Predictive Value of B-Mode Ultrasound Combined with Tumor Markers for Malignant Transformation of Ovarian Mucinous Tumors: Postprint

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Abstract

Background Ovarian mucinous tumors (MOT) can be classified pathologically as benign such as mucinous cystadenoma (MCA), borderline such as borderline mucinous tumor (MBT), and malignant such as mucinous cystadenocarcinoma (MC). Preoperative differentiation is often difficult, with final diagnosis relying on surgical pathology. Improving preoperative diagnostic efficacy is particularly important for clinical decision-making and treatment selection. Objective To investigate high-risk factors for malignant transformation of MOT and evaluate the predictive value of ultrasound combined with tumor markers for MOT malignant transformation. Methods A total of 414 MOT patients who underwent surgical treatment at the First Affiliated Hospital of Nanjing Medical University from 2010 to 2020 were enrolled as study subjects and divided into three groups based on postoperative pathology: MCA group (n=305), MBT group (n=79), and MC group (n=30). Data were collected on patient age, clinical symptoms, ultrasound findings (ovarian tumor size, nature, presence of papillae, detectable blood flow signals, multilocular tumors) and serum tumor markers [carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199), carbohydrate antigen 724 (CA724)] and D-dimer levels. Multivariate logistic regression analysis was applied to investigate risk factors for MOT malignant transformation, and receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of ultrasound combined with tumor markers for MOT malignant transformation, with the area under the ROC curve (AUC) and its 95% confidence interval (CI) calculated. Results Comparisons of ultrasound findings and serological indicators among the three patient groups showed statistically significant differences ($P<0.05$). Multivariate logistic regression analysis revealed that maximum

tumor diameter $ 10$cm[OR = 1.947, 95 35.0$U/ml[OR = 4.307, 95 $39.0U/ml [OR=2.227, 95%CI (1.030, 4.816), P=0.042] were independent risk factors for MOT malignant transformation. The AUC for ultrasound combined with tumor markers in predicting MOT malignant transformation was 0.868 [95%CI (0.825, 0.912), P<0.001], with an optimal cutoff value of 0.354, sensitivity of 72.5%, and specificity of 90.8%. Conclusion When ovarian tumor maximum diameter is $ 10$cm, ultrasound shows solid components, papillae, blood flow signals within the tumor, multilocular tumor app the possibility of MOT malignant transformation should be considered. Ultrasound combined with tumor markers has certain predictive value for MOT malignant transformation.

Full Text

Prediction Value of B-ultrasound with Tumor Markers for Malignant Transformation of Mucinous Ovarian Tumors

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Abstract

Background: Mucinous ovarian tumors (MOT) can be divided into three types: benign [such as mucinous cystadenoma (MCA)], borderline [such as mucinous borderline tumor (MBT)], and malignant [such as mucinous cystadenocarcinoma (MC)]. It is difficult to differentiate between the types preoperatively, and the final diagnosis depends on surgical pathology. Improving preoperative diagnostic accuracy is particularly important for clinical decision-making and treatment selection.

Objective: To explore the high-risk factors associated with malignant transformation of MOT and evaluate the predictive value of B-ultrasound combined with tumor markers for malignant transformation of MOT.

Methods: This retrospective observational study included 414 women who underwent surgical treatment at the First Affiliated Hospital of Nanjing Medical University between 2010 and 2020. Based on postoperative pathology, patients were divided into three groups: MCA group (n = 305), MBT group (n = 79), and MC group (n = 30). Clinical data were collected, including age, clinical symptoms, sonographic features (ovarian tumor size, nature, presence of papillary projections, detectable blood flow signals, multilocular appearance), serum tumor markers [carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199), carbohydrate antigen 724 (CA724)], and D-dimer levels. Multivariate logistic regression analysis was used to identify risk factors for malignant transformation of MOT. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of B-ultrasound combined with tumor markers, and the area under the curve (AUC) with 95% confidence intervals (CI) was calculated.

Results: Statistically significant differences were observed among the three groups in B-ultrasound manifestations and serological indicators ($P < 0.05$). Multivariate logistic regression analysis revealed that maximum tumor diameter $\geq$ 10 cm [OR = 1.947, 95% CI (1.066, 3.556), P = 0.030], presence of solid components [OR = 9.862, 95% CI (4.465, 21.782), $P < 0.001$], papillary projections [OR = 2.320, 95% CI (1.100, 4.893), P = 0.027], blood flow signals [OR = 2.289, 95% CI (1.104, 4.747), P = 0.026], multilocular morphology [OR = 5.722, 95% CI (3.034, 10.789), $P < 0.001$], CA125 $\geq$ 35.0 U/ml [OR = 4.307, 95% CI (1.963, 9.452), $P < 0.001$], and CA199 $\geq$ 39.0 U/ml [OR = 2.227, 95% CI (1.030, 4.816), P = 0.042] were independent risk factors for malignant transformation of MOT. The AUC for B-ultrasound combined with tumor markers in predicting malignant transformation of MOT was 0.868 [95% CI (0.825, 0.912), $P < 0.001$], with an optimal cutoff value of 0.354, sensitivity of 72.5%, and specificity of 90.8%.

Conclusion: When an ovarian tumor has a maximum diameter $\geq$ 10 cm and B-ultrasound reveals solid components, papillary projections, blood flow signals, and multilocular morphology, combined with serum CA125 $\geq$ 35.0 U/ml and CA199 $\geq$ 39.0 U/ml, the possibility of malignant transformation of MOT should be considered. B-ultrasound combined with tumor markers demonstrates good predictive value for malignant transformation of MOT.

Keywords: Ovarian neoplasms; Biomarkers, tumor; Mucinous ovarian tumor; Mucinous borderline tumor; Mucinous cystadenocarcinoma; Ultrasonography; CA-125 antigen

Introduction

Mucinous ovarian tumors (MOT) are common epithelial ovarian neoplasms, accounting for approximately 15% of all primary ovarian tumors. According to the *WHO Classification of Tumours of Female Reproductive Organs (2014 Edition)*

[1], MOT are classified into mucinous cystadenoma (MCA)/mucinous adenofibroma (MA), mucinous borderline tumor (MBT)/atypical proliferative mucinous tumor (APMT), and mucinous cystadenocarcinoma (MC). MCA and MA are benign; MBT and APMT, while not malignant, exhibit mild nuclear atypia and cellular proliferation without stromal invasion, displaying biological behavior intermediate between malignant and benign tumors, thus requiring careful attention in clinical diagnosis and treatment. MC represents the malignant form. Due to this heterogeneity, the three pathological components may coexist within the same tumor. Treatment for MOT is primarily surgical, with the extent of surgery determined by patient age and pathological stage. However, because of high heterogeneity, intraoperative frozen section diagnosis has low sensitivity [2], making surgical planning challenging. Inadequate surgical scope may lead to secondary surgery or early recurrence, while overly extensive surgery may compromise fertility and quality of life.

Currently used tumor markers for ovarian cancer diagnosis include carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199), and carbohydrate antigen 724 (CA724). CEA was first extracted from colon cancer and embryonic tissue by GOLD et al. [3] in 1965 and is widely used in gastrointestinal malignancies, later found to be elevated in other conditions including pancreatitis, cirrhosis, and ovarian cancer [4]. CA125 is widely used for ovarian cancer diagnosis, treatment response evaluation, and prognosis monitoring with high sensitivity [5]. CA199 is a selective indicator for pancreatic, intestinal, and gastric tumors with high expression in ovarian epithelial tissue [6]. CA724 serves as a broad-spectrum tumor antigen playing an important role in ovarian cancer detection [7]. Serum D-dimer (DD2) levels are elevated in malignant tumor patients, and this study included DD2 as a risk factor analysis variable, with MC considered as malignant tumor for evaluating its biological behavior and molecular mechanisms.

This study retrospectively analyzed clinical characteristics, B-ultrasound features, and serological indicators of MOT patients to explore risk factors for malignant transformation and evaluate the predictive value of B-ultrasound combined with tumor markers, aiming to provide more reliable diagnostic and treatment protocols for MOT patients.

Methods

1.1 Study Subjects We selected 414 MOT patients who underwent surgical treatment at the First Affiliated Hospital of Nanjing Medical University between 2010 and 2020. Based on postoperative pathology, patients were divided into three groups: MCA group (n = 305), MBT group (n = 79), and MC group (n = 30). Inclusion criteria were: (1) postoperative pathological diagnosis of MOT; (2) complete clinical data. Exclusion criteria were: (1) patients with concurrent endometriosis or other reproductive system malignancies; (2) patients with a

history of appendiceal or gastrointestinal mucinous tumors. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (approval number: 2022-SRFA-486), and informed consent was obtained from all patients.

1.2 Research Methods Clinical and pathological data of 414 MOT patients were collected and recorded in detail, including: (1) general information: age, history of previous adnexal surgery; (2) clinical symptoms: abdominal pain, abdominal distension, urinary frequency, palpable abdominal mass, menstrual abnormalities; (3) B-ultrasound features: ovarian tumor size, nature, presence of papillary projections, detectable blood flow signals, multilocular appearance; (4) serological indicators: preoperative serum levels of CEA, CA125, CA199, CA724, and DD2. Based on previous research [8] and our hospital' s testing standards, elevated levels were defined as: CEA $\geq$ 4.7 g/L, CA125 $\geq$ 35.0 U/ml, CA724 $\geq$ 6.9 U/ml, CA199 $\geq$ 39.0 U/ml, and DD2 $\geq$ 0.55 U/ml.

1.3 Statistical Analysis Statistical analysis was performed using SPSS 23.0 software. Normally distributed continuous data were expressed as mean $\pm$ standard deviation and compared among the three groups using one-way ANOVA. Categorical data were expressed as percentages and compared using ^{2} test or trend ^{2} test. Multivariate logistic regression analysis was used to explore risk factors for malignant transformation of MOT. ROC curve analysis was used to evaluate the predictive value of B-ultrasound combined with tumor markers, and the AUC with 95% CI was calculated. $P < 0.05$ was considered statistically significant.

Results

2.1 Clinical Features of the Three Groups The mean ages of patients in the MCA, MBT, and MC groups were (40.3 $\pm$ 17.2) years, (43.9 $\pm$ 19.3) years, and (42.0 $\pm$ 19.5) years, respectively, with no statistically significant difference ($F = 1.342$, $P = 0.262$). The proportions of patients with previous unilateral adnexal surgery history were 15 (4.9%), 9 (11.4%), and 1 (3.3%) in the MCA, MBT, and MC groups, respectively, also showing no significant difference ($^2 = 3.066$, $P = 0.169$). Most MOT patients were first diagnosed with ovarian tumors during physical examination, while a minority presented with compression symptoms such as abdominal pain, abdominal distension, or urinary frequency due to tumor enlargement (Table 1).

2.2 B-ultrasound Manifestations and Serological Indicators Significant differences were observed among the three groups in B-ultrasound manifestations and serological indicators ($P < 0.05$). The proportions of patients with maximum tumor diameter $\geq$ 10 cm, solid components on B-ultrasound,

and elevated serum CA199 $\geq$ 39.0 U/ml and DD2 $\geq$ 0.55 U/ml were significantly lower in the MCA group compared to the MBT and MC groups (all P $<$ 0.01). MBT patients were more likely than MCA patients to exhibit multilocular morphology, papillary projections, and blood flow signals on B-ultrasound (P $<$ 0.05). Compared with MCA and MBT patients, MC patients showed significantly higher proportions of elevated CEA $\geq$ 4.7 g/L and CA724 $\geq$ 6.9 U/ml (P $<$ 0.001). The proportion of patients with CA125 $\geq$ 35.0 U/ml differed significantly among all three groups (P $<$ 0.001), with an increasing trend as malignancy increased (^{2} trend = 75.346, P $<$ 0.001). Results are shown in Table 2 .

2.3 Multivariate Logistic Regression Analysis of Risk Factors for MOT Malignant Transformation Since MBT possesses certain malignant potential with histological nuclear atypia and mitotic activity, this study combined MBT and MC as non-benign MOT, with MCA considered benign MOT. Using benign versus non-benign status (assignment: benign = 0, non-benign = 1) as the dependent variable, and B-ultrasound features (maximum tumor diameter $\geq$ 10 cm, presence of solid components, papillary projections, blood flow signals, multilocular morphology) and serological indicators (CEA $\geq$ 4.7 g/L, CA125 $\geq$ 35.0 U/ml, CA199 $\geq$ 39.0 U/ml, CA724 $\geq$ 6.9 U/ml, DD2 $\geq$ 0.55 U/ml) as independent variables, multivariate logistic regression analysis showed that maximum tumor diameter $\geq$ 10 cm, presence of solid components, papillary projections, blood flow signals, multilocular morphology, CA125 $\geq$ 35.0 U/ml, and CA199 $\geq$ 39.0 U/ml were independent risk factors for malignant transformation of MOT (P $<$ 0.05, Table 3).

2.4 ROC Curve for B-ultrasound Combined with Tumor Markers in Predicting MOT Malignant Transformation B-ultrasound features (maximum tumor diameter $\geq$ 10 cm, solid components, papillary projections, blood flow signals, multilocular morphology) combined with tumor markers (CA125 $\geq$ 35.0 U/ml, CA199 $\geq$ 39.0 U/ml) were incorporated into a prediction model: Y = -3.556 + 0.666 $\times$ (maximum tumor diameter $\geq$ 10 cm) + 2.289 $\times$ (solid components) + 0.842 $\times$ (papillary projections) + 0.828 $\times$ (blood flow signals) + 1.744 $\times$ (multilocular morphology) + 1.460 $\times$ (CA125 $\geq$ 35.0 U/ml) + 0.801 $\times$ (CA199 $\geq$ 39.0 U/ml). ROC curve analysis yielded an AUC of 0.868 [95% CI (0.825, 0.912), P $<$ 0.001] for predicting malignant transformation of MOT, with an optimal cutoff value of 0.354, sensitivity of 72.5%, and specificity of 90.8% (Figure 1 [Figure 1: see original paper]).

Discussion

MOT represents a common pathological type of epithelial ovarian tumors, classified as benign, borderline, or malignant based on pathological type and malignant potential. MOT are characterized by heterogeneity [9], with benign,

borderline, and malignant components potentially coexisting within the same tumor. MCA is more likely to progress to malignant ovarian tumors compared to serous ovarian tumors [10]. Unlike other ovarian tumors, rupture of benign MOT can cause peritoneal implantation, leading to pseudomyxoma peritonei—a low-grade malignant condition with good prognosis but high recurrence risk [11]. Treatment for MOT is primarily surgical, with the surgical approach determined by patient age, fertility requirements, and pathological stage. Due to MOT heterogeneity, intraoperative frozen section diagnosis often has low accuracy, making preoperative diagnostic improvement crucial for surgical planning and treatment selection.

The International Ovarian Tumor Analysis (IOTA) group developed simple rules (SR) for color Doppler ultrasound to differentiate benign and malignant ovarian tumors [12], proposing five key features of ovarian malignancy: irregular solid tumors, ascites, presence of at least 4 papillary structures within the tumor, irregular multilocular solid tumors with maximum diameter $\geq$ 10 cm, and prominent blood flow signals. This model significantly improved diagnostic efficacy. Similarly, MORO et al. [13] reported that multilocular morphology and solid components on B-ultrasound were significantly more common in MBT and MC patients than in MCA patients, warranting clinical vigilance.

Our study results showed that maximum tumor diameter $\geq$ 10 cm, presence of solid components, papillary projections, and blood flow signals are high-risk factors for MOT malignant transformation, consistent with previous research. Serum CA125 is widely used for ovarian cancer diagnosis, treatment response evaluation, and prognosis monitoring with high sensitivity, but its specificity is limited as elevated levels can also occur in other malignancies (gastric cancer, lung cancer) and benign gynecological conditions (endometriosis) [5-6]. Our study found significant differences in the proportions of patients with elevated CEA $\geq$ 4.7 g/L, CA125 $\geq$ 35.0 U/ml, CA199 $\geq$ 39.0 U/ml, and CA724 $\geq$ 6.9 U/ml between MCA and MC groups ($P < 0.001$), suggesting these markers are useful for distinguishing benign from malignant MOT. CA125 $\geq$ 35.0 U/ml and CA199 $\geq$ 39.0 U/ml were independent high-risk factors for malignant transformation ($P < 0.05$). Notably, CA125 $\geq$ 35.0 U/ml was the only indicator showing statistically significant differences in pairwise comparisons among all three groups ($P < 0.001$), with an increasing proportion as malignancy increased. LERTKHACHONSUK et al. [8] also reported that elevated preoperative serum CA125, CA199, and CEA were predictive indicators for distinguishing benign, borderline, and malignant MOT, with CA125 being the best predictor, followed by CA199 and CEA.

Human epididymis protein 4 (HE4) is a novel tumor marker first discovered in epididymal epithelial cells with high expression in ovarian cancer patients. It has been widely applied in ovarian cancer diagnosis with sensitivity comparable to CA125 but slightly better specificity [14]. Multiple studies have demonstrated that HE4 has excellent diagnostic efficacy for predicting ovarian tumor malignancy and outperforms CA125 in detecting tumor recurrence [15-16]. To

compensate for CA125' s low specificity, the ROMA index (Risk of Ovarian Malignancy Algorithm) was developed based on serum CA125 and HE4 levels through regression modeling, significantly improving diagnostic efficacy for ovarian malignancy [17-18]. However, due to incomplete serum HE4 data in our clinical records, HE4 was not included in this study.

As malignant tumors progress, procoagulant substances such as D-dimer increase in patient serum, significantly elevating the risk of deep vein thrombosis [19-20]. Cancer patients often exhibit hypercoagulable states, and abnormal coagulation function can promote tumor growth and invasion, indicating a reciprocal relationship [21]. In our study, the proportion of patients with DD2 $\geq$ 0.55 U/ml was significantly higher in non-benign MOT patients than in benign MOT patients, but showed no significant difference between MBT and MC patients.

In summary, maximum tumor diameter $\geq$ 10 cm, presence of solid components, papillary projections, blood flow signals, multilocular morphology on B-ultrasound, and serum CA125 $\geq$ 35.0 U/ml and CA199 $\geq$ 39.0 U/ml are high-risk factors for MOT malignant transformation. B-ultrasound combined with tumor markers achieved high specificity (90.8%) for evaluating MOT malignant transformation, and elevated CA125 levels have value in distinguishing MCA, MBT, and MC. As a pathological type of epithelial ovarian tumor, MOT has distinct biological behavior, molecular mechanisms, and prognosis compared to other ovarian epithelial tumors. Current diagnostic and treatment protocols for MOT are largely based on serous ovarian tumors, resulting in suboptimal management efficiency. This study focused on MOT and utilized B-ultrasound combined with tumor markers to preoperatively differentiate benign from malignant MOT, aiming to compensate for the low accuracy of intraoperative frozen section due to heterogeneity and provide guidance for surgical approach and subsequent treatment planning.

References

[1] KURMAN R J. WHO classification of tumours of female reproductive organs[M]. 4th ed. Lyon: International Agency for Research on Cancer, 2014: 307.
[2] YOSHIDA H, TANAKA H, TSUKADA T, et al. Diagnostic discordance in intraoperative frozen section diagnosis of ovarian tumors: a literature review and analysis of 871 cases treated at a Japanese cancer center[J]. Int J Surg Pathol, 2021, 29(1): 30-38. DOI: 10.1177/1066896920960518.
[3] GOLD P, FREEDMAN S O. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques[J]. J Exp Med, 1965, 121(3): 439-462. DOI: 10.1084/jem.121.3.439.
[4] HAO C, ZHANG G Q, ZHANG L J. Serum CEA levels in 49 different types of cancer and noncancer diseases[J]. Prog Mol Biol Transl Sci, 2019, 162:

213-227. DOI: 10.1016/bs.pmbts.2018.12.011.
[5] ZHANG M H, CHENG S S, JIN Y, et al. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer[J]. Biochim Biophys Acta Rev Cancer, 2021, 1875(2): 188503. DOI: 10.1016/j.bbcan.2021.188503.
[6] ALI F T, SOLIMAN R M, HASSAN N S, et al. Sensitivity and specificity of microRNA-204, CA125, and CA19.9 as biomarkers for diagnosis of ovarian cancer[J]. PLoS One, 2022, 17(8): e0272308. DOI: 10.1371/journal.pone.0272308.
[7] LI M L, MEN X J, ZHANG X J. Diagnostic value of carbohydrate antigen 72-4 combined with carbohydrate antigen 15.3 in ovarian cancer, cervical cancer and endometrial cancer[J]. J BUON, 2020, 25(4): 1918-1927.
[8] LERTKHACHONSUK A A, BURANAWONGTRAKOON S, LEKSKUL N, et al. Serum CA19-9, CA-125 and CEA as tumor markers for mucinous ovarian tumors[J]. J Obstet Gynaecol Res, 2020, 46(11): 2287-2291. DOI: 10.1111/jog.14427.
[9] XU X, ZHANG C Y. Methods for identifying the origin of ovarian epithelial carcinoma[J]. J Pract Obstet Gynecol, 2017, 33(10): 747-750.
[10] DAL MASO L, CANZONIERI V, TALAMINI R, et al. Origin of ovarian cancer from benign cysts[J]. Eur J Cancer Prev, 2001, 10(2): 197-199. DOI: 10.1097/00008469-200104000-00016.
[11] FONSECA C, CARVALHO S, CUNHA T M, et al. The many faces of pseudomyxoma peritonei: a radiological review based on 30 cases[J]. Radiol Bras, 2019, 52(6): 372-377. DOI: 10.1590/0100-3984.2019.0044.
[12] GIAMPAOLINO P, DELLA CORTE L, FORESTE V, et al. Unraveling a difficult diagnosis: the tricks for early recognition of ovarian cancer[J]. Minerva Med, 2019, 110(4): 279-291. DOI: 10.23736/S0026-4806.19.06086-5.
[13] MORO F, ZANNONI G F, ARCIUOLO D, et al. Imaging in gynecological disease (11): clinical and ultrasound features of mucinous ovarian tumors[J]. Ultrasound Obstet Gynecol, 2017, 50(2): 261-270. DOI: 10.1002/uog.17222.
[14] KIM B, PARK Y, KIM B, et al. Diagnostic performance of CA125, HE4, and risk of Ovarian Malignancy Algorithm for ovarian cancer[J]. J Clin Lab Anal, 2019, 33(1): e22624. DOI: 10.1002/jcla.22624.
[15] SCALETTA G, PLOTTI F, LUVERO D, et al. The role of novel biomarker HE4 in the diagnosis, prognosis and follow-up of ovarian cancer: a systematic review[J]. Expert Rev Anticancer Ther, 2017, 17(9): 827-839. DOI: 10.1080/14737140.2017.1360138.
[16] CAO H Y, YOU D, LAN Z, et al. Prognostic value of serum and tissue HE4 expression in ovarian cancer: a systematic review with meta-analysis of 90 studies[J]. Expert Rev Mol Diagn, 2018, 18(4): 371-383. DOI: 10.1080/14737159.2018.1457436.
[17] DOCHEZ V, CAILLON H, VAUCEL E, et al. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review[J]. J Ovarian Res, 2019, 12(1): 28. DOI: 10.1186/s13048-019-0503-7.
[18] WANG H X, LIU P P, XU H, et al. Early diagnosis of ovarian cancer: serum HE4, CA125 and ROMA model[J]. Am J Transl Res, 2021, 13(12): 14141-14148.
[19] WU J C, FU Z Y, LIU G Q, et al. Clinical significance of plasma D-dimer

in ovarian cancer: a meta-analysis[J]. Medicine (Baltimore), 2017, 96(25): e7062. DOI: 10.1097/MD.0000000000007062.
[20] CHEN L F, WANG X Y, SHU J, et al. Diagnostic value of serum D-dimer, CA125, and neutrophil-to-lymphocyte ratio in differentiating ovarian cancer and endometriosis[J]. Int J Gynaecol Obstet, 2019, 147(2): 212-218. DOI: 10.1002/ijgo.12949.
[21] SWIER N, VERSTEEG H H. Reciprocal links between venous thromboembolism, coagulation factors and ovarian cancer progression[J]. Thromb Res, 2017, 150: 8-18. DOI: 10.1016/j.thromres.2016.12.002.

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Note: Figure translations are in progress. See original paper for figures.