	0.18 (0.04–0.52)[b]	0.17 (0.04–0.69)	0.036

a – Friedman test; b – the difference between baseline and first-month AMH was found significant by using the Wilcoxon signed rank test (p = 0.009).

Table 3. Coefficient of correlation and materiality levels of BMI and age relative to the baseline, first and third post-operative month changes in serum FSH, E2 and AMH levels

	Age		BMI	
	r	p [a]	r	p [a]
E_2				
Baseline – 1 Month	0.391	0.036	–0.103	0.594
Baseline – 3 Months	0.320	0.091	–0.268	0.160
FSH				
Baseline – 1 Month	–0.055	0.776	–0.296	0.119
Baseline – 3 Months	–0.037	0.849	0.145	0.453
AMH				
Baseline – 1 Month	0.032	0.870	–0.377	0.044
Baseline – 3 Months	–0.015	0.938	–0.317	0.094

a – $p < 0.017$ was accepted as statistically significant for the Bonferroni correction.

Discussion

In this longitudinal prospective study, ovarian function was evaluated in 29 women aged 39 to 48 years and subjected to TAH for benign diseases of the uterus. The serum levels of AMH, FSH and E2 were measured pre-operatively and in the first and third post-operative months, and transient changes in serum AMH levels were detected. Subsequently, all of the hormone levels reached normal ranges by the third month.

AMH is a promising screening test for ovarian function. Low threshold values of AMH have a good specificity for poor ovarian reserve. FSH and E2 serum levels were also used to evaluate ovarian reserve. However, fluctuating levels of FSH and E2 may result in abnormal evaluations of ovarian function [3].

Conservation of the ovaries protects women from bone resorption in the premenopausal and postmenopausal period [10, 11]. Surgically induced menopause may also increase the risks of cardiovascular diseases and of psychosexual and cognitive dysfunction [12–14].

In some past studies, a decline in ovarian function after hysterectomy was demonstrated; however, some of those studies were designed retrospectively [15, 16] or were based on a questionnaire-style survey about climacteric complaints [17, 18].

Souza et al. [5] evaluated ovarian histology and function before and after TAH in 25 patients with symptomatic uterine fibroids. They did not find any change in the serum levels of hormones. Histologically; however, they demonstrated a statistically significant decrease in ovarian reserve.

In a rat model study, Ozdamar et al. reported ovarian histological changes after hysterectomy such as an increased number of atretic and cystic follicles and a decline in normal follicle count on the ovaries [19]. In another experimental rat model study, Tapisiz et al. found histological changes in ovaries that may adversely affect ovarian reserve [20].

In a recent prospective cohort study, Moorman et al. evaluated ovarian function after hysterectomy and found risk ratios for ovarian failure to be 2.93 (95% CI 1.57–5.49) in women who underwent unilateral oophorectomy, and 1.74 (95%

CI 1.14–2.65) in women in whom both ovaries remained [21]. Farquar et al. investigated the association between menopause and hysterectomy, and demonstrated that the onset of menopause in women who underwent hysterectomy retaining both ovaries was nearly four years earlier when compared to women with intact *uteri* and also that the onset of menopause in women who retained one ovary more than four years earlier than women who retained both ovaries [22].

After hysterectomy, evaluation of ovarian arterial blood flow may be helpful to predict ovarian function [23, 24]. Lee et al. [25] designed a prospective study to determine ovarian function after hysterectomy that evaluates both ovarian arterial blood flow indices and serum AMH levels. They stated that there is no association between hysterectomy and a decline in ovarian function for up to 3 months post-operatively. In another study, despite a decline in the ovarian blood flow in women who underwent hysterectomy, total antral follicle count and total ovarian volume were similar, and those results suggest changes in ovarian function after hysterectomy [26].

AMH is a valuable marker for assessing ovarian function. In a recent study, Atabekoglu et al. [27] investigated serum AMH levels during a 24-month follow-up period in women who had undergone TAH. They demonstrated a 30% loss of ovarian reserve in hysterectomized women when compared with controls; however, these findings did not reach statistical significance.

In a prospective randomized trial, serum AMH levels were evaluated in subjects who had undergone uterine artery embolization and hysterectomy [28]. The mean AMH levels were significantly decreased at 6 weeks, but a recovery of AMH levels occurred during the 24-month post-operative follow-up period. Those data are similar to the results of the current study, in which a significant difference was found in serum AMH levels when the baseline and first post-operative month were compares, but subsequently the difference decreased by the third month.

In this study, to prevent the probable adverse effects of ovarian diseases on ovarian functions, only cases with uterine pathologies were included in the study. The authors think that removal of the uterine arteries, which are an important blood supply to the ovaries, causes an acute decrease in serum AMH levels. In the recovery period, ovarian arteries, which are the main blood supply to the ovaries, may compensate for the loss of the uterine arteries in the ovarian blood supply.

In the current study, transient changes in serum levels of AMH were found in the first post-operative month, which improved by the third post-operative month. The authors therefore conclude that ovarian function is affected after TAH, but those effects are not permanent and recovery takes only a few months.

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Address for correspondence:

Hasan Onur Topçu
Zekai Tahir Burak Women's Health Education and Research Hospital
Talatpasa Avenue, Hamamönü
Ankara
Turkey
Tel: +90 532 635 95 38
E-mail: dronurtopcu@gmail.com

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