Ultrasonographic criteria and tumor marker assay are good procedures for the diagnosis of ovarian neoplasia in preselected outpatients

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Summary

Purpose of investigation: To identify parameters for the diagnosis of ovarian neoplasia using ultrasonography (US) and serum tumor marker (TM: CA125, CA19.9, CA15.3, AFP, CEA and estradiol) assay.

Methods: Prospective study which included 373 women with increased ovarian volume (> 18 cm^3 in premenopause and > 8 cm^3 in postmenopause). US criteria (≥ 1) for surgery were: persistent (> 4 months) or increased cyst, cysts with > 1 thick septum or ≥ 2 thin septa, cyst diameter ≥ 7 cm, vegetation, calcification or cystic predominance (> 50%), solid tumor (> 50%). Doppler with a resistance index (RI) < 0.4 was considered abnormal.

Results: Laparotomy was performed in 164 (44%) patients with 66 (40.2%) benign neoplasias and 19 (11.6%) malignant cases (73.6% at Stage I or II). Two hundred and nine patients were maintained on clinical follow-up. The sensitivity for neoplasia and malignant neoplasia was, respectively, for RI: 17 and 63.6 and RI plus TM: 53.1 and 90.9.

Conclusion: Ultrasound criteria and TM assay were indicated for the diagnosis of ovarian neoplasia.

Key words: Ovarian neoplasia; Ultrasonography; Tumor markers; Doppler.

Introduction

Among the types of malignant gynecological neoplasias, ovarian cancer is the third most common in frequency and the first in mortality [1, 2]. Because of its particular growth and dissemination, most cases of ovarian malignant neoplasia do not present signs and/or symptoms in the initial stages. At advanced stages, the clinical state is similar to diseases of the abdominal origin, which may hold back early diagnosis. The majority of cases occur in elderly women and are diagnosed at advanced stages. These factors limit the currently recommended treatments which include surgery and chemotherapy [3, 4].

The systemic quantification of tumor markers (TM) has been considered an alternative approach for the diagnosis of ovarian neoplasia. Systemic levels of CA125 have been found to be useful for monitoring therapeutic responses and making differential diagnoses between benign and malignant neoplasias [5]. Nevertheless, the results obtained from the assaying of systemic CA15.3 and CA19.9 are contradictory [6, 7]. Chorionic gonadotrophin (b-hCG) and a-fetoprotein (AFP) assist in the diagnosis and follow-up of women with ovarian tumors of germinative origin [8]. In tumors of sex-cord and stromal origin, plasma estrogen levels can also be used as tumor markers [9].

The use of ultrasound morphological criteria may improve the sensitivity and positive predictive value (PPV) [10]. Screening combining ultrasonography (US) and CA125 assay has shown high specificity and low sensitivity, which thus does not justify its use at a populational level yet [11]. Nonetheless, for the follow-up of women at high risk of developing ovarian cancer, the use of CA125 and transvaginal US with Doppler has been an indicated procedure [1, 12].

The combination of a gynecological exam, US and quantification of systemic TM is currently considered to be a good strategy for the early diagnosis of ovarian neoplasia. Nevertheless, the low sensitivity of such screening is questioned, and in a large proportion of diagnoses the staging is advanced. The aim of this work was to identify parameters for the diagnosis of ovarian neoplasia (benign and malignant) through a prospective study of patients with increased ovarian volume detected by gynecological and/or US examination. The sensitivity, specificity, positive and negative predictive values for the approachs using US plus Doppler, TM assay or both were calculated. We tested the hypothesis that the association of US criteria, Doppler plus a pool of TM would improve the diagnosis of ovarian neoplasia.

Patients and Methods

Patients

Patients attending the Gynecology and Obstetrics Outpatient Service of the hospital of the Faculty of Medicine of Triângulo Mineiro (FMTM) were prospectively identified as having increased ovarian volume (detected by gynecological and/or US examinations). The US criteria for increased ovarian (one or both) volume (product of the anteroposterior, longitudinal and

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transverse diameters by 0.52 value) were: volume > 18 cm^3 before menopause or > 8 cm^3 before menarche or after menopause, or one ovary with twice the contralateral volume. These patients were referred to the Pelvic Mass Outpatient Service, which attended 423 women from February 1996 to July 2001. Fifty (11.8%) patients did not attend the return visits, while 373 (88.2%) were enrolled in this study; kept on clinical follow-up or underwent surgery. The study protocol was approved by the FMTM Committee on the Use of Human Subjects, and free and written informed consent was obtained from patients or their caretakers.

Definition of Clinical Follow-up or Surgery Groups by US Criteria

According to the first gynecological and/or US exam, patients immediately underwent surgery or were kept on clinical follow-up at two to three-month intervals consisting of gynecological and US examinations and TM assay. During the clinical follow-up, surgery could be indicated by US criteria. US apparatus was the HD1 1000 – ATL with a 3.5 MHz sectoral transducer and a 6 MHz endovaginal transducer or Synergy – Diasonics Multisync XE15 (GE colors) with a 3.5 MHz sectoral transducer and a 6 MHz endovaginal transducer.

Indications for exploratory laparotomy (immediate or late) were based on one or more of the following US criteria: 1) cysts with > 1 thick (> 3 mm) septum or ≥ 2 thin septa, 2) largest cyst diameter ≥ 7 cm, 3) persistence or increase of the cyst or ovarian volume over a minimum of two follow-up periods, 4) vegetation, calcification or cystic predominance (> 50% cystic area), 5) solid or predominantly (> 50%) solid tumor, and 6) two or more of the above associated criteria.

Increased ovarian volume (assessed by US) was analyzed considering the largest ovarian diameter as follows: ≤ 5, 5 ≤ 7, 7 ≤ 10, or > 10 cm. Doppler was added as an approach during the course of the study with the purpose of comparing with TM only. Doppler fluxometry was considered abnormal with a resistance index (RI) < 0.4, calculated via the formula RI = (A-B)/A, where A represents the maximum Doppler signal and B the minimum Doppler signal. The Doppler test was performed inside the septa or projections of vascularized adnexal masses, and in the corresponding ovarian artery in cases of nonvascular adnexal masses.

Systemic Tumor Marker Assay

Venous blood (5 ml) without anticoagulant was aseptically collected from patients, centrifuged (1800 rpm, 15 min) and the serum samples obtained were stored (–20°C) until the TM assay. TM used were CA125, CA19.9, CA15.3, AFP and carcinoembryonic antigen (CEA), in cases of cystic growth. In cases with solid growth, estradiol levels were also quantified. In the follow-up, the same markers were assayed at each return visit. Assays were performed in kits using the Immulite system (DPC - Medlab), and the markers were: 1) OM-MA (CA 125): normal value (NV) below 200 IU/ml or below 35 IU/ml before or after menopause, respectively; 2) BR-MA (CA15.3): NV < 53 IU/ml; 3) GI-MA (CA19.9): NV < 37 IU/ml; 4) CEA: NV < 4.5 ng/ml among non-smokers or < 7.5 ng/ml among smokers; 5) AFP: NV < 30 ng/ml; 6) Estradiol: NV < 355 pg/ml.

Statistical Analysis

The results from the different groups were compared according to the distribution by the Fisher exact test or Mann-Whitney test. Significance level was established at $p < 0.05$. Sensitivity (S), specificity (SP), the positive (PPV) and negative predictive values (NPV) from the US plus Doppler, TM assay or both were calculated.

Results

Study Population

From 373 women, 209 (56%) were kept on clinical follow-up and 164 (44%) underwent surgical treatment according to US criteria. Among the women under clinical follow-up, 133 (63.6%) had regression of the adnexal cyst by four months, 45 (21.6%) from four to six months and 31 (14.8%) after six months. One patient, who refused surgical intervention for a persistent cyst, had an adnexal mass which regressed after 30 month's follow-up. To our knowledge, no patient in this group had ovarian neoplasia diagnosed later – until the end of the study. Among the 164 patients undergoing surgery, in 120 (73.2%) cases the indication was immediate, i.e., after the first consultation, while 44 (26.8%) were first kept on clinical follow-up and subsequently underwent surgery due to US criteria.

Anatomopathological Findings

The anatomopathological evaluation of the 164 cases undergoing surgery was performed according to the International Federation of Gynaecology and Obstetrics (FIGO) classification. In the non-neoplastic group (n = 79, 48.2%) the diagnoses included 26 (32.9%) serous ovarian cysts, 24 (30.9%) cysts (peritoneal inclusion, hemorrhagic, follicular or paratubal cysts), 11 (13.9%) hydrosalpinx or hematosalpinx, 9 (11.3%) endometriomas, 3 (3.7%) myomas, 2 (2.5%) organized ectopic pregnancies, and one (1.2%) each chronic salpingitis, foreign body granuloma, xanthogranulomatous oophoritis and white laparotomy. Sixty-six (40.2%) patients had benign neoplasia with 21 (31.8%) mature teratomas, 16 (24.3%) serous and 11 (16.8%) mucinous cystadenomas, 5 (7.6%) serous cystadenofibromas, 2 (3%) each adenofibromas of transitional cells, fibromas, and serous cystadenomas associated with adenofibroma, and one each (1.5%) serous cystadenoma associated with thecafibroma, serous cystadenoma associated with mucinous cystadenoma, benign fusocellular tumor, ovarian adenoleiomyoma, thecoma, mixed epithelial tumor (serous and transitional) and atypical leiomyoma. In 19 (11.6%) patients with malignant neoplasia, the diagnoses and respective stages were five (26.2%) granulosa cell tumors (60% IA, 20% IC, 20% IIIC), four (21%) serous adenocarcinomas (25% IB, 75% IIIC, one case associated with granulosa cell tumor in the contralateral ovarian), three (15.7%) serous cystadenomas of borderline malignancy (100% IA), and one each (5.3%) embryonic carcinoma (IC), serous cystadenofibroma of borderline malignancy (IC); anaplasic adenocarcinoma (IIA), steroid cell tumor

(IC), immature teratoma with epidermoid carcinoma (IIB), mucinous cystadenoma of borderline malignity (IIB) and paraganglioma (IIIC). We observed 14 (73.7%) cases in Stage I (78.5%) or II (21.5%).

Clinical Findings

In the clinical follow-up group the median age was 40.5 (5-71) years. In the surgery group with posterior diagnoses of non-neoplastic tumors, benign neoplasia or malignant neoplasia, the median for age was, respectively, 42 (19-67) years, 36 (15-86) and 51 (17-72) years. A significant difference was found in the median age in the malignant neoplasia group compared to the non-neoplastic or benign neoplasia groups ($p < 0.05$, Mann-Whitney test).

Patient distribution with regard to clinical state and the therapeutic strategy is presented in Table 1. It can be seen that one-third (33.5%) of the women with increased ovarian volume were asymptomatic at the first consultation, although the absence of signs and symptoms was less frequent (15.8%) in patients with malignant neoplasia. In this group increased abdominal volume and chronic pelvic pain were the most frequent signs or symptoms found, respectively (Table 1). Considering the asymptomatic women, the gynecological exam was altered at the first consultation in five (7.1%) of the patients in clinical follow-up, eight (22.2%) with non-neoplastic findings, ten (47.6%) with benign neoplasia and three (100%) with malignant neoplasia. A significant difference in this parameter was found between the clinical follow-up group and surgery group ($p < 0.0001$, Fisher's exact test). For the remaining asymptomatic patients, increased ovarian volume was detected by US exam.

Table 1. — *Patient distribution according to clinical state and treatment (clinical or surgical with anatomopathological findings) undertaken.*

Clinical state	Surgical Treatment									
	Clinical follow-up (n = 209)		Non-neoplastic (n = 79)		Benign neoplasia (n = 66)		Malignant neoplasia (n = 19)		Total	
	n	%	n	%	n	%	n	%	n	%
Asymptomatic	71	33.9	30	37.9	21	31.8	3	15.8	125	33.5
chronic pelvic pain (> 6 months)	52	24.9	20	25.3	14	21.2	4	21.0	90	24.1
Menstrual alterations or postmenopausal bleeding	51*	24.4	8	10.1	8	12.1	2	10.5	69	18.5
Acute pelvic pain	30	14.3	16	20.2	14	21.2	3	15.8	63	16.9
Increased abdominal volume	3**	1.4	2#	2.5	6	9.1	5	26.3	16	4.3
Acute abdomen (adnexal torsion)	–	–	1	1.2	3	4.5	1	5.2	5	1.3
Deep dyspareunia	2	0.9	2	2.5	–	–	–	–	4	1.0
Masculinization	–	–	–	–	–	–	1	5.2	1	0.2

*$p < 0.05$ compared to all surgical groups, **$p < 0.01$ compared to benign and malignant neoplasia, #$p < 0.01$ compared to malignant neoplasia (Fisher's exact test).

Ultrasound Findings

The distribution of patients according to US criteria and the anatomopathological diagnosis is shown in Table 2. The presence of two or more criteria was the most frequent (34.2%) US alteration indicative for surgery, followed by persistent or increased cyst or one ovary twice the contralateral volume after menopause (26.8%). In patients with two or more criteria, 48.2% had benign neoplasias and 21.4% were malignant cases. Malignant neoplasia was mainly found (26.7%) in patients with predominantly solid tumors and was not detected in cases of persistent or increased cyst or one ovary twice the contralateral size after menopause (Table 2).

Table 2. — *Distribution of patients according to US criteria for surgery and anatomopathological findings.*

Ultrasound Criteria	Anathomopathological Diagnosis							
	Non-neoplastic (n = 79)		Benign neoplasia (n = 66)		Malignant neoplasia (n = 19)		Total	
	n	%	n	%	n	%	n	%
Persistence or increase of the cyst or one ovary twice the contralateral size after the menopause	38	48.1 (86.4)	6	9.1 (13.6)	–	–	44	26.8
thin septa ≥ 2 cm or thick septum > 1 cm	5	6.4 (55.6)	3	4.5 (33.3)	1	5.3 (11.1)	9	5.5
Largest cyst diameter > 7 cm	15	19.0 (46.9)	16	24.2 (50)	1	5.3 (3.1)	32	19.5
≥ 2 US criteria	17	21.5 (30.4)	27	41.0 (48.2)	12	63.1 (21.4)	56	34.2
Vegetation, calcification or cystic predominance (> 50%)	2	2.5 (25.0)	5	7.6 (62.5)	1	5.3 (11.5)	8	4.9
Solid or predominantly (> 50%) solid	2	2.5 (13.3)	9	13.6 (60)	4	21.0 (26.7)	15	9.1

( ) percentages of diagnoses for surgical indications for the same US criterion.

Table 3 presents the patients with altered gynecological exams in each group according to the size of the largest ovarian diameter seen by US and the treatment undertaken. Considering the 198 women kept on clinical follow-up who underwent gynecological probing, the adnexa were altered in 35 (17.7%) cases. In the surgery group, increased ovarian volume was found in 33 (43.4%) patients with non-neoplastic findings, 46 (76.7%) benign neoplasias and in 17 (89.5%) malignant cases. It was seen that increased ovarian volume detected by gynecological examination was more common in cases of neoplasia and, addionally, with the largest diameter > 7 cm (Table 3). Table 4 differs from Table 3 in that

Table 3. — *Distribution of patients with altered gynecological exams according to the largest ovarian diameter seen in US and the treatment undertaken.*

Largest ovarian diameter in US (cm)	Surgical Treatment									
	Clinical follow-up (n = 198)		Non-neoplastic (n = 76)		Benign neoplasia (n = 60)		Malignant neoplasia (n = 19)		Total	
	n	%	n	%	n	%	n	%	n	%
≤ 5	29 *	82.8	9	11.8	7	15.2	1	5.3	46	35.1
5 ≤ 7	5 **	14.3	14#	42.5	9	19.6	5	26.3	33	25.2
7 ≤ 10	1 #	2.9	5#	15.1	17##	36.9	2	11.8	25	19.1
> 10	–	–	5##	15.1	13##	28.3	9	52.9	27	20.6

The numbers in parentheses represent the total number of patients in each group. *$p < 0.05$ compared to all surgical subgroups, **$p < 0.05$ compared to non-neoplastic tumors, #$p<0.05$ compared to benign neoplasias, ##$p < 0.05$ compared to malignant neoplasias (Fisher's exact test).

Table 4. — *Distribution of patients according to the largest ovarian diameter seen in US and the treatment undertaken.*

Largest ovarian diameter in US (cm)	Surgical Treatment: Clinical follow-up (n = 198)		Non-neoplastic (n = 76)		Benign neoplasia (n = 60)		Malignant neoplasia (n = 19)		Total	
	n	%	n	%	n	%	n	%	n	%
≤ 5	183 *	92.4	36 **	47.4	17	28.3	2	10.6	238	67.4
5 ≤ 7	14 *	7.1	29 **	38.1	12	20.0	5	26.3	60	17
7 ≤ 10	1 *	0.5	6 **	7.9	18	30.0	3	15.8	28	7.9
> 10	–	–	5 **	6.6	13 #	21.6	9	47.3	27	7.7

*p < 0.05 compared to all surgical subgroups, **p < 0.05 compared to benign and malignant neoplasias, #p < 0.05 compared to malignant neoplasias (Fisher's exact test).

the distribution of all patients enrolled in the study in relation to the size of the largest ovarian diameter can be observed. Most (92.4%) patients kept on clinical follow-up had the largest ovarian diameter ≤ 5 cm. Considering neoplasia, the largest ovarian diameter was over 5 cm in 43 (71.7%) benign and 17 (89.4%) malignant cases, showing that the largest ovarian diameters were mainly found in neoplastic tumors. Gynecological probing was not done at the first consultation because of complete hymen in 11 (5.3%) and nine (5.4%) cases from the clinical follow-up and surgical group, respectively.

Doppler Analysis

Doppler was added as an approach during the course of the study and thus performed on 191 (51.2%) cases from the 373 women enrolled. In the clinical follow-up group 84 cases were analyzed and no alterations were detected. From the 164 women who underwent laparotomy, Doppler was performed in 107 cases, from which 60 were found to have non-neoplastic tumors, with no alterations found in these cases. Considering the 36 US examinations with Doppler on benign neoplasia, RI < 0.4 was detected in just one case (2.8%). In contrast, in the malignant neoplasia group Doppler was altered in seven (63.6%) of 11 cases, showing a 63.6% sensitivity (Table 5).

Serum Tumor Marker Concentrations

Increased levels of serum TM were found in 13 (6.2%) cases placed on clinical follow-up, 10 (12.6%) non-neoplastic tumors, 14 (21.2%) benign neoplasia and 11 (57.8%) malignant cases. In the clinical follow-up group CA15.3 and CA19.9 levels were higher in five and two cases, respectively, returning to normal values during follow-up. Another five patients had persistent increased levels of one of these TM, even after regression of the adnexal mass. Increased CA125 levels were detected in one patient but regressed thereafter in the follow-up.

In the non-neoplastic group TM concentrations were found to be elevated in ten (12.6%) cases, with CA15.3 in five (3 follicular cysts, 2 follicular cysts plus xanthogranulomatous oophoritis), CA19.9 in four (2 serous cysts, 1 each hydrosalpinx and follicular cyst), and β-hCG in one (organized ectopic pregnancy). In 14 (21.2%) cases of benign neoplasia increased TM levels were accounted for by CA19.9 in nine (5 mature teratoma, 2 serous cystadenomas, 1 each mucinous cystadenoma and atypical leiomyoma), CA15.3 in four (2 serous cystadenomas, 2 cystic teratomas) and CA125 in one case of myoma. Among the malignant cases, 12 (63.1%) had at least one TM at an increased level, without relation to staging. CA125 was higher in six (1 serous cystadenofibroma of borderline malignity, 2 serous adenocarcinomas), CA19.9 in four (1 each steroid cell tumor, serous cystadenoma of borderline malignity, immature teratoma plus epidermoid carcinoma and serous adenocarcinoma), estradiol in one (granulosa cell tumor), AFP in one (embryonic carcinoma), CA15.3 in four (serous adenocarcinoma). All patients with improved CA15.3 also had augmented levels of CA125.

The values for sensitivity, specificity, PPV and NPV from US plus Doppler, TM or both are presented in Table 5. We observed that the association of Doppler with a pool of TM improved the diagnosis of benign and malignant ovarian neoplasias.

Discussion

This study prospectively evaluated patients with increased ovarian volume maintained on clinical follow-up or undergoing surgery by defined US criteria. The sensitivity, specificity, positive and negative predictive values obtained by the approaches using US plus Doppler, TM assay or both were calculated.

The median age of patients in the malignant group was greater compared to the non-neoplastic tumor or benign neoplasia group although lower than reported data [1]. This finding can be explained by inclusion in this work of neoplasias such as granulosa cell tumors, more common in younger ages. Notwithstanding the histological type of the tumor, postmenopausal women present

Table 5. — *Distribution of sensitivity (S), specificity (SP), positive and negative predictive values (PPV, NPV) related to the approaches: US plus Doppler (D, n = 107), tumor markers (TM; CA125, CA15.3, CA19.9, AFP, CEA, and estradiol; n = 164), D plus TM, one tumor marker (CA125 or CA15.3 or CA19.9), one tumor marker plus D, and association of three tumor markers both (3TM; CA125, CA15.3, CA19.9) with association or not with D in the diagnosis of ovarian (benign and malignant) neoplasia (ON; n = 47) and malignant ovarian neoplasia (MN; n = 11).*

	D		TM		D + TM		CA 125		CA 15.3		CA 19.9		3 TM		D+3TM		D+CA 125		D+CA 15.3		D+CA 19.9	
	ON	MN	ON*	MN*	ON	MN	ON	MN	ON	MN	ON	MN	ON	MN	ON	MN	ON	MN	ON	MN	ON	MN
S	17	63.6	30.5	63.1	53.1	90.9	8.2	31.5	10.5	21	14.1	21	28.2	52.6	51	81.8	17	54.5	21.2	45.4	29.7	54.5
SP	100	98.9	87.3	83.4	83.3	84.3	97.4	97.9	94.9	93.7	96.2	92.4	88.6	84.1	85	75	96.6	95.8	93.3	90.6	95	88.5
PPV	100	87.5	72.2	33.3	71.4	40	77.7	66.6	69.2	30.7	80	26.6	72.7	30.3	72.7	27.2	72.7	60	71.4	35.7	82.3	35.2
NPV	60.6	95.9	53.9	94.5	69.4	98.7	49.6	91.6	49.6	90	51	89.9	53.4	93.1	68.9	97.2	60.4	94.8	60.2	93.5	63.3	94.4

* ON: n = 66 * MN: n = 19.

greater chances of developing ovarian cancer, especially if they fall within the group at risk for this disease [12, 13] .

Increased abdominal volume followed by chronic pelvic pain were the main complaints among patients with malignant neoplasias. However while pelvic pain occurred in a similar percentage in patients with non-neoplastic tumors or benign neoplasias, increased abdominal volume was not common in these groups. A retrospective study of 72 women with ovarian cancer showed that 78% presented one or more signs or symptoms such as pelvic or abdominal pain and increased abdominal volume. Asymptomatic patients had mainly tumors of borderline malignancy [14]. These and our data show that malignant ovarian neoplasia is mainly accompanied by signs and/or symptoms, although these may not be specific.

The majority of ovarian masses with the largest diameter ≤ 5 cm were not detected at gynecological examination which reinforces the importance of US exam in the diagnosis of adnexal masses. It has been described as having 17% sensitivity and 92% specificity of clinical evaluations for detecting ovarian masses before menopause and 68% and 85% after menopause, respectively [15]. In our study 73.6% patients from the cancer group were in Stage I or II and a pelvic or abdominal mass was clinically detected in almost 90% cases. A retrospective study found the same clinical alteration in 72.2% patients in Stages I or II [14]. Taken together the data point out that ovarian cancer, even at the initial stagings, presents in greater frequency with an altered gynecological exam accompanied by some type of symptomatology.

We have observed that simple cysts may be maintained on clinical follow-up because most of them regressed, ranging from four to six months. Moreover, no case of cancer was detected in patients undergoing surgery for persistent or increased cyst. In 196 adolescents with cystic ovarian tumors on clinical follow-up, around 90% had cyst regression after two to four months of hormone therapy. Malignant neoplasia was not found [16]. Considering 225 women in pre- and postmenopause, the regression rate for ovarian cysts was 73% over six months, while the remaining persisted or increased [3]. In cases of endometrioma and dermal cysts, the US morphological criteria improves the clinical examination considering the PPV of 96.4% and 97.1%, respectively [17].

In patients who underwent laparotomy by US criteria, non-neoplastic tumors were found in around 50%. This percentage is similar to others [18] and is probably the result of the low sensitivity methods available for neoplasia detection. Most of these patients were followed up for four to six months and the main US criterion for surgery was the persistence or increase of the cyst. Interestingly, this US alteration was not related to any case of cancer or to the minority of benign neoplasias, and most cases underwent surgery for large cysts > 7 cm in diameter. In malignant neoplasia the main indication for surgery was the presence of a predominant solid tumor followed by more than one US criterion. Our results emphasize that if there is an association of an altered gynecological exam plus two or more US criteria a malignant neoplasia can not be ruled out. A study involving 378 cases of ovarian tumors analyzed by US and compared with the anatomopathological diagnosis showed sensitivity and specificity of 84.6% and 99.2%, respectively, and positive and negative predictive values of 98% and 93.5%, respectively [19].

In this study the systemic quantification of TM, considered as a sole parameter, was superior to Doppler only in the sensitivity for detection of ovarian neoplasia. Combined with Doppler increased sensitivity was obtained for detection of ovarian neoplasias and, mainly, cancer. Nevertheless, the PPV was reduced compared to Doppler alone. In this context, the analysis of 252 women at increased family risk for ovarian cancer, using Doppler plus CA125, demonstrated a high rate of false-positive results [12]. Another study using US with Doppler plus CA125 found 90% sensitivity, 97% specificity, 82% PPV and 99% NPV for the diagnosis of malignant ovarian neoplasia [20]. Compared to this data we have detected, by Doppler plus TM, similar sensitivity and NPV, but lower PPV. Maybe the fact that we have assayed varied TM types could have resulted in increased variability. The Doppler plus TM can be considered a reasonable alternative for the diagnosis of ovarian cancer, although false positive cases are not uncommon. Nonetheless, it has been considered that multimodal screening for ovarian cancer using CA125 and transvaginal US is not justifiable on a routine basis [21].

Approximately two-thirds of malignant ovarian tumors are still diagnosed in later stages [1]. In our study 73% cases were diagnosed in Stages I or II, suggesting that the strategy of more than one approach such as specific patient follow-up, US criteria, Doppler and TM is valid for the early diagnosis of ovarian neoplasia and must be specialized through further research. The use of a risk malignancy index has significant limitations in borderline ovarian tumors, Stage I invasive cancers and non-epithelial tumors [22]. It has been shown that US is a useful diagnostic method for the initial screening of ovarian cancer [23, 24]. In our work, the Doppler or TM isolated presented low sensitivity for detecting ovarian neoplasia. The PPV of Doppler plus TM was also low, although in particular cases of RI < 0.4 it was high. The low specificity of TM, which is mainly used for patient follow-up, has already been described [25].

In conclusion, our study has demonstrated that the gynecological examination was considered normal for almost all tumors with the largest diameter less than 5 cm, indicating that a complementary US exam is important to increase the detection of ovarian alterations. The main US criteria suggestive of ovarian neoplasia were presence of a solid area or combined criteria. We recommend the use of a pelvic mass outpatient service for the follow-up of ovarian alterations detected by US exam. In this preselected group, US criteria, Doppler and TM should be added for an early diagnosis of ovarian neoplasia.

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