Corpus Luteum Morphology and Vascularization Assessed by Transvaginal Two-dimensional and Three-dimensional Ultrasound

Gómez B, Álvarez P, Bajo JM, Engels V, Martínez A, De la Fuente J

Obstetrics and Gynecology Department, Santa Cristina University Hospital, Madrid, Spain

Background: Our aim was to describe the corpus luteum morphology by two-dimensional ultrasound correlated by its vascularization and volume by 3D ultrasound and study the possible relationship between serum progesterone levels and the corpus luteum morphology.

Methods: Thirty-eight women were included in an intrauterine insemination program (IUI) in Santa Cristina University's Hospital. All the patients were evaluated in mesoluteal phase, the day +7 after hCG administration, by two-dimensional and three-dimensional ultrasound. The volume and vascular indices of the corpus luteum were calculated off-line using virtual organ computer-aided analysis (VOCAL™) software.

Results: Four different morphologies were described in the corpus luteum: echo-positive, echo-negative or sonoluscent, mixed echogenicity or nonvisible. Corpus luteum with mixed echogenicity was the most frequent one with 37.5% (12 cases). The corpus luteum vascular indices change in each morphology type, but there was statistically significant association just in vascularization index between echo-negative and mixed echogenicity corpus luteum morphologies, with $p = 0.034$. The rest of vascular indices do not change in each morphology corpus luteum types. There was statistically significant difference in mean gray value between echo-negative and mixed echogenicity morphologies, with $p = 0.007$. There were no statistically significant correlations between the corpus luteum morphology and the corpus luteum volume of any of the different types. There either was no statistically significant correlation between the corpus luteum morphology and progesterone serum levels on day +7 postovulation.

Conclusions: The mixed echogenicity corpus luteum morphology has more vessels and more cell mass than echo-negative ones. Progesterone serum levels in mid-luteal phase has no influence in corpus luteum morphology and vascularization.

INTRODUCTION

The corpus luteum morphology is widely studied by transvaginal ultrasound. It is many times diagnosed as an ovarian tumoral pathology or functioning cysts, which sometimes result in unnecessary surgical intervention.

There are some studies that try to describe the corpus luteum morphology assessed by two-dimensional ultrasound. The introduction of three-dimensional ultrasound provides the sonographists to study the ovarian volume and its flow index, which may have many utilities in fertility and clinical practice.

Three-dimensional ultrasound has an advantage, that is, the simultaneous assessment of the ovarian volume and its perfusion. After displaying the ovarian volume and its vessels through 3D power Doppler angiography, the VOCAL™ program (Virtual Organ Computer-aided Analysis) is applied to calculate the corpus luteum perfusion by applying three flow indices by mean of the "histogram" tool.

The ovary is a well-vascularized organ. Angiogenesis is an essential factor for the growth and regression of follicles and the corpus luteum.[1,2] Therefore, the investigation of vascular changes in the ovaries, follicles and corpus luteum may help us describe their characteristics and morphology.

Vascular changes as assessed by color and spectral Doppler ultrasound have been described in the uterus and ovaries during the normal menstrual cycle.[3-5]

Three-dimensional power Doppler has been used to quantify vascularity in the ovary in the late follicular phase,[6] to study changes in blood flow in the ovarian stroma with age[7] and to compare intraovarian vascularization in polycystic ovaries with that in normal ovaries.[8]

To the best of our knowledge, there are no published studies where 3D power Doppler ultrasound has been used to study the corpus luteum vascularity and its relationship with its 2D morphology.

Although the corpus luteum morphology can be assessed by two-dimensional ultrasound, three-dimensional ultrasound permits new characteristics as blood flow and volume, which may improve and change this unclear classification.

In this study we used three-dimensional ultrasound to assess the corpus luteum volume and its vascularization index to find any correlation with two-dimensional corpus luteum morphology.

The aim of our study is to describe the corpus luteum morphology by two-dimensional ultrasound correlated by its vascularization and volume by 3D ultrasound and study the possible relationship between serum progesterone levels and the corpus luteum morphology.

MATERIAL AND METHODS

Patients

Thirty-eight women were included in an intrauterine insemination program (IUI) in Santa Cristina University's Hospital in 2005 and 2006. The inclusion criteria were age between 18 to 40 years with primary or secondary infertility lasting for ≥ 12 months; REM above 5 mill; serum progesterone levels above 10 ng/ml and female infertility (as cervical infertility, ovulatory dysfunction, endometriosis I and II and at least one permeable tube), immunological infertility or unknown infertility. The exclusion criteria were not to fulfill the inclusion criteria, progesterone levels on the day +7 after hCG administration under 10 ng/ml and FSH serum levels on cycle day 2nd, 3rd or 4th above 10 UI/L. We excluded six women because of low serum progesterone levels.

FSH, LH and E2 were analyzed before inclusion by a competitive immunoassay method on cycle day 2nd, 3rd or 4th. All the patients underwent a gonadotropins ovarian stimulation with subcutaneous recombinant FSH (50, 75 or 100 UI depending on the woman age) (Puregon®, Spanish Organon INC, Spain or Gonal-F®, Serono INC Laboratories, Spain). The follicle response was controlled by ultrasound each 2nd or 3rd days. When the average diameter of the dominant follicle was ≥ 18 mm, we induce ovulation with recombinant hCG (Ovitrelle, Serono INC Laboratories, Spain) with a 250 UI unique subcutaneous injection.

Equipment

All the patients were explored in gynecological position with the ultrasound transducer VOLUSON 730 (Iberian Kretztechnik, INC, Madrid) equipped with a vaginal multifrequency probe between 3 and 9 MHz and with a vision angle of 146 degrees.

Study Design

This is an analytic observational study of a hospital concurrent cohort. All women underwent a baseline transvaginal ultrasound examination on cycle day 2nd, 3rd or 4th, then each one or two days to control ovarian stimulation, until follicular rupture. The ovary bearing the ovulatoring follicle and posterior corpus luteum was called the dominant ovary and the contralateral ovary the nondominant ovary. We called the ovulating follicle as the dominant follicle. All the examinations were carried out for three examiners (BG, PA, VE), always the same examiner performing.

All the patients were evaluated in mesoluteal phase, the day +7 after hCG administration, by two-dimensional and three-dimensional ultrasound. The same day, serum progesterone levels were realized in all women. We presumed ovulation when serum progesterone levels are above 10 ng/ml. We excluded six patients because of low progesterone levels.

The women were examined in the lithotomy position with an empty bladder. Two-dimensional ultrasound was applied first to obtain the corpus luteum morphology and its power Doppler flow. We look for the corpus luteum in the dominant ovary where dominant follicle was seen in the previous examinations. After this, the 3D ultrasound mode was switched on. The woman was asked to remain as still as possible, and a 3D power Doppler data set of the corpus luteum was acquired. The power Doppler box was placed on the maximum longitudinal plane of the corpus luteum, covering completely its whole surface. When an adapted devices free color sign was obtained, we placed the 3D box to obtain the volume on region of interest. Then, the sonographist acquired, from the ovarian longitudinal plane, the corpus luteum volume. Volume acquisition interval oscillated between 10 and 15 seconds for the corpus luteum. All patients were requested to remain immobile and the probe movements were avoided during the measurements acquisition time. If artefacts[9] appeared during the volume acquisition due to the patient intestine movements, the volume was taken again until the image obtained was acceptable. We obtained 38 corpus luteum volumes that were stored on the ultrasound transducer hard disk, transferred to USB memory and studied later on.

All the analyses of stored ultrasound volumes were done off-line by one author (BG). The volumes were processed by the VOCAL imaging program (Virtual Organ Computer-aided Analysis). The acquired volumes yielded multiplanar views of the corpus luteum in the midsagittal, transverse and coronal planes. All calculations were done on these multiplanar images. Using manual mode, the different ovarian contour rotation cuts were traced using as work pattern A plane (longitudinal) and a 30 degrees rotational step,[10] resulting in the definition of six contours of the corpus luteum. These options were chosen for the reason that A plane is the habitual one in the ovary visualization and it was previously demonstrated that there are no significant statistical differences in reproducibility among A and C plane in the endometrium study.[11,12] Also in the ovary, the reproducibility with this characteristics was proved.[13]

Three-dimensional power Doppler indices were calculated using histogram facility. The analyzed parameters were: the corpus luteum volume (CLV), corpus luteum vascularization index (VI), flow index (FI) and vascularization-flow index (VFI). The vascularization index (VI) measures the number of color voxels in the ovarian volume, representing the number of ovarian vessels expressed as a percentage. The flow index (FI) is the average color value in all color voxels, meaning the average intensity of ovarian blood flow. The vascularization flow index (VFI) is the average value of the color in all gray and color voxels of the ovarian volume, expressing this way the total vascularization of the ovary.[14] The contours of the corpus luteum were drawn manually following the outer contour of the thick color ring surrounding it.

Statistical Analysis

Statistical analysis was performed by the SPSS® 11.5 version for windows (SPSS Inc., Chicago, IL, USA). Quantitative values analyzed were mean, minimum, maximum and standard deviation and qualitative values percentages and absolute case numbers.

Possible correlations were assessed using Pearson's rank correlation coefficient for quantitative variables and one-way ANOVA test for quantitative and qualitative variables correlation. The statistical significance of differences in results between corpus luteum morphology and the rest of parameters (corpus luteum volume, mean gray value, vascularization index, flow index, vascularization flow index and progesterone serum levels), vas determined using Sidak and Tukey's Post Hoc tests. The P-value <0.05 was regarded as statistically significant.

RESULTS

Six women were excluded from our study, all because serum progesterone levels were under 10 ng/ml in the mid-luteal phase. The mean progesterone serum value the day +7 after hCG administration in the thirty two cycles analyzed was 20.9 ng/ml (range 10.7-40).

The mean age of the 32 women studied was 34.62 ± 3,122 years (range 29-40). Descriptive values are summarized in Tables 1 to 3.

Four different morphologies were described in the corpus luteum: echo-positive (Fig. 1), echo-negative or sonoluscent (Fig. 1), mixed echogenicity (Fig. 3) or non visible. Corpus luteum with mixed echogenicity was the most frequent one with 37.5% (12 cases). The rest of the values are summarized in Table 2: echo-positive 28.1% (9 cases), echo-negative 25% (8 cases) and nonvisible 9.4% (3 cases) (Figs 2 to 4). Sometimes, ultrasound corpus luteum recognition is difficult. We used progesterone serum levels and dominant follicle control to control real ovulation and the corpus luteum is therefore present. But its variable appearance makes some time truly difficult to identify it. In these cases, 3D ultrasound, with multiplanar views, allow the examiner to find the corpus luteum inside the ovary volume and study its vascularization.

The corpus luteum vascular indices changes in each morphology type, but there was statistically significant association just in vascularization index between echo-negative and mixed echogenicity corpus luteum morphologies (Table 4), with p = 0.034, as Sidak post Hoc test shows (Table 5) . The rest of vascular indices not change in each morphology corpus luteum types.

Analyzing corpus luteum morphology and mean gray values (Table 6), there was statistically significant difference in mean gray value between echo-negative and mixed echogenicity morphologies, with p = 0.007 (Table 7). The difference in mean gray between echo-negative and echo-positive morphologies was near the statistical significance, with p = 0.074.

Table 1: Descriptive statistic of women age, IMC, weight and height

	N	*Minimum-maximum*	*Mean ± Std. deviation*
Age (years)	29	29-40	34.62 ± 3.122
IMC	29	18.5-26.37	21.69 ± 2.42
Weight (kg)	29	44-78	57.64 ± 9.7
Height (cm)	29	150-175	162.78 ± 5.73
Days of treatment	29	7-21	12.2 ± 4.38
Serum progesterone	29	10.7-40	20.9 ± 9.3
Valid N (listwise)	29		

Table 2: Descriptive statistic of corpus luteum morphology

	Frequency	*Percent*
Echo-positive	9	28.1
Echo-negative	8	25.0
Mixed	12	37.5
Nonvisible	3	9.4
Total	32	100.0

Table 3: Descriptive statistic of corpus luteum vascularity indexes

	N	*Minimum-Max*	*Mean+/- Sd.*
ECHO CL VOL cm^3	32	2.61-59.10	16.03831+/–12.65
ECHO MG CL		17.03-44.07	30.92+/–6.51
ECHO CL IV		0.72-21.01	7.69+/–5.83
ECHO CL IF		27.69-54.07	40.70+/–7.00
ECHO CL IFV		0.25-11.36	3.26+/–2.88

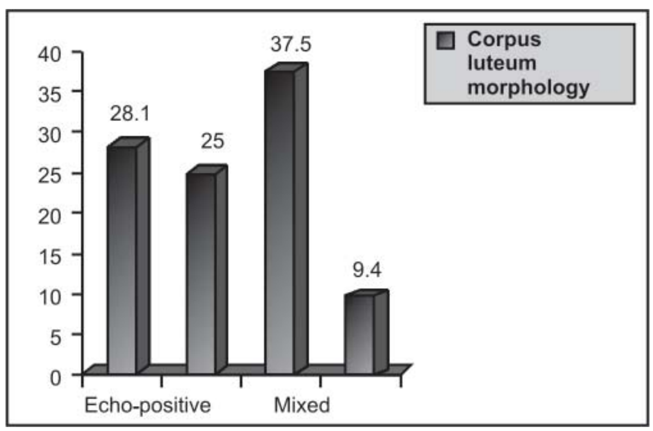

Fig. 1: Corpus luteum morphology

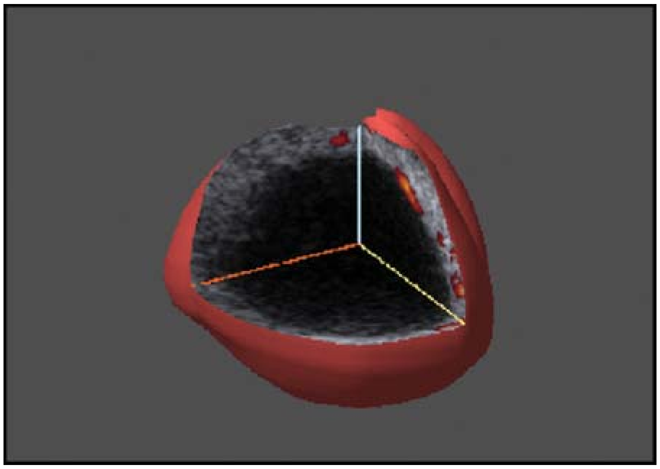

Fig. 2: Echo-negative corpus luteum morphology

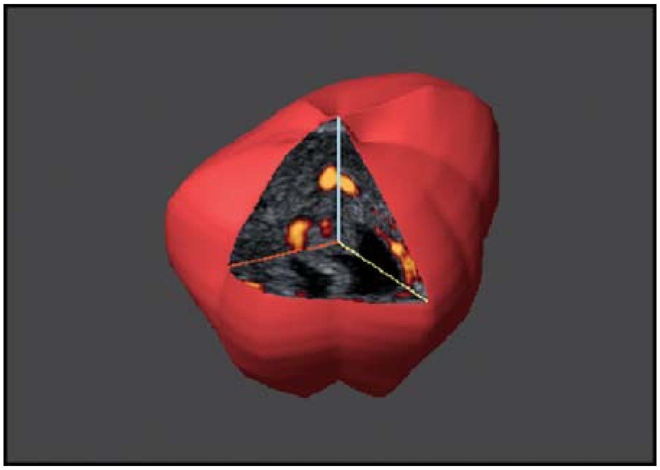

Fig. 4: Mixed echogenicity corpus luteum morphology

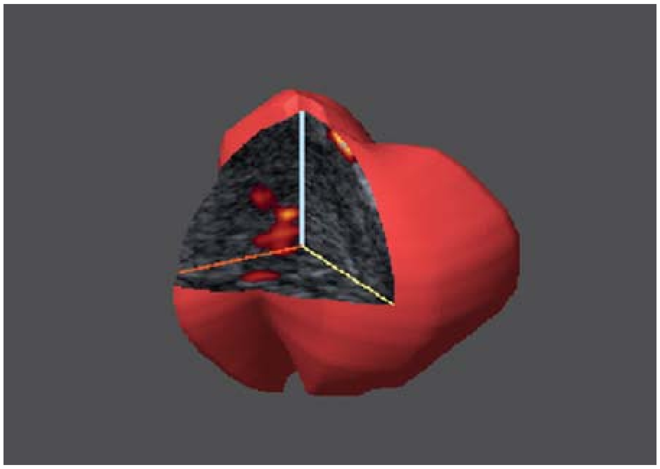

Fig. 3: Echo-positive corpus luteum morphology

There were no statistically significant correlations between the corpus luteum morphology and the corpus luteum volume of any of the different types (echo-positive, echo-negative, mixed echogenicity or non visible) (Table 8). There either was no statistically significant correlation between the corpus luteum morphology and progesterone serum levels on day +7 post-ovulation (Table 9).

DISCUSSION

Our results suggest that the corpus luteum volume assessed by three-dimensional ultrasound do not depend on its morphology. The corpus luteum vascular indices assessed by three-dimensional ultrasound do not correlate with the different 2D morphologies, excluding vascularization index. It is reasonable to believe that the changes in vascular indices parallel

Table 4: ANOVA test

		N	*Mean ± Std. deviation*	*95% Confidence interval for mean*		*p*
				Lower Bound	*Upper Bound*	
ECHO CL IV	ECHO-POSITIVE	9	8.86 ± 6.77	3.66	14.07	
	ECHO-NEGATIVE	8	3.22 ± 2.04	1.51	4.93	
	MIXED	12	10.41 ± 5.57	6.86	13.95	
	NON-VISIBLE	3	5.24 ± 4.31	–5.48	15.96	
	Total	32	7.69 ± 5.83	5.59	9.79	0.03
ECHO CL IF	ECHO-POSITIVE	9	42.37 ± 5.67	38.01	46.73	
	ECHO-NEGATIVE	8	42.56 ± 6.69	36.96	48.15	
	MIXED	12	40.33 ± 7.75	35.41	45.26	
	NON-VISIBLE	3	32.16 ± 2.70	25.45	38.86	
	Total	32	40.70 ± 7.00	38.17	43.22	0.03
ECHO CL IFV	ECHO-POSITIVE	9	4.00 ± 3.51	1.30	6.70	
	ECHO-NEGATIVE	8	1.31 ± 0.79	0.65	1.97	
	MIXED	12	4.38 ± 2.91	2.54	6.23	
	NON-VISIBLE	3	1.75 ± 1.49	–1.95	5.47	
	Total	32	3.26 ± 2.88	2.22	4.30	0.03

Table 5: Post Hoc Sidak test

Dependent variable Sidak	*(I) MORPHOLOGIA CL*	*(J) CL MORPHOLOGY*	*Mean difference (I-J)*	*Sig.*	*95% Confidence interval*	
					Lower bound	*Upper bound*
ECHO CL IV	ECHO-POSITIVE	ECHO-NEGATIVE	5.63	0.197	–1.59	12.87
		MIXED	–1.54	0.986	–8.11	5.02
		NON-VISIBLE	3.62	0.893	–6.30	13.55
	ECHO-NEGATIVE	ECHO-POSITIVE	–5.63	0.197	–12.87	1.59
		MIXED	–7.18 (*)	**0.034**	–13.98	–0.38
		NON-VISIBLE	–2.01	0.994	–12.10	8.06
	MIXED	ECHO-POSITIVE	1.54	0.986	–5.02	8.11
		ECHO-NEGATIVE	7.18(*)	**0.034**	0.38	13.98
		NON-VISIBLE	5.16	0.594	–4.44	14.78
	NON-VISIBLE	ECHO-POSITIVE	–3.62	0.893	–13.55	6.30
		ECHO-NEGATIVE	2.01	0.994	–8.06	12.10
		MIXED	–5.16	0.594	–14.78	4.44

Table 6: ANOVA test

	N	*Mean ± Std. deviation*	*95% Confidence interval for mean*		*p*
			Lower bound	*Upper bound*	
ECHO-POSITIVE	9	32.38 ± 6.34	27.50	37.26	
ECHO-NEGATIVE	8	25.17 ± 5.15	20.87	29.48	
MIXED	12	34.34 ± 5.25	31.00	37.69	**0.008**
NON-VISIBLE	3	28.17 ± 5.28	15.03	41.30	
Total	32	30.92 ± 6.51	28.57	33.27	

Table 7: Post Hoc Sidak test

Dependent Variable: ECHO MG CL

	(I) CL MORPHOLOGY	*(J) CL MORPHOLOGY*	*Mean difference (I-J)*	*Sig.*	*95% Confidence interval Lower bound*	*Upper bound*
Sidak	ECHO-POSITIVE	ECHO-NEGATIVE	7.20	0.074	–0.44	14.86
		MIXED	–1.96	0.966	–8.91	4.98
		NON-VISIBLE	4.21	0.844	–6.29	14.72
	ECHO-NEGATIVE	ECHO-POSITIVE	–7.20	0.074	–14.86	0.44
		MIXED	–9.17 (*)	**0.007**	–16.36	–1.97
		NON-VISIBLE	–2.99	0.967	–13.66	7.67
	MIXED	ECHO-POSITIVE	1.96	0.966	–4.98	8.91
		ECHO-NEGATIVE	9.17 (*)	**0.007**	–1.97	16.36
		NON-VISIBLE	6.17	0.457	–3.99	16.34
	NON-VISIBLE	ECHO-POSITIVE	–4.21	0.844	–14.72	6.29
		ECHO-NEGATIVE	2.99	0.967	–7.67	13.669
		MIXED	–6.17	0.457	–16.34	3.99

*The mean difference is significant at the 0.05 level.

Table 8: ANOVA test

ECHO CL VOL cm^3

	N	*Mean ± Std. deviation*	*95% Confidence interval for mean*		*p*
			Lower bound	*Upper bound*	
ECHO-POSITIVE	9	11.42 ± 2.00	6.79	16.06	
ECHO-NEGATIVE	8	23.96 ± 7.10	7.17	40.76	
MIXED	12	16.11 ± 2.66	10.25	21.97	0.14
NON-VISIBLE	3	8.40 ± 2.73	-3.34	20.15	
Total	32	16.03 ± 2.23	11.47	20.60	

Table 9: Post Hoc Sidak test

SERUM PROGESTERONE MID-LUTEAL PHASE

	N	*Mean ± Std. deviation*	*95% Confidence interval for mean*		*p*
			Lower bound	*Upper bound*	
ECHO-POSITIVE	9	21.86 ± 7.09	16.41	27.32	
ECHO-NEGATIVE	8	19.51 ± 10.19	10.99	28.03	
MIXED	12	19.35 ± 9.62	13.23	25.46	
NON-VISIBLE	3	28.00 ± 12.87	-3.98	59.98	
Total	32	20.90 ± 9.30	17.55	24.26	0.522

true changes in vascularization, and that the more solid corpus luteum is more vessels are in its stroma. Those vascularization changes are characterized by appearance of numerous arteriovenous shunts during the luteal phase. Nevertheless we found no correlation with flow index or vascularization flow index. That would be explained by the idea that more vessels not always involve more flow inside them.

Increasing 3D power Doppler vascular indices in the dominant follicle in the late follicular phase and especially after follicular rupture can be explained by physiological vascular changes. The granulosa layer of the follicle is avascular until the time of ovulation,[2] but the newly formed corpus luteum contains developing capillaries in its luteinized granulosa cell layer.[1] The amount of blood vessels and the volume of granulosa cells in the corpus luteum increase until 7 days after follicular rupture, and blood vessels in the corpus luteum do not become less abundant until in the follicular phase of the following menstrual cycle.[15]

Nakata *et al* twelve years ago, investigated the corpus luteum by mean of two-dimensional ultrasound in women undergoing hysterectomy, before the corpus luteum was extirpated.[16] Their ultrasound pictures showed that the corpus luteum had a slightly cloudy central part, which can vary from hypoechoic to hyperechoic. The peripheral part (corpus luteum 'wall') had a stronger echo and the maximal and minimal thicknesses could be measured. The results showed correlations between ultrasound measurements and anatomical measurements. Based on these findings, they suggested that an ultrasound investigation of the corpus luteum in the mid-luteal phase should use those criteria to classify it into four types: Type A: hypoechoic central part with wall of < 3 mm; Type B: hyperechoic central part with wall of < 3 mm; Type V: hypoechoic central part with wall of > or = 3 mm; and Type F: hyperechoic central part with wall of > or = 3 mm.

Ottander *et al* evaluated the morphologic characteristics underlying the ultrasonographic appearance and blood flow dynamics in the human corpus luteum of the menstrual cycle. They studied twenty-six healthy women with proven fertility and a history of regular menstrual cycles, scheduled for elective hysterectomy or tubal sterilization. Before surgery, a standardized ultrasonographic examination of the corpus luteum, including B-mode and color Doppler ultrasonography measurements, was performed. Upon commencing the minilaparotomy, the corpus luteum was excised and measured using a digital slide-caliper. They concluded that there was a high degree of agreement between ultrasonographic and anatomic measurements of surgically removed corpus luteum.

The corpus luteum is usually diagnosed as pathological ovarian cysts. Mercé *et al* studied real ovulation diagnose to assess ultrasound the recognition of corpus luteum.[17,18] They widely studied the echographic assessment of the cyclic changes of the functional ovarian compartments. They suggest that the ovulation diagnose during mid-luteal phase, just with the assist of ultrasound has the disadvantage of the corpus luteum recognize. The corpus luteum morphology is variable and in a 55% of its cases studied, it was not identified. That is why they suggest Doppler to evaluate follicle and corpus luteum blood flow during the whole ovarian cycle.[19,20]

Despite progesterone serum levels on day +7 after hCG administration is the best marker of real ovulation, in our study we found no correlation between the progesterone serum levels and the different corpus luteum morphologies. Mercé *et al* agree that the progesterone serum levels in mid-luteal phase is the most used parameter to confirm corpus luteum presence.[21] This is the best parameter to confirm ovulation, but it is not able to discern between normal ovulation and luteinized unruptured follicle.[22]

We either found no correlation between progesterone serum levels in mid-luteal phase > 10 ng/ml and 3D ultrasound vascular indices. It would explain that progesterone levels not determine the corpus luteum vascularization.

We have found no published studies where 3D ultrasound was used to assess corpus luteum morphology and its vascularization compared with 2D ultrasound. All currently available corpus luteum studies were conducted to find 2D vascularization models and its relationship with progesterone serum levels and pregnancy outcomes. Volumes calculated using 3D ultrasound are more accurate than those calculated using 2D ultrasound.[23] 3D power Doppler is a new method of studying vascularization. What 3D power Doppler might add is more accuracy, so we used it to study corpus luteum morphology ant its vascularization and try to find some improves in its classification.

Our results dismiss this hypothesis, but more studies are needed to corroborate our findings.

Summarising, this association in vascularization index between echo-negative and mixed morphology is evidently explained because of the more intensive peripheral vascularization in mixed forms than echo-negative forms. We can also explain the association in the main gray index between echo-negative and mixed morphologies owing to the higher quantity of cells and vessels in mixed corpus luteum morphology (Figs 5 to 7).

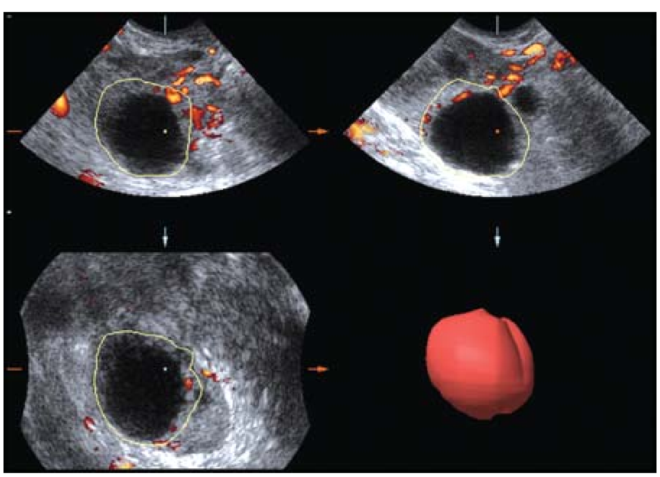

Fig. 5: Multiplanar view in echo-negative morphology

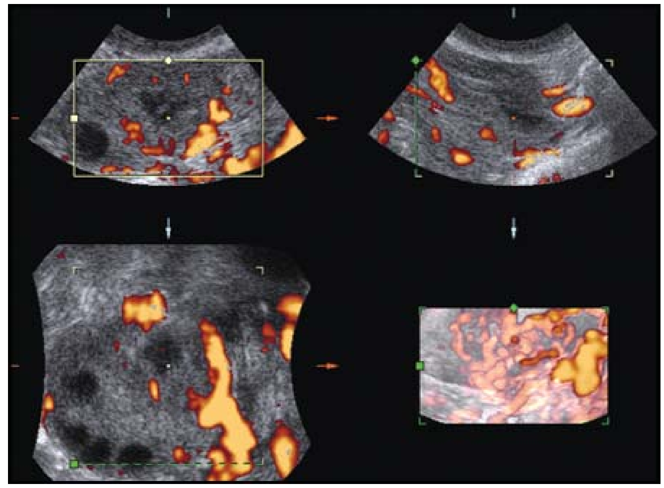

Fig. 6: Render mode in mixed echogenicity morphology

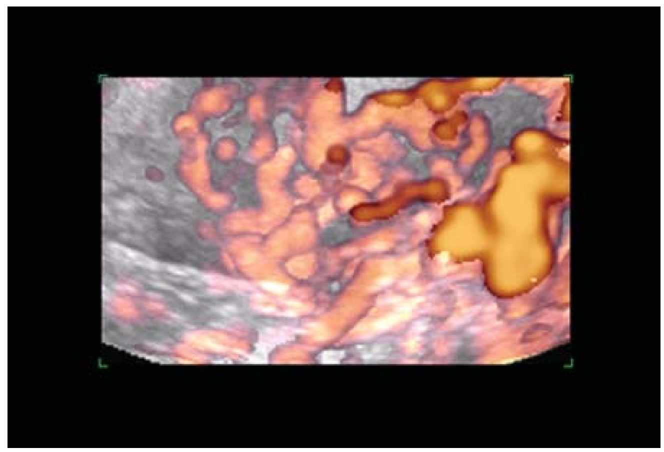

Fig. 7: Vascularization in mixed echogenicity morphology, render mode

Our study is still open to increase the case number and try to find some relationship between corpus luteum morphology and perifollicular, endometrial vascularization and pregnancy outcomes.

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