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Review Article

Ovarian hormone levels before and after tubal ligation: a systematic review and meta-analysis

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Abstract: Background: Tubal ligation (TL) is an efficient, permanent, and convenient contraceptive method. However, there are conflicting results regarding postoperative ovarian hormone levels. The aim of this study was to determine whether TL alters ovarian hormone levels. Study design: Pubmed and Embase databases, from January 1980 to March 2017, were searched to identify relevant studies reporting ovarian hormone assessment before and after TL. Meta-analyses were performed with Stata 12.0. Results: Seventeen studies with a total of 620 women were included in this meta-analysis. Pooling of the results showed no significant differences in serum levels of follicle-stimulating, luteinizing and anti-Mullerian hormones, estradiol, and inhibin in pre-sterilization and post-sterilization assessments. However, progesterone levels were significantly decreased after TL when using Pomeroy or Falope-ring methods ($P < 0.05$). Conclusion: TL does not affect ovarian reserves but results in luteal function deficiency. However, further research is necessary to confirm the long-term effects of TL on ovarian function.

Keywords: Hormone, systematic review, tubal ligation

Introduction

Tubal ligation (TL) is a widely accepted method of destroying the fallopian tubes as a permanent method of contraception [1]. However, the effects of TL on ovarian function have been a matter of debate. Some patients have complained of irregular menstrual cycles, pelvic pain, dysmenorrhea, and spotting after TL [2-6]. Complications have been correlated with the degree of surrounding tissue damage, particularly affecting uterine-ovarian blood flow, which can influence short-term ovarian function. However, numerous studies have shown no side effects of TL on ovarian reserves and luteal function [7-15].

Various methods can be utilized to perform selective tubal sterilization, including vaginal colpotomy, post-partum laparotomy, minilaparotomy, laparoscopy, and hysteroscopy, which has been widely accepted as it is minimally invasive with rapid recovery [16]. However, hysteroscopic sterilization requires a hysterosalpingogram at least three months after the initial procedure to confirm bilateral tubal occlusion before women can rely on this method of contraception [17]. Therefore, minilaparotomy and laparoscopy methods of TL remain the preferred methods due to widespread use, cost-effectiveness, and fewer short- and long-term risks.

At present, many surgery methods are being employed to perform minilaparotomy and laparoscopy methods of TL, including Pomeroy, modified Pomeroy, Uchida, Hulka or Filshie clips, silastic bands, fimbriectomy, bipolar coagulation, and Falope rings. Pomeroy, modified Pomeroy, and Falope rings cause greater destruction of surrounding blood flow. To evaluate ovarian function, levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), anti-Mullerian hormone (AMH), and inhibin (INH) in the early follicular phase can be measured, as well as progesterone (P) in the mid-luteal phase. To assess the endocrine consequences of TL, this study conducted a

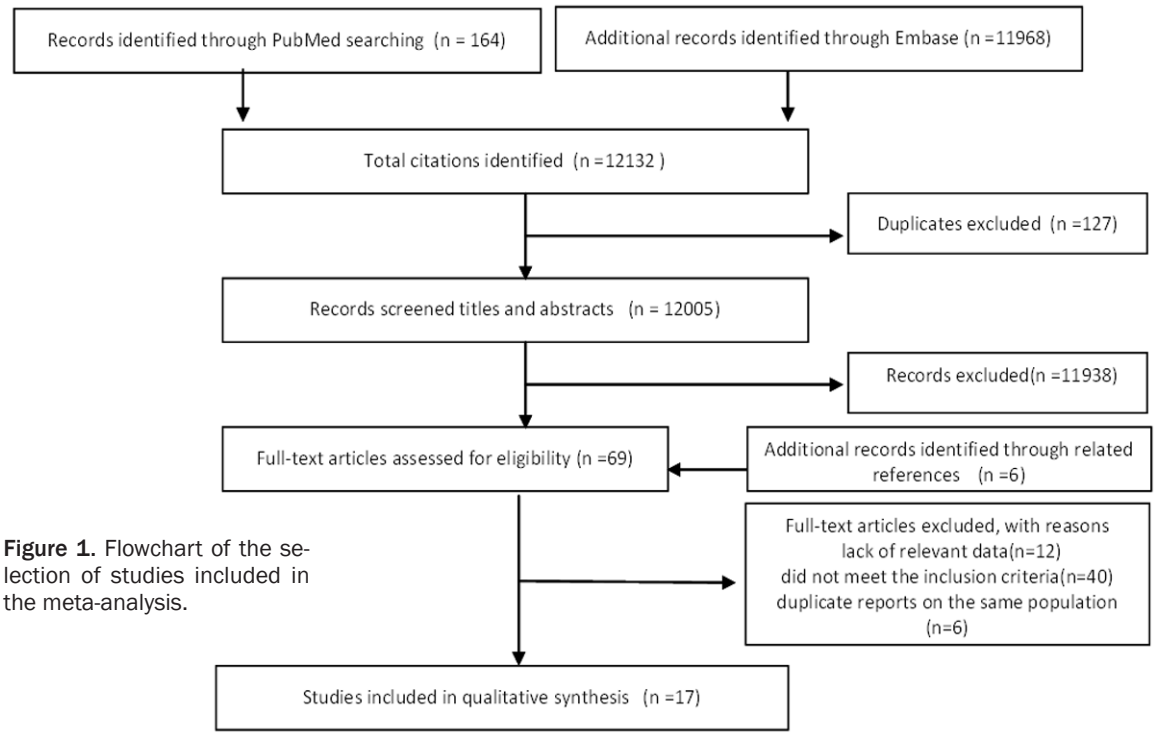

Figure 1. Flowchart of the selection of studies included in the meta-analysis.

meta-analysis of hormone levels before and up to one year after TL performed via minilaparotomy and laparoscopy.

Materials and methods

Search strategy

Pubmed, Embase, China National Knowledge Infrastructure, and Chinese Biomedical Literature Service System were searched for articles published before July 2017, using the following terms: “tubal ligation”, “tubal sterilization”, “tubal blockage”, “oviduct ligation”, “fallopian tube ligation”, “female sterilization”, OR “tubal occlusion” AND “ovarian function”, “ovarian reserve”, “hormone”, OR “luteal function”. No search limits were set concerning study type, population, and language. However, no eligible articles were found in the Chinese database. Studies reporting levels of at least one of the ovarian hormones (FSH, LH, E2, AMH, INH, or P) were selected. After extracting full-text papers, reference lists were searched by hand to identify additional relevant studies.

Inclusion criteria

Criteria for inclusion in this meta-analysis were: 1) Human studies; 2) Prospective studies; 3) Blood-sample studies; 4) Discontinuation of hormone contraception > 3 months; and 5) Studies including before and after operation parameters. For studies reporting multiple end-points, data for the longest end-point within one year was selected. Reviews, conference articles, letters to the editor, and case reports were excluded.

Data extraction

Two reviewers, independently, extracted data from eligible studies. Disagreements between the two reviewers were resolved by consensus with a third author. The following data were recorded from each study: name of first author, year and location (country) the study was performed, type of study, number and age of patients, patient body mass index (BMI), gravidity and parity information, study end-point duration, and method and type of hormone assessments.

Statistical analysis

Stata 12.0 software (StataCorp LP, College Station, TX, USA) was used to analyze data. Effect estimates were pooled using fixed effects meta-analysis with a non-standard method and statistical heterogeneity was assessed using

Table 1. Studies reporting hormone changes after tubal ligation included in meta-analysis

Author	Year	Location	Type	Method	*n*	Age (y)	BMI (kg/m^2)	Gravity (*n*)	Parity (*n*)	Duration (mo)	Hormone (assay)
Alvarez et al. [18]	1989	Dominican Republic	CCT	Pomeroy	8	< 38	NR	NR	NR	6	FSH, LH, E2, P (RIA)
				Uchida	8						
Garza-Flores et al. [25]	1991	Mexico	CCT	Pomeroy	14	24.7±4.2	NR	NR	2.8±0.9	3	FSH, LH, E2, P (RIA)
Thranov et al. [29]	1992	Denmark	CCT	Falope-ring or Filshie clips	27	(25-38)	NR	NR	≥ 1	12	FSH, LH, E2, P (RIA)
Hakverdi et al. [4]	1994	Turkey	CCT	Pomeroy, silastic bands or fimbriectomy	43	32.6±4.1	NR	6.8±2.1	5.7±1.6	12	FSH, LH, E2, P (RIA)
Sumiala et al. [28]	2000	Finland	CCT	Hulka or Filshie clips	46	(31-43)	NR	NR	NR	12	FSH, LH, E2, P (RIA)
Bulent Tiras et al. [20]	2001	Turkey	CCT	Bipolar coagulation	13	33.1±3.9	NR	NR	NR	3	FSH, LH, E2, P (ELISA)
Timonen et al. [30]	2002	Finland	CCT	Hulka or Filshie clips	33	37 (31-43)	24 (19-33)	NR	NR	12	FSH, LH, E2, P (RIA)
Carmona et al. [21]	2003	Spain	CCT	Bipolar coagulation	26	36.4±1.1	22.7±2.1	NR	1.9±0.2	12	FSH, LH, E2, P (ECLIA), INH (ELISA)
Yazici et al. [31]	2004	Turkey	CCT	Bipolar coagulation	19	37.6±3.8	NR	NR	NR	12	FSH, LH, E2, P (ECLIA)
Cevrioglu et al. [22]	2004	Turkey	RCT	Pomeroy	15	36.9±3.8	28.3±2.8	3.0±0.9	2.4±0.4	6	FSH, LH, E2, P (ECLIA)
				Bipolar cauterization	14	35.8±3.6	27.5±3.1	3.3±0.9	2.5±0.4		
Kutlar et al. [26]	2005	Turkey	Unblinded RCT	Pomeroy	14	36.4±2.5	NR	5.1±2.0	3.6±0.8	3	FSH, LH, E2, P (ECLIA)
				Fimbriectomy	13	36.8±2.0	NR	4.7±1.8	3.8±1.2		
				Bipolar coagulation	15	36.7±2.2	NR	5.3±1.9	4.1±1.2		
Fagundes et al. [24]	2005	Brazil	CCT	Modified Pomeroy	16	34.1±1.3	NR	NR	NR	6	FSH, LH, E2, P (RIA)
Baloglu et al. [19]	2005	Turkey	RCT	Bipolar electrocoagulation	47	31.4±4.9	NR	NR	NR	12	FSH, LH, E2, P (ECLIA)
Dede et al. [23]	2006	Turkey	CCT	Bipolar electrocautery	60	34.2±4.2	NR	4.8±1.8	2.9±1.0	3	FSH, LH, E2, P (RIA)
Goynumer et al. [3]	2009	Turkey	Unblinded RCT	Electrocoagulation	44	(35-40)	NR	NR	NR	10	NR
				Mechanical clips	44						
Ercan et al. [8]	2012	Turkey	CCT	Bipolar electrodesiccation and transection	49	36.6±3.4	NR	4 (2-7)	3 (2-5)	3	FSH, LH, E2, P (ECLIA), AMH (ELISA)
Silva et al. [27]	2013	Brazil	Prospectiv cohort	Bipolar coagulation or Pomeroy	52	32.5±4.5	29.9±4.8	NR	NR	12	AMH (ELISA)

Abbreviations: AMH, anti-Mullerian hormone; BMI, body mass index; CCT, controlled clinical trial; E2, estradiol; ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; FSH, follicle-stimulation hormone; INH, inhibin; LH, luteinizing hormone; NR, not reported; P, progesterone; RCT, randomized controlled trial; RIA, radioimmunoassay. Note: data are expressed as mean ± standard deviation, or as median (range).

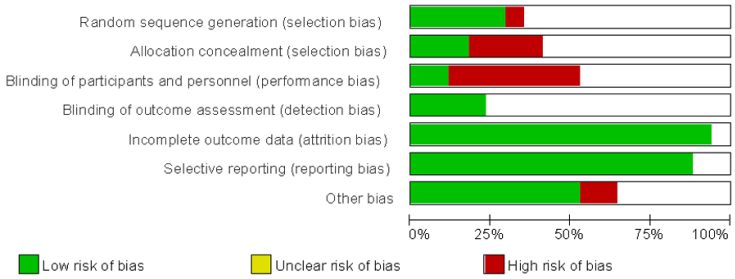

Figure 2. Quality of studies included in the meta-analysis.

Table 2. Comparison of hormones before and after tubal ligation

Hormone	Studies (*n*)	Patients (*n*)	WMD (95% CI)	I^2	*P*
FSH	11	364	0.046 (-0.233-0.325)	0.0%	0.745
LH	10	290	-0.024 (-0.230-0.182)	70.0%	0.821
E2	9	349	0.728 (-1.669-3.125)	0.0%	0.552
P	8	264	-1.528 (-2.753-0.304)	69.1%	0.014
INH	2	114	-1.370 (-6.726-3.987)	0.0%	0.616

Abbreviations: CI, confidence interval; E2, estradiol; FSH, follicle-stimulation hormone; INH, inhibin; LH, luteinizing hormone; P, progesterone; WMD, weighted mean difference.

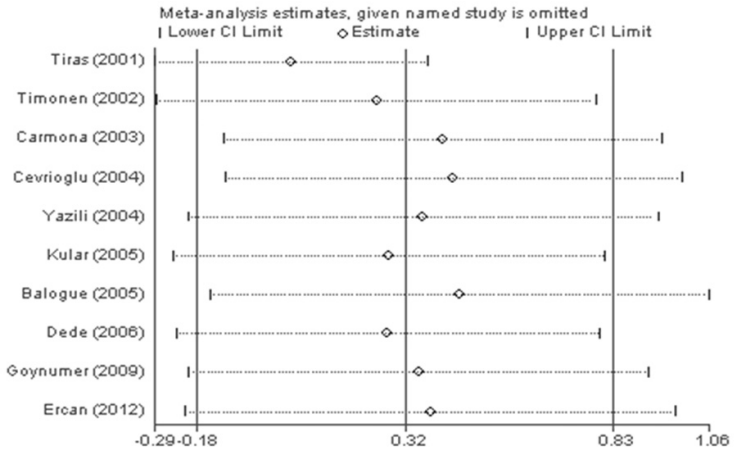

Figure 3. Sensitivity analysis of the effects of tubal ligation on luteinizing hormones in the early follicular phase. CI, confidence interval.

the I^2 statistic. A random effects model was used if substantial heterogeneity was detected (I^2 > 50%). Further sensitivity analysis was performed to verify the robustness of the assumption. Cochrane's Collaboration tool was used to assess bias with Review Manager 5.2. Randomization and concealment were not reported in most studies, though one randomized controlled trial reported allocation concealment. Selection bias would likely not affect the outcome of analyses, as every patient acted as their own control. The ≥ 80% completion rate per study group indicates a lack of attrition bias. Hormone concentrations are presented as mean ± standard deviation. $P < 0.05$ is considered statistically significant.

Results

Study selection

A total of 12,132 studies were initially retrieved from Pubmed and Embase databases (**Figure 1**). After excluding duplicates, studies that were not self-controlled trials, cross-sectional studies, and those without a comparison group were excluded, as well as studies including patients that did not meet the inclusion criterion (premenopausal or menopausal, use of hormone contraception < 1 mo before TL). A total of 17 studies comprising 620 patients remained for further analyses [3, 4, 8, 18-31] (**Table 1**). Risk of bias assessment of included trials is presented in **Figure 2**.

Effects of TL on follicular phase ovarian hormones

Meta-analyses demonstrated that TL had no effect on post-procedural levels of FSH, LH, E2, or INH (**Table 2**). However, moderate heterogeneity was observed among studies with respect to LH assessment, which may have been due to differences in operation techniques and methods of detection. Therefore, sensitivity analysis was performed to verify the robustness of the outcome (estimate = 0.323, 95% CI: -1.840-0.829) (**Figure 3**).

AMH levels were measured in three studies. However, values reported by Silva et al. [27] were not normally distributed and Ercan et al. [8] reported median (range), whereas Goynumer et al. [3] reported means and standard deviations. Although AMH could not be assessed by

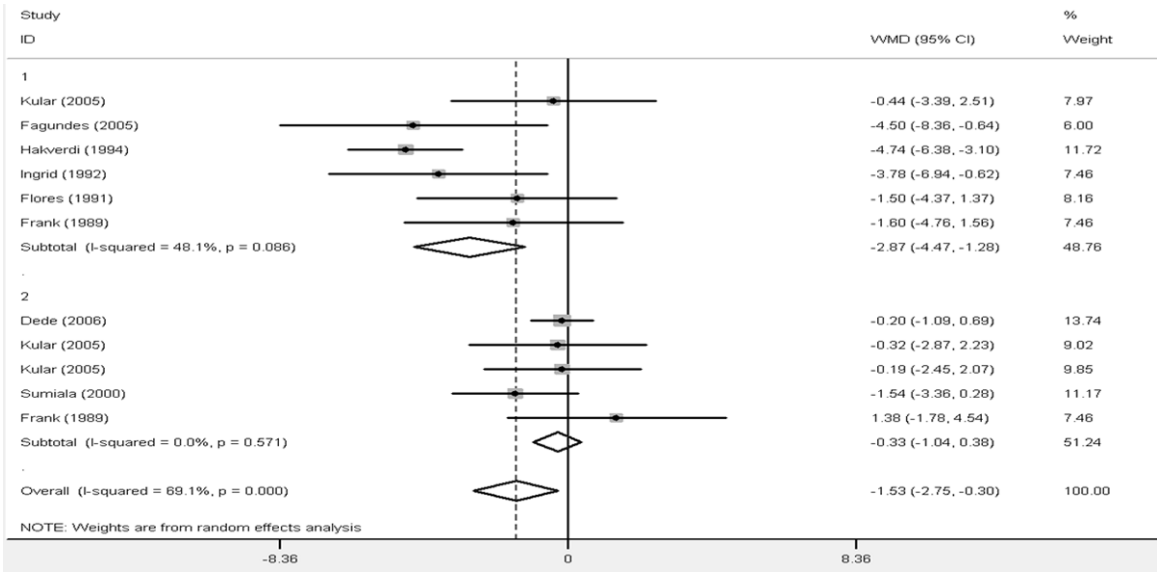

Figure 4. Subgroup analysis of the effects of tubal ligation on progesterone in the mid-luteal phase. CI, confidence interval; WMD, weighted mean difference.

meta-analysis, each of the three studies found no changes in AMH after TL.

Effects of TL on mid-luteal phase ovarian hormone

Pooled data from eight studies showed significant alteration in P levels after TL (P = 0.014) (**Table 2**). However, there was significant heterogeneity among the studies (I^2 = 69.1%; P < 0.001). Thus, subgroup analyses according to surgery type were performed. As Pomeroy and Falope-ring methods tend to more seriously damage surrounding tissue, they were included together as subgroup 1. The remaining operation types were classified as subgroup 2. Data reported by Hakverdi et al. [4] was not included in subgroup analyses, as P levels were not distinguished among the three methods used (Pomeroy, silastic bands, and fimbriectomy). Subgroup analysis revealed a significant decrease in P levels after TL in subgroup 1 (P < 0.001), but not in subgroup 2 (P = 0.358) (**Figure 4**). There was no heterogeneity within the subgroups.

Discussion

Results of the present meta-analysis indicate that TL does not influence the secretion of FSH, LH, INH, or E2. Furthermore, although TL by bipolar electrocoagulation, fimbriectomy, or Hulka and Filshie clips did not significantly alter P levels in the mid-luteal phase, levels were significantly decreased when using Pomeroy or Falope-ring methods. These techniques resulted in the formation of a loop in the tube, which could impair the mesosalpinx vessels and damage circulation to the ovaries, as well as contribute to tubal ligation syndrome. This may lead to irregular menstrual cycles and spotting. Alternative methods leave the mesosalpinx vessels intact, reducing the probability of influencing ovarian function. For example, laparoscopic tubal bipolar coagulation has no permanent effects on luteal function, particularly in younger women [32].

Although the heterogeneity among studies concerning the effects of LT on P was not significant, the presence of mild heterogeneity may be attributed to the inclusion of various operation techniques that could not be further subdivided. In addition, most studies collected blood samples on the 21st day of the menstrual cycle, though some studies obtained samples eight to ten days post-ovulation. For example, time of blood draw can influence levels of P, which change rapidly in the corpus luteum maturation period. It is also possible that varying methods of sample management and testing contributed to these findings.

There were several limitations to the present study. First, the limited number of studies restricted the ability to clarify the effects of

specific surgical techniques, particularly in subgroup analysis. Thus, these results should be interpreted carefully. Second, the quality of evidence was insufficient. More adequately powered clinical trials are needed. Third, only one study included patients that were over 30 years of age. Thus, future studies are needed to more clearly describe the effects among women of various ages. Because the secretion of P is pulsatile, additional studies with larger samples and definitive blood draw timing are necessary to verify the influence of TL on the corpus luteum maturation period. Moreover, recent studies have suggested that AMH is an indicator of ovarian function [33-35] and should, therefore, be included in future studies evaluating the impact of TL.

Conclusion

This meta-analysis demonstrates that TL does not significantly alter the profile of follicular phase ovarian hormones. However, procedures utilizing Pomeroy or Falope-ring methods may damage the vasculature and impact luteal function, evidenced by an alteration in P levels. It is, therefore, important to apply the appropriate method resulting in the least tubal damage.

Disclosure of conflict of interest

None.

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References

[1] Rodriguez MI, Gordon-Maclean C. The safety, efficacy and acceptability of task sharing tubal sterilization to midlevel providers: a systematic review. Contraception 2014; 89: 504-11.

[2] Cappa F, Mascaretti G, Barchiesi S. Endocrine and psychological problems in women subjected to tubal sterilization. Patol Clin Ostet Ginecol 1984; 12: 209-13.

[3] Goynumer G, Kayabasoglu F, Aydogdu S, Wetherilt L. The effect of tubal sterilization through electrocoagulation on the ovarian reserve. Contraception 2009; 80: 90-4.

[4] Hakverdi AU, Taner CE, Erden AC, Satici O. Changes in ovarian function after tubal sterilization. Adv Contracept 1994; 10: 51-6.

[5] MacKenzie IZ, Thompson W, Roseman F, Turner E, Guillebaud J. A prospective cohort study of menstrual symptoms and morbidity over 15 years following laparoscopic Filshie clip sterilisation. Maturitas 2010; 65: 372-7.

[6] Ozkaya E, Gokmen O, Tosun A, Kucuk E, Baris S, Korkmaz V, Usta M. Unfavorable lipid profile and higher frequency of hot flashes during perimenopausal years after fallopian tube ligation. Gynecol Endocrinol 2013; 29: 559-62.

[7] Berwanger Da Silva AL, Da Re C, Dietrich C, Fuhrmeister IP, Pimentel AM, Corleta HV. Impact of tubal ligation on ovarian reserve measured by Anti-Mullerian hormone: a prospective cohort study. Human Reproduction 2012; 27.

[8] Ercan CM, Sakinci M, Coksuer H, Keskin U, Tapan S, Ergun A. Ovarian reserve testing before and after laparoscopic tubal bipolar electrodesiccation and transection. Eur J Obstet Gynecol Reprod Biol 2013; 166: 56-60.

[9] Gentile GP, Helbig DW, Zacur H, Park T, Lee YJ, Westhoff CL. Hormone levels before and after tubal sterilization. Contraception 2006; 73: 507-11.

[10] Gentile GP, Kaufman SC, Helbig DW. Is there any evidence for a post-tubal sterilization syndrome? Fertil Steril 1998; 69: 179-86.

[11] Helm G, Sjoberg NO. Corpus luteum function after tubal sterilization using endothermic coagulation. Acta Obstet Gynecol Scand 1986; 65: 741-4.

[12] Kelekci S, Yilmaz B, Yakut Y, Yasar L, Savan K, Sonmez S. Hormonal and ovarian stromal blood supply changes after laparoscopic tubal sterilization: a prospective controlled study. Contraception 2006; 73: 279-83.

[13] Peterson HB, Jeng G, Folger SG, Hillis SA, Marchbanks PA, Wilcox LS; U.S. Collaborative Review of Sterilization Working Group. The risk of menstrual abnormalities after tubal sterilization. U.S. Collaborative Review of Sterilization Working Group. N Engl J Med 2000; 343: 1681-7.

[14] Shobeiri MJ, Atashkhoii S. The risk of menstrual abnormalities after tubal sterilization: a case control study. BMC Womens Health 2005; 5: 5.

[15] Wu E, Xiao B, Yan W, Li H, Wu B. Hormonal profile of the menstrual cycle in Chinese women after tubal sterilization. Contraception 1992; 45: 583-93.

[16] Cooper JM, Carignan CS, Cher D, Kerin JF; Selective Tubal Occlusion Procedure 2000 Investigators Group. Microinsert nonincisional hysteroscopic sterilization. Obstet Gynecol 2003; 102: 59-67.

[17] Gariepy AM, Creinin MD, Schwarz EB, Smith KJ. Reliability of laparoscopic compared with

hysteroscopic sterilization at 1 year: a decision analysis. Obstet Gynecol 2011; 118: 273-9.
[18] Alvarez F, Faundes A, Brache V, Tejada AS, Segal S. Prospective study of the pituitary-ovarian function after tubal sterilization by the Pomeroy or Uchida techniques. Fertil Steril 1989; 51: 604-8.
[19] Baloglu A, Uysal D, Karci L, Guven CM, Yavuz E. Effects of laparoscopic tubal ligation on ovarian blood flow and steroidogenesis. Clin Exp Obstet Gynecol 2005; 32: 230-2.
[20] Bulent Tiras M, Noyan V, Ozdemir H, Guner H, Yildiz A, Yildirim M. The changes in ovarian hormone levels and ovarian artery blood flow rate after laparoscopic tubal sterilization. Eur J Obstet Gynecol Reprod Biol 2001; 99: 219-21.
[21] Carmona F, Cristobal P, Casamitjana R, Balasch J. Effect of tubal sterilization on ovarian follicular reserve and function. Am J Obstet Gynecol 2003; 189: 447-52.
[22] Cevrioglu AS, Degirmenci B, Acar M, Yilmazer M, Erol D, Kahraman A, Demirel R, Coksuer H. Examination of changes caused by tubal sterilization in ovarian hormone secretion and uterine and ovarian artery blood flow rates. Contraception 2004; 70: 467-73.
[23] Dede FS, Dilbaz B, Akyuz O, Caliskan E, Kurtaran V, Dilbaz S. Changes in menstrual pattern and ovarian function following bipolar electrocauterization of the fallopian tubes for voluntary surgical contraception. Contraception 2006; 73: 88-91.
[24] Fagundes ML, Mendes MC, Patta MC, Rodrigues R, Berezowski AT, de Moura MD, Yazlle ME. Hormonal assessment of women submitted to tubal ligation. Contraception 2005; 71: 309-14.
[25] Garza-Flores J, Vazquez-Estrada L, Reyes A, Valero A, Morales del Olmo A, Alba VM, Bonilla C. Assessment of luteal function after surgical tubal sterilization. Adv Contracept 1991; 7: 371-7.
[26] Kutlar I, Ozkur A, Balat O, Ugur MG, Genco Y, Aksoy F. Effects of three different sterilization methods on utero-ovarian Doppler blood flow and serum levels of ovarian hormones. Eur J Obstet Gynecol Reprod Biol 2005; 122: 112-7.
[27] Silva AL, Re C, Dietrich C, Fuhrmeister IP, Pimentel A, Corleta HV. Impact of tubal ligation on ovarian reserve as measured by anti-Mullerian hormone levels: a prospective cohort study. Contraception 2013; 88: 700-5.
[28] Sumiala S, Tuominen J, Irjala K, Klemi P, Maenpaa J. Luteal function declines after laparoscopic sterilization by Hulka or Filshie clips. Contraception 2000; 62: 177-80.
[29] Thranov I, Hertz JB, Kjer JJ, Andresen A, Micic S, Nielsen J, Hancke S. Hormonal and menstrual changes after laparoscopic sterilization by Falope-rings or Filshie-clips. Fertil Steril 1992; 57: 751-5.
[30] Timonen S, Tuominen J, Irjala K, Maenpaa J. Ovarian function and regulation of the hypothalamic-pituitary-ovarian axis after tubal sterilization. J Reprod Med 2002; 47: 131-6.
[31] Yazici G, Arslan M, Pata O, Oz U, Aban M. Ovarian function and vascular resistance after tubal sterilization. J Reprod Med 2004; 49: 379-83.
[32] Brosens I, Koninckx P, Boeckx W. Endometriosis. Clin Obstet Gynaecol 1981; 8: 639-51.
[33] Dayal M, Sagar S, Chaurasia A, Singh U. Antimullerian hormone: a new marker of ovarian function. J Obstet Gynaecol India 2014; 64: 130-3.
[34] Lunsford AJ, Whelan K, McCormick K, McLaren JF. Antimullerian hormone as a measure of reproductive function in female childhood cancer survivors. Fertil Steril 2014; 101: 227-31.
[35] Peigne M, Decanter C. Serum AMH level as a marker of acute and long-term effects of chemotherapy on the ovarian follicular content: a systematic review. Reprod Biol Endocrinol 2014; 12: 26.