International Journal of General Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical Value of Combined Multi-Indicator Tests in Diagnosis of Benign Ovarian

Lunyun Yang[1], Lin Du[2], Bailong Hou[1], Xiaoqin Niu[1], Wei Wang[1], Weifeng Shen[1]

[1]Department of Laboratory Medicine, The Affiliated Hospital of Jiaxing University, Jiaxing, 314000, People's Republic of China; [2]The Third Xiangya Hospital of Central South University, Changsha, 430074, People's Republic of China

Correspondence: Weifeng Shen, Department of Laboratory Medicine, The Affiliated Hospital of Jiaxing University, No. 1882, Zhonghuan South Road, Nanhu District, Jiaxing, Zhejiang, 314000, People's Republic of China, Tel +86-18868345828, Email swf15960220793@126.com

Background: To investigate the existence and degree of correlation between benign ovarian tumors and physiological indicators such as reproductive hormones and tumor markers.

Methods: A total of 150 patients with benign ovarian tumors admitted to Jiaxing First Hospital between January 1, 2019, and May 30, 2021, were enrolled as research subjects, while 104 healthy women were enrolled in the control group. Comparative analysis of the correlation between the reproductive hormones LH, FSH, T, E2, and the tumor indicators AMH, AFP, CEA, CA125, and CA199 between the groups was performed.

Results: There was no statistical difference in LH, FSH, T, AMH, and CEA expression levels between the experimental and control groups ($p \geq 0.05$); E_2, CA125, and CA199 levels were higher significantly in the experimental group than in the control group ($P<0.001$); AFP levels were significantly lower in the experimental group than in the control group ($P<0.05$). CA125 (0.762) had the highest AUC when diagnosing the value of each index of E2, CA125, and CA199 for benign ovarian tumors. CA125 had the highest sensitivity (56.7%), followed by E_2 (50.0%); CA199 had the highest specificity (84.5%), followed by CA125 (83.7%). The combined diagnosis of benign ovarian tumors was performed using different combinations of the indicators. When the two indicators were combined for diagnosis, the combination of E2 + CA199 had the highest sensitivity (82.6%), whereas the combination of CA125 + CA199 had the largest AUC (0.783) and the highest specificity (86.4%). The combined diagnosis of E_2+CA125+CA199 had a higher AUC than the combined diagnosis of the two indicators (0.805), with a sensitivity of 77.2%, and a specificity of 70.9%.

Conclusion: The most relevant factors for benign ovarian tumors are E2, CA125, and CA199 and the combination of these three indicators has the highest AUC for disease prediction while increasing the detection rate of benign ovarian tumors.

Keywords: benign ovarian tumors, tumor markers, reproductive hormones

Introduction

Ovarian tumor is the most common tumor in women's reproductive systems, accounting for approximately 70% of benign tumors. Their incidence rate is higher than other gynecological diseases, and they have a significant risk for malignant transformation, which has a greater impact on women health and safety.[1,2] Ovarian benign tumors (OBTs) can occur at any age in women, but is more common during the reproductive years.[3] There are numerous types of benign ovarian tumors, which include ovarian epithelial tumors, ovarian mesenchymal tumors, and germ cell tumors.[4] In terms of the malignant ovarian tumors, 90% are of an epithelial cell type and comprise multiple histologic types, with various specific molecular changes, clinical behaviours, and treatment outcomes. The remaining 10% are non-epithelial ovarian cancers, which include mainly germ cell tumours, sex cord-stromal tumours, and some extremely rare tumours such as small cell carcinomas.[5] Due to its inherent risk of malignancy and wide variety, the prediction and diagnosis of benign ovarian tumors are particularly important.[6,7] As clinical progress in tumor marker research slows down, an increasing number of additional factors are being discovered to have a possible correlation with benign ovarian tumors. Therefore, additional research is required to improve the disease prediction. At present, the majority of clinical indicators are non-specific, they may exhibit abnormal levels in a variety of tumor types, and hence have low sensitivity and specificity

Received: 28 February 2023
Accepted: 16 May 2023
Published: 29 May 2023

when used alone as diagnostic indicators to predict benign ovarian tumors. Clinical research has shifted to determining how to accurately predict benign ovarian tumors using an accurate combination of relevant factors. Therefore, this study aimed to investigate whether a correlation exists between ovarian benign tumors and physiological indicators such as reproductive hormones and tumor markers, as well as and the degree of correlation.

Materials and Methods

Subjects

150 patients with benign ovarian tumors admitted to Jiaxing First Hospital between January 1, 2019, and May 30, 2021, aged 18–45 years with a mean of (31.72±7.51) years, were enrolled as study subjects; whereas 104 physically healthy females aged 19–45 years with a mean of (31.20± 6.79) years were selected as the control group from the hospital's patient record system. There was no statistically significant difference in age between the group of patients with benign ovarian tumors and the healthy population control group. This study was approved by the ethics committee of the Jiaxing First Hospital (No: LS2021-KY-129).

Inclusion and Exclusion Criteria

Inclusion Criteria

(I) pathological biopsy confirmed the diagnosis of benign ovarian tumor; (II) no other congenital diseases; (III) all relevant patient clinical data were complete.

Exclusion Criteria

(I) those with a previous history of thoracic or abdominal surgery (except cesarean delivery); (II) those with severe underlying diseases; (III) those with a history of psychiatric or neurological diseases; (IV) those with infectious diseases; (V) those with liver and kidney dysfunction; (VI) those receiving adjuvant therapy such as radiotherapy and chemotherapy.

Methods

Each clinical index collected in the experimental and control groups was analyzed retrospectively: LH, FSH, T, E2, AMH, AFP, CEA, CA125, CA199. Abbott's fully automated chemiluminescence immunoassay was used to detect all indexes using the chemiluminescence double antibody sandwich method. The test kits were supplied by Abbott Diagnostics Ireland. The detailed operating procedure was performed according to the manufacturer's instructions.

Statistical Analysis

SPSS Statistics 25.0 was used to organize and analyze the data. Normally distributed data were expressed as x±s, while non-normally distributed data were expressed as median and quartiles. The *t*-test was used to compare normal measures, while non-normal measures were compared using the Wilcoxon rank-sum test for the statistical significance of the differences between the two groups. Pearson's correlation coefficient (r) was used to determine the association between two normally distributed continuous variables. Spearman correlation coefficient (ρ) was used to determine the association between two variables when at least one variable was skewed or ranked. Logistic regression analysis was performed when the dependent variable was categorical. OR (dominance ratio) refers to the ratio of the number of exposed to non-exposed subjects in the case group. The OR value can be used to determine the extent to which exposure factors influence the occurrence of positive events. The subject operating characteristic curve (ROC) was plotted to determine the optimal diagnostic cut-off for predicting disease, as well as the sensitivity and specificity. p-values <0.05 were considered statistically significant.

Results

Basic Information About the Study Population

We collected data on 150 patients with benign ovarian tumors. The age of the patient group was (31.72±7.51) years, while that of the control group was (31.29±6.79) years, and the age difference between the two groups was not statistically significant (t=0.738, P=0.461). The differences in the indicators LH, FSH, T, AMH, and CEA, between the two groups, were not statistically significant, but the differences in E2, AFP, CA125, and CA199 were statistically significant (Table 1).

Table 1 Basic Information of the Study Population

Variables	Patients (n=150)	Control (n=104)	t/Z	P
Age (years)	31.72±7.51	31.29±6.79	0.738	0.461
LH (mIU/mL)	5.19 (3.11, 8.07)	4.39 (3.06, 5.91)	1.595	0.111
FSH (mIU/mL)	4.83 (3.32, 6.12)	5.09 (4.12, 6.20)	1.271	0.204
T (nmol/L)	1.07±0.34	1.02±0.32	1.000	0.318
E_2 (pmol/L)	291.12 (140.93, 472.80)	172.57 (108.67, 340.61)	3.581	<0.001
AMH (ng/mL)	2.68 (1.33, 4.59)	2.65 (1.22, 4.43)	0.460	0.646
AFP (ng/mL)	1.90 (1.30, 3.00)	2.50 (1.70, 3.40)	3.227	0.001
CEA (ng/mL)	1.20 (0.80, 1.75)	1.20 (0.90, 1.80)	1.233	0.218
CA125 (U/mL)	21.40 (13.95, 53.70)	12.00 (8.50, 18.20)	7.100	<0.001
CA199 (U/mL)	14.10 (6.65, 27.70)	7.70 (3.50, 15.00)	4.618	<0.001

Multifactorial Logistic Regression Analysis

Multi-factor logistic regression equations were constructed by including E2, AFP, CA125, and CA199. $P < 0.001$ for the model coefficients in the Omnibus test (likelihood ratio test) indicated that this fitted model was significant. Second, the Hosmer-Lemesho test revealed a good model fit superiority effect with a −2 log-likelihood value of 254.862 and P=0.993 ($P > 0.05$). The results indicated that elevated levels of E2, CA125, and CA199 significantly increased the risk of developing benign ovarian tumors. There was no statistically significant difference between AFP and the presence of benign ovarian tumors. Table 2 further analysis was performed, and the statistically significant indicators E2, CA125, and CA199 were incorporated into a new multi-factor logistic regression model, yielding the logistic regression equation. $\text{logit}(P) = \ln(P/(1-P)) = -2.244 + 0.001 * E_2 + 0.082 * \text{CA125} + 0.046 * \text{CA199}$, Table 3.

Correlation Analysis Between AMH and Various Indicators

Due to the possibility of a correlation between AMH and benign ovarian tumors, we performed a correlation analysis of AMH with each index. The results indicated a negative correlation between AMH and E2, but a positive correlation between AMH and T. Correlation between AMH and age was relatively high, whereas correlations between T and E2 were low. There was no correlation between AMH and other factors, such as LH, FSH, AFP, CEA, CA125, and CA199 (Table 4).

Table 2 Multi-Factor Logistic Regression Analysis of Patients with Benign Ovarian Tumors

Indicators	B-value	B-value Standard Error	Wald	OR (95% CI)	P
E_2	0.001	0.001	7.214	1.001 (1.000, 1.003)	0.007
AFP	−0.071	0.052	1.823	0.932 (0.841, 1.032)	0.177
CA125	0.083	0.018	20.113	1.086 (1.048, 1.126)	<0.001
CA199	0.045	0.015	9.316	1.046 (1.016, 1.077)	0.002

Table 3 One-Way Logistic Regression Analysis versus Multivariate Logistic Regression Analysis in Patients with Benign Ovarian Tumors

Indicators	One-Way Logistic Regression			Multi-Factor Logistic Regression		
	OR	OR95%CI	P	OR	OR95%CI	P
E_2	1.001	1.000–1.002	0.014	1.001	1.000–1.002	0.019
CA125	1.086	1.050–1.123	<0.001	1.085	1.047–1.125	<0.001
CA199	1.059	1.032–1.087	<0.001	1.047	1.017–1.078	0.002

Table 4 Correlation Analysis Between AMH and Various Indicators

	Age	LH	FSH	T	E_2	AFP	CEA	CA125	CA199
ρ (rho)	−0.459	0.103	−0.079	0.255	−0.280	−0.052	−0.009	0.063	0.107
P	<0.001	0.107	0.216	<0.001	<0.001	0.414	0.883	0.322	0.094

The Value of Each Single Index in the Diagnosis and Prediction of Benign Ovarian Tumors

The AUC of CA125 (0.762) was the highest when the value of every single index, including E2, CA125, and CA199 was used to diagnose benign ovarian tumors. CA125 had the highest sensitivity (56.7%), followed by E2 (50.0%), while CA199 had the highest specificity (84.5%), followed by CA125 (83.7%). Because the sensitivity and specificity of each index are difficult to balance in predicting the disease, a combination of additional indexes was performed (Table 5).

The Predictive Value of Combination Diagnosis in Benign Ovarian Tumors

In this study, different combinations of indicators were used to make a combined diagnosis of benign ovarian tumors. When the two indicators were combined for diagnosis, the combination of E2 +CA199 had the highest sensitivity (82.6%), whereas the combination of CA125 + CA199 had the highest AUC (0.783) and specificity (86.4%). The AUC for the combined diagnosis of E2+CA125+CA199 was greater than the AUC for the combined diagnosis of the two indicators (0.805), where the sensitivity was 77.2% and the specificity was 70.9%, with Y=−0.022 for the multifactorial logistic regression equation (Table 6). The ROC curves for each indicator diagnostic for predicting benign ovarian tumors were plotted with 1-specificity as the horizontal coordinate and sensitivity as the vertical coordinate, as shown in Figure 1.

Discussion

Benign ovarian tumors are common clinical tumors of the reproductive system that are highly prevalent in women during their reproductive years, and their incidence is increasing year by year due to the influence of modern women's lifestyle and dietary habits, as well as food safety concerns.[8] Ovarian cancer has the highest mortality rate of any gynecologic tumor, with no distinctive symptoms in the early stages, and about 75% of patients are diagnosed in the middle and late stages.[9] It reported that BRCA1/2 germline mutations are the strongest known genetic risk factors for epithelial ovarian cancers and are found in 6–15% of women with diagnosed with that disease. The BRCA1/2 status can be used for patients' counselling regarding expected survival, as BRCA1/2 carriers with epithelial ovarian cancers respond better than non-carriers to platinum-based chemotherapies. This yields greater survival, even though the disease is generally

Table 5 The Value of Each Single Index in the Diagnosis and Prediction of Benign Ovarian Tumors

Indicators	AUC	P	95% CI	Cut-Off Threshold	Sensitivity (%)	Specificity (%)
E_2	0.632	<0.001	0.562–0.702	290.74	50.0	75.0
CA125	0.762	<0.001	0.705–0.819	18.70	56.7	83.7
CA199	0.671	<0.001	0.605–0.737	17.40	43.6	84.5

Table 6 The Predictive Value of Combination Diagnosis in Benign Ovarian Tumors

Indicators	AUC	P	95% CI	Logistic Y	Sensitivity (%)	Specificity (%)
E_2+CA125	0.777	<0.001	0.721–0.833	0.128	66.7	76.9
E_2+CA199	0.717	<0.001	0.653–0.780	−0.168	82.6	51.5
CA125+CA199	0.783	<0.001	0.728–0.838	0.423	61.1	86.4
E_2+CA125+CA199	0.805	<0.001	0.753–0.858	−0.022	77.2	70.9

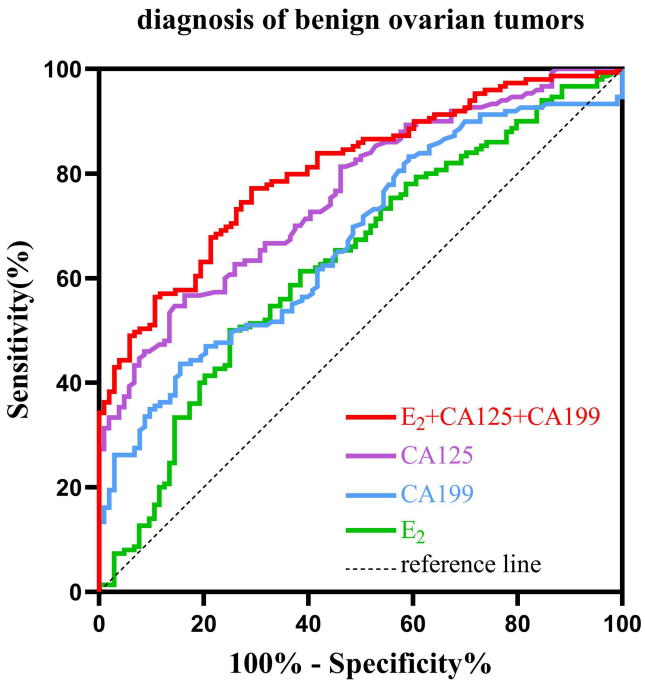

Figure 1 ROC curves for the E2, CA125, and CA199 indicators for the diagnosis of benign ovarian tumors.

diagnosed at a later stage and higher grade.[10] Early detection of patients who are still in the benign tumor stage can aid in the diagnosis, treatment, and prognosis of this disease, reducing the occurrence of the clinical process of benign ovarian tumors transforming into ovarian cancer due to late diagnosis.

Female reproductive hormones are commonly used to evaluate the ovarian function and other gynecologic endocrine disorders. In this study, five hormones, including LH, FSH, T, E2, and AMH, were selected as predictors, and only E2 was found to be significantly different between the patient and control groups. Although sex hormones are affected by diet, medication, strenuous exercise, and mood swings, their inclusion in the joint diagnosis with other factors can improve diagnostic efficacy. Because few multifactorial correlation analyses on benign ovarian tumors have discussed whether reproductive hormones are associated with the disease, they were included in this study. Whereas the results of Natalia Buza[11] showed that serum levels were significantly lower in all patients one week after surgery, these results indicate that serum levels were significantly higher, which is consistent with the findings of this experiment regarding patients with higher E2 and lower FSH levels than controls.

When female ovarian granulosa cells secrete AMH, it inhibits the initial follicle's recruitment, preventing it from entering the growing follicular pool;[12] it also prevents the growth of antral and small sinus follicles by decreasing their sensitivity to FSH, which eventually leads to follicular development arrest and ovulation disorders.[13] According to one study, AMH levels were significantly lower in all patients with ovarian endometriosis cysts than in patients with simple ovarian cysts, with a statistically significant difference between the two groups.[14] In contrast, there was no statistically significant difference in AMH between the group of patients with benign ovarian tumors and the normal control group in this study, confirming that AMH can be used as a basis for pathological classification of benign ovarian tumors but not as a diagnostic indicator for the presence of benign ovarian tumors. AMH was positively correlated with T and negatively correlated with age and E2 in this study. In contrast, Han Xiaojie[15] conducted a study and found that AMH levels were significantly positively correlated with E2 and T, but significantly negatively correlated with FSH and LH. Ye et al[16] discovered the same correlations: AMH levels were significantly positively correlated with E2 and T, but negatively correlated with age, FSH, and LH. In contrast to these literature reports, the present study found no significant correlation between AMH and FSH or LH, and a negative correlation with E2. Additionally, some studies found no significant correlation between AMH and E2,[17] and these differences could be explained by the fact that different correlates were used, implying that additional research is needed to corroborate their findings.

Tumor markers are critical for the diagnosis and prediction of benign and malignant tumors. CA125 is one of the most often used markers for benign ovarian tumors and is presently regarded as the most valuable tumor marker in the clinical examination of ovarian tumors.[18] According to one, serum CA125 and CA199 levels were significantly higher in the benign ovarian tumor group compared to the control group, although differences in AFP, CEA, and HE4 levels were not statistically significant.[19] This is supported by the study by Lahlou et al,[20] which reached the same conclusion as this paper. However, it has also been suggested that HE4 levels are lower in Chinese women with the benign disease compared to CA125 levels, making it a more suitable biomarker.[21] AFP was not an important parameter for differentiating benign ovarian tumors from the healthy population, but it was a significant predictor when all factors were included in the analysis. While AFP levels may be decreased in patients with benign ovarian tumors, there is still debate about whether AFP can be used as a predictor of benign ovarian tumors. Currently, there is limited knowledge regarding the ovarian germ cell tumours in postmenopausal patients. However even uncommon – postmenopausal women with an ovarian mass and an elevated serum AFP level should be suspected for ovarian germ cell tumours.[22]

In this study, ROC curves were used to identify indicators of diagnostic value for predicting the development of benign ovarian tumors, with the single indicator CA125 having the highest sensitivity and CA199 having the highest specificity, but both indicators had low sensitivity and specificity when diagnosing and predicting the disease. Although the AUC of the combination diagnosis of serum E2+CA125+CA199 was the greatest, which also improved the sensitivity, its specificity was lower than that of the single and combined prediction of the two indices, and comprehensive analysis with additional laboratory tests is required to improve the specificity. The optimal diagnostic cut-off value for E2 was found to be 290.74 pmol/L, for CA125 to be 18.70 U/mL, and for CA199 to be 17.40 U/mL. Correspondingly, the optimal cut-off value for CA125 was found to be 36.2 U/mL and for CA199 was 17.8 U/mL in a study by Park et al.[23] Thus, whereas the optimal diagnostic cut-off values for CA199 were not significantly different between the two studies, the optimal diagnostic cut-off values for CA125 varied widely. Gomes et al[19] demonstrated that CA125 ≥65 U/mL was associated with benign and non-malignant gynecological tumors in approximately 13% of patients.

Conclusion

In this study, AMH was positively correlated with T and negatively correlated with age and E2. The presence or absence of benign ovarian tumors was correlated with E2, CA125, and CA199, and the AUC was greatest for the combined diagnosis of the three indices to predict the disease while improving the detection rate of benign ovarian tumors. However, additional prospective studies are needed to validate our findings.

Data Sharing Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Jiaxing First Hospital (No: LS2021-KY-129). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Acknowledgments

We would like to acknowledge the hard and dedicated work of all the staff that implemented the intervention and evaluation components of the study.

Funding

No external funding received to conduct this study.

Disclosure

The authors declare that they have no competing interests.

References

1. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. *J Ovarian Res*. 2019;12(1):1–9. doi:10.1186/s13048-019-0503-7
2. Rao S, Smith DA, Guler E, et al. Past, present, and future of serum tumor markers in management of ovarian cancer: a guide for the radiologist. *RadioGraphics*. 2021;41(6):1839–1856. doi:10.1148/rg.2021210005
3. Li J, Bao R, Peng S, Zhang C. The molecular mechanism of ovarian granulosa cell tumors. *J Ovarian Res*. 2018;11(1):13. doi:10.1186/s13048-018-0384-1
4. Clendenen TV, Ge W, Koenig KL, et al. Breast cancer risk factors and circulating anti-Müllerian hormone concentration in healthy premenopausal women. *J Clin Endocrinol Metab*. 2021;106(11):e4542–e4553. doi:10.1210/clinem/dgab461
5. Cheung A, Shah S, Parker J, et al. Non-epithelial ovarian cancers: how much do we really know? *Int J Environ Res Public Health*. 2022;19(3):1106. doi:10.3390/ijerph19031106
6. Jeon JH, Park SY, Lee SR, Jeong K, Chung HW. Serum anti-Müllerian hormone levels before surgery in patients with ovarian endometriomas compared to other benign ovarian cysts. *J Menopausal Med*. 2015;21(3):142–148. doi:10.6118/jmm.2015.21.3.142
7. Wang H, Liu P, Xu H, Dai H. Early diagonosis of ovarian cancer: serum HE4, CA125 and ROMA model. *Am J Transl Res*. 2021;13(12):14141.
8. Guleria S, Jensen A, Toender A, Kjaer SK. Risk of epithelial ovarian cancer among women with benign ovarian tumors: a follow-up study. *Cancer Causes Control*. 2020;31(1):25–31. doi:10.1007/s10552-019-01245-4
9. Ren X, Zhang H, Cong H, et al. Diagnostic model of serum miR-193a-5p, HE4 and CA125 improves the diagnostic efficacy of epithelium ovarian cancer. *Pathol Oncol Res*. 2018;24(4):739–744. doi:10.1007/s12253-018-0392-x
10. Shah S, Cheung A, Kutka M, et al. Epithelial ovarian cancer: providing evidence of predisposition genes. *Int J Environ Res Public Health*. 2022;19(13):8113. doi:10.3390/ijerph19138113
11. Buza N. Frozen section diagnosis of ovarian epithelial tumors: diagnostic pearls and pitfalls. *Arch Pathol Lab Med*. 2019;143(1):47–64. doi:10.5858/arpa.2018-0289-RA
12. von Wolff M, Roumet M, Stute P, Liebenthron J. Serum anti-Mullerian hormone (AMH) concentration has limited prognostic value for density of primordial and primary follicles, questioning it as an accurate parameter for the ovarian reserve. *Maturitas*. 2020;134:34–40. doi:10.1016/j.maturitas.2020.02.001
13. Buratini J, Dal Canto M, De Ponti E, et al. Maternal age affects the relationship of basal FSH and anti-Müllerian hormone concentrations with post-ICSI/IVF live birth. *Reprod Biomed Online*. 2021;42(4):748–756. doi:10.1016/j.rbmo.2020.12.005
14. Taniguchi F, Sakamoto Y, Yabuta Y, et al. Analysis of pregnancy outcome and decline of anti-Müllerian hormone after laparoscopic cystectomy for ovarian endometriomas. *J Obstetr Gynaecol Res*. 2016;42(11):1534–1540. doi:10.1111/jog.13081
15. Moolhuijsen LM, Visser JA. Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function. *J Clin Endocrinol Metab*. 2020;105(11):3361–3373. doi:10.1210/clinem/dgaa513
16. Ye X-P, Yang Y-Z, Sun X-X. A retrospective analysis of the effect of salpingectomy on serum antiMüllerian hormone level and ovarian reserve. *Am J Obstet Gynecol*. 2015;212(1):53. e51–53. e10. doi:10.1016/j.ajog.2014.07.027
17. Bachelot A. Polycystic ovarian syndrome: clinical and biological diagnosis. Paper presented at: Annales de Biologie Clinique; 2016.
18. Biggs WS, Marks ST. Diagnosis and management of adnexal masses. *Am Fam Physician*. 2016;93(8):676–681.
19. Gomes TA, Campos EA, Yoshida A, Sarian LO, Andrade L, Derchain SF. Preoperative differentiation of benign and malignant non-epithelial ovarian tumors: clinical features and tumor markers. *Revista Brasileira de Ginecologia e Obstetrícia*. 2020;42:555–561. doi:10.1055/s-0040-1712993
20. Lahlou N, Brun J. Ovarian tumor markers of presumed benign ovarian tumors. *J Gynecol Obstet Biol Reprod*. 2013;42(8):752–759. doi:10.1016/j.jgyn.2013.09.030
21. Zhang Y, Qiao C, Li L, Zhao X, Li Y. Serum HE4 is more suitable as a biomarker than CA125 in Chinese women with benign gynecologic disorders. *Afr Health Sci*. 2014;14(4):913–918. doi:10.4314/ahs.v14i4.20
22. Boussios S, Attygalle A, Hazell S, et al. Malignant ovarian germ cell tumors in postmenopausal patients: the royal Marsden experience and literature review. *Anticancer Res*. 2015;35(12):6713–6722.
23. Park SY, Oh YT, Jung DC. Differentiation between borderline and benign ovarian tumors: combined analysis of MRI with tumor markers for large cystic masses (≥ 5 cm). *Acta Radiol*. 2016;57(5):633–639. doi:10.1177/0284185115597266