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Does bilateral uterine artery ligation have negative effects on ovarian reserve markers and ovarian artery blood flow in women with postpartum hemorrhage?

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Objective: Bilateral uterine artery ligation (UAL) is a fertility-preserving procedure used in women experiencing postpartum hemorrhage (PPH). However, the long-term effects of this procedure on ovarian function remain unclear. The aim of this study was to investigate whether bilateral UAL compromised ovarian reserve and ovarian blood supply.
Methods: This prospective study included 49 women aged between 21 and 36 years who had undergone a cesarean section for obstetric indications. Of these, 25 underwent uterine bilateral UAL to control intractable atonic PPH. The control group consisted of 24 women who had not undergone bilateral UAL. Standard clinical parameters, the results of color Doppler screening, and ovarian reserve markers were assessed in all participants at 6 months after surgery. The clinical parameters included age, parity, cycle history, body mass index, and previous medication and/or surgery. Color Doppler screening findings included the pulsatility index (PI) and resistance index (RI) for both the uterine and ovarian arteries. The ovarian reserve markers included day 3 follicle-stimulating hormone (FSH) levels, antral follicle count, and anti-Müllerian hormone (AMH) levels.
Results: There were no significant differences in the ovarian reserve markers of day 3 FSH levels, antral follicle count, and AMH levels between the study and control groups ($p > 0.05$ for all). In addition, no significant differences were observed in the PI and RI indices of the uterine and ovarian arteries ($p > 0.05$ for all).
Conclusion: In this study, we showed that bilateral UAL had no negative effects on ovarian reserve or ovarian blood supply, so this treatment should be used as a fertility preservation technique to avoid hysterectomy in patients experiencing PPH.

Keywords: Ovarian blood flow; Ovarian reserve; Uterine artery ligation; Uterine blood flow

Introduction

Postpartum hemorrhage (PPH) is a life-threatening complication.

Uterine atony is considered to be the most common cause [1]. The other known risk factors for PPH include placenta accreta, placental abruption, retained placenta, genital tract lacerations, uterine rupture, and coagulation disorders [1].

Bimanual uterine compression, pharmacological therapies, and intrauterine balloon tamponade are the first-line therapies for atonic PPH [2]. If these therapies fail, surgery may be needed to control the hemorrhage. Hysterectomy is the definitive surgical procedure for blood loss; however, it is a radical procedure, especially in young women [2]. For this reason, several fertility-preserving surgical tech-

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niques have been developed, such as uterine artery ligation (UAL), internal iliac artery ligation, the B-Lynch technique, and modified compression sutures [2].

UAL is one of the most popular fertility-preserving surgical techniques. It is easy to perform and effective for controlling PPH [1]. It is also relatively safe and allows patients to bear more children in the future. Furthermore, is success rate is over 90% [3].

Diminished ovarian reserve is a major cause of infertility. Widely-used markers of ovarian reserve, which is a proxy for the likelihood to conceive, include age, follicle-stimulating hormone (FSH) levels, antral follicle count (AFC), anti-Müllerian hormone (AMH) levels, and inhibin B levels.

It is widely known that the blood supply to the ovaries comes from the ovarian arteries which are direct branches of the abdominal aorta, and the uterine arteries. Many studies have reported that hysterectomy can lead to decreased ovarian reserve and early menopause, even when the ovaries are not removed [4-7]. FSH levels were found to be elevated in women who had undergone hysterectomies, even when one ovary had been removed [5]. Another study reported that inhibin B levels had decreased at 6 and 12 months after abdominal hysterectomy [6]. Finally, reduced ovarian reserve was observed after uterine artery embolization (UAE) [4]. However, the effects of UAL on ovarian reserve and ovarian artery blood flow have not been adequately studied. The aim of this study was to investigate whether UAL had any negative effects on ovarian reserve markers and ovarian blood flow in young women with PPH.

Methods

This prospective study included 49 women aged between 21 and 36 years who received care at the Department of Obstetrics and Gynecology at Suleymaniye Maternity, Research and Training Hospital between October 2012 and October 2013. All participants who underwent a cesarean section for obstetric indications were included in the study, unless they satisfied the exclusion criteria described below. Of the 49 participants, 25 received uterine bilateral UAL by the same surgeon to control intractable atonic PPH. The control group consisted of 24 healthy women who had not undergone bilateral UAL or any other interventions for PPH. Fundal massage, bimanual compression, oxytocin administration (40 IU in 500 mL intravenously), methylergonovine maleate (0.20–0.40 mg, intramuscularly), and rectal misoprostol (0.8–1 mg rectally) were applied to all patients before bilateral UAL.

Patients with other causes of PPH, such as traumatic PPH, disseminated intravascular coagulation, bleeding disorders, retained placenta, and uterine rupture were excluded from the study. Other exclusion criteria were receiving B-Lynch or other hemostatic sutures, stepwise uterine devascularization, internal iliac artery ligation, or

hysterectomy; being older than 37 years; and obesity (body mass index [BMI], > 30 kg/m^2). None of the patients had previously been diagnosed with endometriosis or had any clinical symptoms thereof, and they had no other known risk factors for diminished ovarian reserve, such as infertility, a history of ovarian surgery, the presence of neoplastic disease, infectious diseases, autoimmune diseases, liver or kidney disease, diabetes, vascular disease, irregular menstrual cycles, smoking, or alcohol consumption.

Blood transfusion, plasma expanders, and fibrinogen were administered depending on the patients' needs. The study was approved by our Institutional Review Board (IRB No. 13.06.2012-03). Written informed consent was obtained from all patients.

PPH was defined as blood loss greater than 1,000 mL following a cesarean section. Intractable PPH was defined as PPH that persisted despite standard medical treatment (oxytocin, methylergonovine maleate, and misoprostol), fundal massage, and bimanual compression.

Bilateral UAL was performed 2 cm below the Kerr incision (lower segment transverse). A 0-Vicryl absorbable suture (Ethicon, Neuilly-sur-Seine, France) was placed from the anterior to posterior aspects of the myometrium 2–3 cm medial to the descending part of the uterine vessels through an avascular space in the broad ligament and tied. Uterine tonus and bleeding were then controlled after the procedure.

Standardized clinical parameters, color Doppler screening findings, and ovarian reserve markers were assessed in all participants at 6 months after surgery. The clinical parameters included age, parity, cycle history, BMI, and previous medication and/or surgery. Color Doppler screening findings included the pulsatility index (PI) and resistance index (RI) for both the uterine and ovarian arteries. The ovarian reserve markers included day 3 FSH levels, AFC, and AMH levels.

1. Blood sample collection

Blood samples were collected at 9:00 and 11:00 AM after an overnight fast between days 3 and 5 of the menstrual cycle. The blood samples were then centrifuged within 2 hours after being obtained and assessed on the same day. AMH concentrations were measured with an enzymatically amplified two-sided immunoassay (AMH Gen II Elisa A79765; Beckman Coulter, Ireland).

2. Doppler scanning

Ultrasound examinations were performed using a Voluson 730 Expert (GE Healthcare, Buckinghamshire, UK) apparatus with a 4–9 MHz endovaginal probe between days 20 and 22 of the menstrual cycle. The ultrasound settings were standardized, with a pulse repetition frequency of 1.3 kHz for the uterine and ovarian arteries and 1.1 kHz for the spiral artery to evaluate a minimum flow velocity of 5 cm/sec, gain of 3.4, a low wall motion filter (1), the harmonic setting at low, and power at 100%. The same procedure was applied to all patients.

Transverse and sagittal imaging of the uterus and ovaries was performed using an endovaginal probe. The spiral arteries were assessed within a 1-mm area parallel to the myometrium–endometrium border by color Doppler. The descending branches of the uterine artery were measured at the level of the internal os of the cervix uteri. The ovarian arteries were evaluated as the large vessels at the level of the ovarian hilum. The PI and RI of both the right and left uterine and ovarian arteries were calculated. Average values were recorded.

3. Statistical analysis

The baseline characteristics of the groups were shown as the mean and standard deviation. The laboratory and anthropometric parameters of patients were compared using the Student t-test for parametric parameters and the Mann-Whitney test for nonparametric parameters. Differences were considered significant at $p < 0.05$.

Results

The demographic characteristics and ovarian reserve markers of the patients are summarized in Table 1. There were no differences in terms of age, BMI, parity, day 3 FSH levels, AFC, and AMH levels between the groups ($p > 0.05$ for all) (Table 1). The results for uterine and ovarian artery PI and RI are shown in Table 2. Likewise, no significant differences were observed in uterine and ovarian artery PI and

RI among patients who underwent bilateral UAL and those who did not ($p > 0.05$ for all) (Table 2).

Discussion

The uterine arteries are sometimes disrupted during surgical procedures such as UAL, hysterectomy, and UAE, resulting in a lack of ovarian blood supply from the uterine arteries. The unresolved question is whether these procedures harm the patient's ovarian reserve. This issue is important because fertility-preserving procedures are often performed in young patients, and we must inform patients and/or their families about not only the reproductive potential of the uterus, but also their ovarian reserve. However, data about the ovarian reserve of these patients are limited. To the best of our knowledge, this is the first prospective study to find that bilateral UAL did not have any negative effects on ovarian reserve markers such as day 3 FSH levels, AFC, and AMH levels. Furthermore, uterine and ovarian blood flow was not found to have been compromised in patients who underwent UAL.

Many studies have investigated the effects of hysterectomy and UAL on ovarian reserve [5,6,8-11]. It has been claimed that hysterectomy compromises ovarian reserve and may accelerate menopause [8]. However, this suggestion was based on the vasomotor symptoms of menopause, which are not a reliable predictor of ovarian re-

Table 1. Demographic characteristics and ovarian reserve markers of the study and control groups

Variable	Bilateral uterine artery ligation group (n = 25)	Control group (n = 24)	*p*-value
Age (yr)	28.16 ± 2.74	27.42 ± 2.58	0.33
Body mass index (kg/m²)	25.81 ± 1.63	25.65 ± 1.67	0.74
Parity	1.80 ± 0.70	1.71 ± 0.75	0.66
Day 3 FSH (mIU/mL)	7.90 ± 1.11	7.52 ± 1.11	0.24
Antral follicle count	10.32 ± 1.99	11.25 ± 2.04	0.11
AMH (ng/mL)	2.17 ± 0.50	2.48 ± 0.64	0.07

Values are presented as mean ± standard deviation.
FSH, follicle-stimulating hormone; AMH, anti-Müllerian hormone.

Table 2. Color Doppler parameters of the study and control groups

Variable	Bilateral uterine artery ligation group (n = 25)	Control group (n = 24)	*p*-value
Right uterine artery RI	0.79 ± 0.07	0.77 ± 0.06	0.61
Left uterine artery RI	0.74 ± 0.07	0.75 ± 0.06	0.76
Right uterine artery PI	1.78 ± 1.13	1.75 ± 1.10	0.33
Left uterine artery PI	1.75 ± 1.19	1.73 ± 1.10	0.78
Right ovarian artery RI	0.64 ± 0.06	0.64 ± 0.03	0.56
Left ovarian artery RI	0.70 ± 0.07	0.70 ± 0.05	0.83
Right ovarian artery PI	1.23 ± 0.23	1.26 ± 0.13	0.56
Left ovarian artery PI	1.24 ± 0.13	1.23 ± 0.12	0.87

Values are presented as mean ± standard deviation.
RI, resistance index; PI, pulsatility index.

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serve. Ovarian function has also been assessed by more reliable ovarian reserve markers in other studies. Cooper and Thorp [5] reported that FSH levels were slightly, but nonsignificantly, elevated in women who underwent hysterectomy without oophorectomy. Another study demonstrated that abdominal hysterectomy without oophorectomy did not affect ovarian reserve and that FSH, luteinizing hormone (LH), and estradiol were at premenopausal levels at 6 months after surgery [9]. Another study reported that FSH and LH were unchanged at 6 and 12 months post-hysterectomy, but inhibin B levels had decreased [6]. However, only 12.9% of those women showed findings compatible with ovarian failure [6]. Furthermore, inhibin B is no longer accepted as a reliable marker of ovarian reserve [12,13]. Lee et al. [10] also found that hysterectomy did not change AMH levels or ovarian arterial blood flow, defined in terms of PI and RI values.

Some studies have also investigated the effects of radical hysterectomy (RH) on ovarian reserve [14-16]. It has been suggested that RH with ovarian preservation did not alter the age of menopause [16]. Ellsworth et al. [14] found that RH conserved ovarian function in 80% of patients. Another study reported that abdominal radical trachelectomy did not affect ovarian reserve or response to ovarian stimulation [15].

Early studies claimed that UAE might lead to ovarian failure via utero-ovarian anastomoses. Inadvertent embolization of the ovarian circulation has been suggested to be the mechanism of post-UAE ovarian insufficiency [17,18]. The size and the type of embolic agent, extent of embolization, and the end point of embolization have also been proposed as factors associated with ovarian failure [19]. However, ovarian artery embolization has not been clearly demonstrated to affect ovarian reserve, and multiple studies have indicated that it does not seem to increase the risks of permanent amenorrhea, premature menopause, or menopausal symptoms compared with UAE [19-21]. Moreover, the natural flow of the embolic agent is not towards the ovaries, and flow to the ovaries may not be present under normal conditions during embolization.

Recent studies demonstrated that UAE had no effect on ovarian reserve markers in patients younger than 40–45 years of age [19,22,23]. No significant differences in AMH and FSH levels were found in women younger than 45 years at 12 months after UAE [22]. Furthermore, no cases of amenorrhea were observed in that group [22]. It was also reported that UAE did not affect ovarian reserve in women younger than 40 years and that ovarian reserve tests did not show any statistically significant differences in those subjects; those findings are similar to our results [23,24]. Another study showed that 48% of UAE patients under 40 years old who desired fertility achieved term pregnancy [25].

In this study, we found that the uterine artery blood supply was not compromised after bilateral UAL. The result is especially important for young women who are expecting future pregnancies, because it is widely known that uterine blood flow is essential for promoting a receptive endometrium, embryo implantation, trophoblast invasion, and successful pregnancy [26]. Chang et al. [27] reported that bilateral UAL through laparoscopic myomectomy did not decrease uterine artery PI and RI values at 3 months after surgery. Moreover, other studies have also demonstrated that uterine artery PI and RI values did not change after bilateral internal iliac artery ligation [28,29].

Preserving ovarian blood supply during surgical procedures is important, especially in young women of reproductive age. Bilateral UAL is one of the most important fertility-preserving techniques in patients experiencing PPH, and our study showed that it did not compromise ovarian blood supply and ovarian reserve in those patients, suggesting that UAL should be used to avoid hysterectomy in cases of PPH.

There may be some explanations for why uterine blood flow was restored 6 months after surgery. We used absorbable suture material, and the recanalization rate of the uterine artery was found to be high at 6 months after surgery [30]. Studies have also documented the possibility of increased collateral blood flow after bilateral UAL [31]. The patients were re-evaluated at 6 months after surgery in this study because Vicryl theoretically undergoes complete absorption within 6 months.

However, there were some limitations of this study. First, the study size was relatively small. Second, we were not able to evaluate the ovarian reserve markers of the patients before pregnancy and surgery, because it was impossible to determine which patients would become pregnant, undergo cesarean sections, develop PPH, and undergo bilateral UAL.

In conclusion, bilateral UAL did not have any negative effects on ovarian reserve. Furthermore, this surgery did not disrupt uterine and ovarian blood flow. More studies with larger groups of patients are needed to support this conclusion.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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