ORIGINAL ARTICLE

CONTENTS

Beyond traditional lipid markers: why lipoprotein(a) screening matters

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ABSTRACT

Aim: To assess the correlation between lipoprotein(a) levels and traditional lipid profile markers in statin-naive men and women without established atherosclerotic cardiovascular disease.

Materials and Methods: Sixty-seven statin-naive adult patients without a prior history of established atherosclerotic cardiovascular disease were included in the study. Lipoprotein(a) levels were determined using nephelometry in all patients.

Results: According to the results of the correlation analysis, it was found that there is no statistically significant correlation between lipoprotein(a) level and traditional parametres of lipid profile in both groups ($p>0.05$). Reliable direct correlation of moderate strength was observed between lipoprotein(a) and age in the group A ($R=0.46$, $p=0.04$).

Conclusions: Elevated lipoprotein(a) levels, independent of other lipid profile parameters, can significantly contribute to cardiovascular risk, emphasizing the importance of routine lipoprotein(a) screening in clinical practice. It is particularly noteworthy that lipoprotein(a) concentrations tend to increase after menopause, potentially placing postmenopausal women at an elevated risk for cardiovascular events. Consequently, it is imperative to monitor lipoprotein(a) levels in females, especially during the peri-menopausal and postmenopausal stages, to more accurately assess and manage cardiovascular risk in this population.

KEY WORDS: Lipoprotein(a), atherosclerotic cardiovascular disease, lipid profile

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INTRODUCTION

Lipoprotein(a) (Lp(a)) has garnered increasing attention in the medical community due to its potential role as a significant biomarker and therapeutic target in cardiovascular and renal diseases. Recent studies have provided substantial evidence linking elevated Lp(a) levels with various health conditions, including calcific aortic valve stenosis (CAVS), chronic kidney disease (CKD), and atrial fibrillation (AF). The findings from several recent studies suggest that Lp(a) may be a modifiable risk factor in these diseases, opening new avenues for prevention and treatment strategies.

A recent systematic review and data analysis examined the relationship between elevated Lp(a) levels and the progression of CAVS. The study revealed a significant association between higher Lp(a) concentrations and accelerated CAVS progression, suggesting the potential for targeting Lp(a) as part of therapeutic strategies for managing this condition. As CAVS continues to rise in prevalence, understanding the underlying mechanisms may provide new insights into its treatment and management [1-3].

Lp(a) is a large macromolecular complex composed of an low-density lipoproteins (LDL) particle containing apolipoprotein B-100 (apoB-100) and a large, highly variable glycoprotein known as apolipoprotein(a) (apo(a)), which is produced by the liver. Apo(a) contains kringle domains, triple-loop structures, which play a crucial role in the particle's structure. A disulfide bond links one of the kringle domains in apo(a) to apoB-100, forming the Lp(a) complex. Lp(a)'s plasma concentration is highly variable, with significant differences between individuals, populations, and even ethnic groups. Lp(a) concentrations range from less than 0.1 mg/dl to over 200 mg/dl, with levels in individuals of African descent being 2–3 times higher than those in Asian and European populations [4,5]. Lipoprotein(a)'s concentration is largely genetically determined, and it

is believed to have atherogenic, proinflammatory, and prothrombotic properties [6].

In renal health research, several studies have explored the link between Lp(a) levels and kidney disease. A Mendelian randomization study investigated the causal relationship between elevated Lp(a) levels and CKD, utilizing genetic variants associated with Lp(a). Analysis of data from large population cohorts showed that higher genetically determined Lp(a) levels were linked to an increased risk of CKD, supporting the notion that Lp(a) may be a causal factor in kidney disease and highlighting its potential as a modifiable risk factor for CKD prevention and treatment.

Another study analyzed the relationship between Lp(a) levels, renal function indicators, and CKD risk in a large cohort of 329,415 participants. With a median follow-up of 12.5 years, it found that elevated Lp(a) levels were associated with a 32% increased risk of CKD, particularly in individuals with high-normal urine albumin-to-creatinine ratio (UACR). These findings underscore the importance of considering both Lp(a) and UACR when assessing CKD risk, offering valuable insights for early detection and prevention strategies [7, 8].

In the cardiovascular field, research explored the role of Lp(a) as a risk factor for cardiovascular events in both diabetic and non-diabetic populations. Analysis of clinical records indicated that elevated Lp(a) levels were independently linked to an increased risk of cardiovascular events in both groups, with a stronger association seen in individuals without diabetes. This highlights the importance of monitoring Lp(a) levels in non-diabetic individuals for early cardiovascular risk assessment and intervention [9].

The potential link between elevated Lp(a) levels and atrial fibrillation (AF) was also explored through a systematic review and meta-analysis of Mendelian randomization studies. The findings revealed a significant association between higher genetically determined Lp(a) concentrations and an increased risk of AF, suggesting a causal relationship. This emphasizes the need to consider Lp(a) in cardiovascular health, particularly in the prevention and management of arrhythmias like AF [10, 11].

Together, these studies contribute to a growing body of evidence supporting the role of Lp(a) as a crucial biomarker and potential therapeutic target in both cardiovascular and renal diseases. Elevated Lp(a) levels are associated with increased risks of CAVS, CKD, cardiovascular events, and AF, underscoring the importance of including Lp(a) in routine clinical assessments. Future research focused on the mechanisms behind these associations could lead to more effective prevention and treatment strategies, ultimately improving patient outcomes.

AIM

To assess the correlation between lipoprotein(a) levels and traditional lipid profile markers in statin-naive men and women without established atherosclerotic cardiovascular disease (ASCVD).

MATERIALS AND METHODS

Sixty-seven statin-naive adult patients without a prior established atherosclerotic cardiovascular disease were included in the study: group A – females (n=34), group B – males (n=33). The study groups did not differ statistically in age. Among the examined patients, 50.7% (34/67) were women, while 49.3% (33/67) were men. The average age of the patients of group A was 48.06±13.67 and the patients of group B – 42.12±6.25 years. Exclusion criteria were established atherosclerotic cardiovascular disease, organic heart pathology, arrhythmias, familial hypercholesterolemia and pregnancy. Peripheral blood was collected from each participant via venipuncture. Lipoprotein(a) levels were determined using nephelometry, a technique that measures the concentration of particles in a sample by detecting the scattering of light. In this method, a sample containing lipoprotein(a) is mixed with specific antibodies that bind to the lipoprotein particles. When light passes through the sample, the scattered light is detected by a photodetector. The intensity of the scattered light correlates with the concentration of lipoprotein(a) in the sample, allowing for quantitative measurement. This technique is highly sensitive and specific, providing accurate results for lipoprotein(a) determination [12].

The results were statistically analyzed using Office Excel 2010 and the Statsoft Statistica 12.0 software on a personal computer. A discrepancy was deemed significant if the probability value was 95% or greater ($p<0.05$). Variational statistics were employed to analyze the data, with average values and standard error (M±m) taken into account. The analysis of the relationship between two features in the presence of a normal distribution of data was carried out according to the data of the Pearson correlation coefficient (r), in the case of a distribution different from the normal - the nonparametric Spearman rank correlation coefficient (R) was calculated. The correlation coefficient was evaluated according to the criteria generally accepted in statistics: $r<0.3$ - weak connection; 0.3-0.49 - moderate; 0.5-0.69 - significant; 0.7-0.89 - strong; >0.9 is very strong, close to a functional relationship [13].

RESULTS

Despite the study group consisting of patients aged 25 to 72 years with no prior history of atherosclerotic cardiovascular disease, the average total cholesterol levels in groups

Table 1. Parameters of lipid profile and age of examined patients (M ± m)

Parameters	Group A (n=34)	Group B (n=33)	p
Age, years	48.06±13.67	42.12±6.25	p=0.06
Total cholesterol, mmol/l	6.74±1.70	6.20±1.53	p=0.28
HDL, mmol/l	1.69±0.31	1.34±0.77	p=0.06
LDL, mmol/l	4.23±1.44	3.85±1.35	p=0.34
VLDL, mmol/l	0.62±0.56	0.78±0.63	p=0.47
Triglycerides, mmol/l	1.22±0.61	1.90±1.56	p=0.39
Lipoprotein(a), mg/dl	46.85±47.20	29.78±42.99	p=0.04*

p – reliability of correlation; * - statistically reliable correlation.

Table 2. Correlation between lipoprotein(a), indicators of lipid profile and age of examined patients

Parameters	Group A (n=34)		Group B (n=33)	
	Spearman R	p	Spearman R	p
Age, years	0,46	0,04*	0,35	0,08
Total cholesterol, mmol/l	0,01	0,97	0,08	0,71
HDL, mmol/l	0,27	0,15	0,17	0,46
LDL, mmol/l	-0,11	0,64	0,29	0,19
VLDL, mmol/l	0,09	0,68	-0,12	0,61
Triglycerides, mmol/l	-0,01	0,96	0,04	0,86

p – reliability of correlation; R-correlation coefficient; * - statistically reliable correlation.

A and B were (6.74±1.70) mmol/l and (6.20±1.53) mmol/l, respectively, suggesting the presence of hyperlipidemia. Regarding HDL levels, the average value in females was (1.69±0.31) mmol/l, whereas in males it was lower at (1.34±0.77) mmol/l, though no statistically significant difference was observed. LDL levels were elevated in both groups, with average values of (4.23±1.44) mmol/l in group A and (3.85±1.35) mmol/l in group B. The triglyceride level was somewhat higher in men, averaging (1.90±1.56) mmol/l, compared to (1.22±0.61) mmol/l in women. No statistically significant differences were found in the traditional lipid profile parameters between groups A and B (p>0.05). This suggests that despite variations in lipid levels, the two groups had comparable lipid profiles overall. Regarding the average lipoprotein(a) levels, a statistically significant difference was observed between groups A and B. In females, the average lipoprotein(a) level was higher, reaching (46.85±47.20) mg/dl, while in males, it was lower, with an average of (29.78±42.99) mg/dl (Table 1). This difference suggests a potential gender-related variation in lipoprotein(a) concentrations, which could have implications for cardiovascular risk assessment and treatment strategies.

According to the results of the correlation analysis, it was found that there is no statistically significant correlation between lipoprotein(a) level and traditional parametres of lipid profile in both groups (p>0.05) (Table 2). Reliable direct correlation of moderate strength was observed between lipoprotein(a) and age in the group A (R=0.46, p=0.04).

The results of the correlation analysis revealed that there was no statistically significant correlation between lipoprotein(a) levels and traditional lipid profile parameters in both groups (p>0.05) (Table 2). However, Reliable direct correlation of moderate strength was observed between lipoprotein(a) and age in group A (R=0.46, p=0.04). This finding suggests that while lipoprotein(a) is generally considered genetically determined, it appears that in women, lipoprotein(a) levels may increase with age. This highlights the potential role of aging in influencing lipoprotein(a) concentrations, which could have significant implications for cardiovascular risk assessment, particularly in postmenopausal women, who may experience an increase cardiovascular risk due to hormonal changes.

DISCUSSION

Lipoprotein(a) is a genetically determined lipoprotein that has been identified as an independent risk factor for cardiovascular disease. Elevated levels of Lp(a) are closely associated with an increased risk of atherosclerotic cardiovascular diseases, including heart attacks and strokes, making Lp(a) a crucial biomarker for assessing cardiovascular risk. Genetic factors predominantly influence Lp(a) concentrations, with approximately 70% to ≥90% of interindividual variability attributed to genetic determinants. Notably, Lp(a) levels remain relatively constant throughout an individual's life and are not

significantly affected by lifestyle factors or conventional lipid-lowering therapies.

It is important to measure Lp(a) levels in individuals with a personal or family history of premature ASCVD. Lp(a) levels can be elevated independently of other lipid parameters, such as total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. This characteristic makes Lp(a) a unique cardiovascular risk factor that can remain hidden unless specifically tested for, even when other lipid markers are within normal ranges. Recognizing elevated Lp(a) levels can aid in identifying individuals at increased risk for ASCVD, facilitating early interventions and personalized treatment strategies [14-16].

Anagnostis, P. et al. suggest in their study that menopause can influence Lp(a) concentrations in women, potentially contributing to their increased cardiovascular risk. They examined the impact of menopause on Lp(a) levels, finding that the transition to menopause is associated with an increased cardiovascular risk, primarily attributed to atherogenic dyslipidemia. However, the study did not establish a clear conclusion regarding the specific effect of menopause on Lp(a) levels, leaving this aspect of the relationship unclear [17].

In contrast, a study by Aljawini, N. et al. explored the relationship between age, menopause, and Lp(a) levels in Saudi women. The findings revealed that Lp(a) concentrations increased significantly after the age of 50, with postmenopausal women exhibiting markedly higher levels than their premenopausal counterparts. This suggests that menopause could be a contributing factor to the elevation of Lp(a) levels in this population, pointing to a potential link between hormonal changes and lipid metabolism during menopause [18].

Additionally, Simony, S. B. et al. examined sex differences in Lp(a) levels and their association with cardiovascular risk. The study found that plasma Lp(a) levels increased with age, with a notable rise around age 50 in women. Postmenopausal women exhibited Lp(a) levels that were 22% higher compared to premenopausal women, underscoring the significant increase in Lp(a) concentrations after menopause [19].

Taken together, these studies suggest that menopause may be associated with increased Lp(a) levels, contributing to the heightened cardiovascular risk observed in postmenopausal women. However, further research is needed to better understand the mechanisms underlying this association and its clinical implications for cardiovascular risk assessment and management in this population.

Understanding the impact of menopause on Lp(a) levels could ultimately guide more precise cardiovascular risk stratification and personalized interventions for postmenopausal women.

CONCLUSIONS

While traditional lipid profile parameters are valuable in assessing cardiovascular risk, they do not encompass the full spectrum of lipid-related risk factors. Elevated Lp(a) levels, independent of other lipid profile parameters, can significantly contribute to cardiovascular risk, emphasizing the importance of routine Lp(a) screening in clinical practice. It is particularly noteworthy that Lp(a) concentrations tend to increase after menopause, potentially placing postmenopausal women at an elevated risk for cardiovascular events. Consequently, it is imperative to monitor Lp(a) levels in females, especially during the peri-menopausal and postmenopausal stages, to more accurately assess and manage cardiovascular risk in this population.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Pathomorphological characteristics of the supravaginal part of the cervix depending on the echogenicity ratios of the cervix to the uterine body

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ABSTRACT

Aim: To analyze the morphological features of the supravaginal part of the cervix depending on the echogenicity ratios of the cervix to the body of the uterus.

Materials and Methods: In 87 reproductive-age patients (30–40 years) with uterine leiomyoma (>14 weeks gestation), morphological features of the supravaginal cervix were analyzed in 23 hysterectomy specimens based on echogenicity ratios: Group I (n = 10): Cervical echogenicity > uterine body. Group II (n = 8): Cervical echogenicity = uterine body. Group III (n = 5): Cervical echogenicity < uterine body.

Results: Histological analysis revealed that increased cervical echogenicity corresponded to a predominance of collagen fibers over smooth muscle bundles. Conversely, when cervical echogenicity was equal to or lower than the uterine body, smooth muscle bundles dominated. These specimens also exhibited destructive changes, connective tissue disorganization, and dystrophic alterations, which are pathognomonic signs of potential lower uterine segment failure during pregnancy.

Conclusions: 1. Comparative studies show that in cases of excess echogenicity of the cervix over the body of the uterus, pathomorphological changes in the supravaginal part of the cervix were not detected. 2. Equal or reduced cervical echogenicity was associated with connective tissue disorganization and dystrophic changes in smooth muscle, indicating structural inferiority. 3. A change in the ratio of echogenicity of the cervix to the body, which is closely related to the morphological structure of the isthmus of the uterus, can serve as one of the criteria for predicting the failure of the lower segment of the uterus in women.

KEY WORDS: Echogenicity, cervix, uterine body

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INTRODUCTION

The increasing frequency of surgical interventions in the lower segment requires improvement of criteria for assessing the morphofunctional state of this anatomical structure even before pregnancy [1-4].

However, only a few scientific works have been devoted to the study of the morphostructure of the lower uterine segment in comparison with the echogenicity of the cervix and uterine body [5].

At the same time, it is known that one of the main contributing factors to inferiority of the lower uterine segment is pathomorphological changes in the area of the lower edge of the uterine body and isthmus, especially after cesarean section [6, 7].

Some authors have established [8] that in conditions of hypo- or hypercollagenosis , the structure of connective tissue may change, becoming more or less elastic in its structure, which affects its elasticity and echo signal reflectivity during ultrasound scanning [9].

Therefore, there are many outstanding issues in early diagnosis of changes in the structural elements of the isthmus of the uterus, which does not allow to improve the prediction of lower uterine segment insufficiency and improve measures to prevent scar incompetence, especially after cesarean section.

AIM

To analyze the morphological features of the supravaginal part of the cervix depending on the echogenicity ratios of the cervix and the body of the uterus.

MATERIALS AND METHODS

Sonographic determination of echogenicity ratios of the tissues of the cervix and uterine body before surgery and pathomorphological examination of the removed uterus and its isthmus after hysterectomy in women of reproductive age (30-40 years) who were diagnosed with uterine leiomyoma > 14 weeks of gestation. According to the ratio of echogenicity of the cervix to the body, three representative study groups were identified in terms of age and uterine pathology:

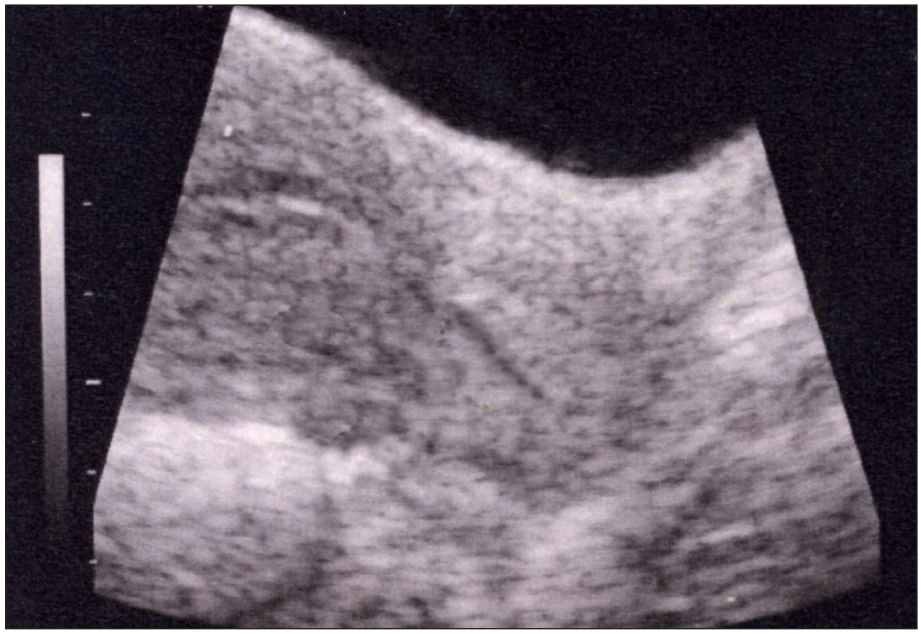

Fig. 1. Echogram of the uterus. The echogenicity of the cervix is higher than the echogenicity of the body of the uterus.

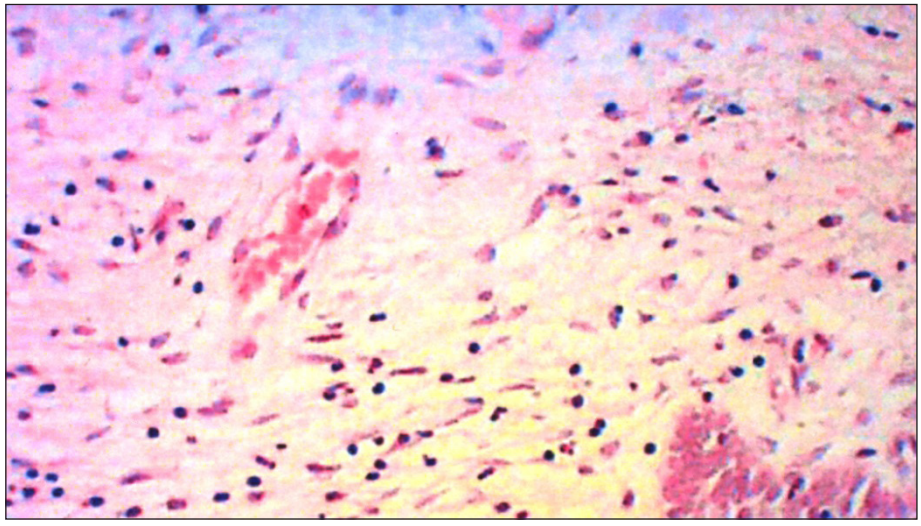

Fig. 2. Biopsy sample supravaginal part of the cervix (isthmus). *Hematoxylin and eosin staining. Predominance of connective tissue (collagen fibers) over smooth muscle bundles. Enlargment: oculus 10, lens 20.

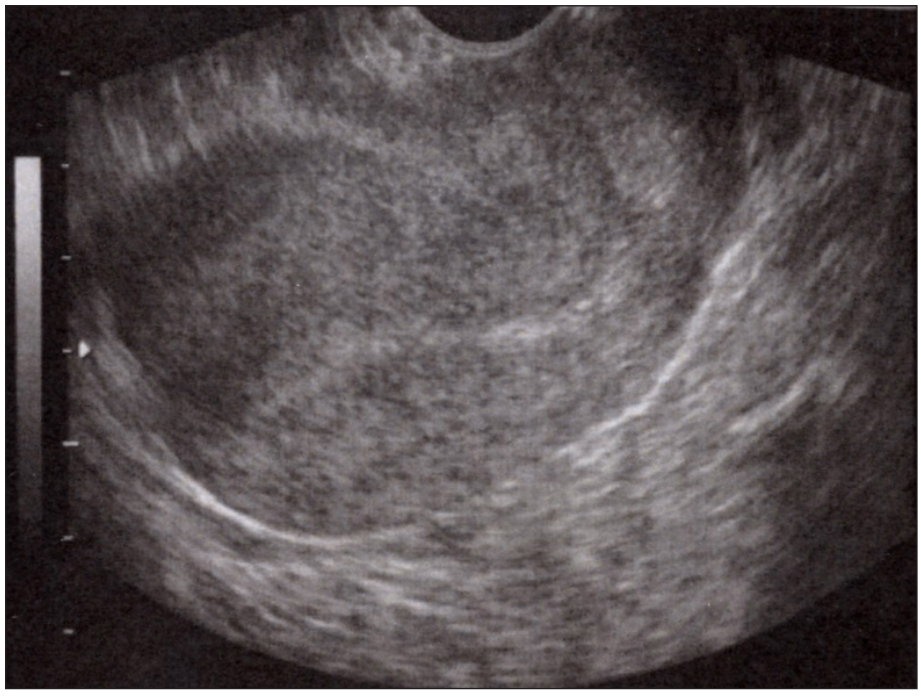

Fig. 3. Echogram of the uterus. The echogenicity of the cervix is the same as the echogenicity of the body of the uterus.

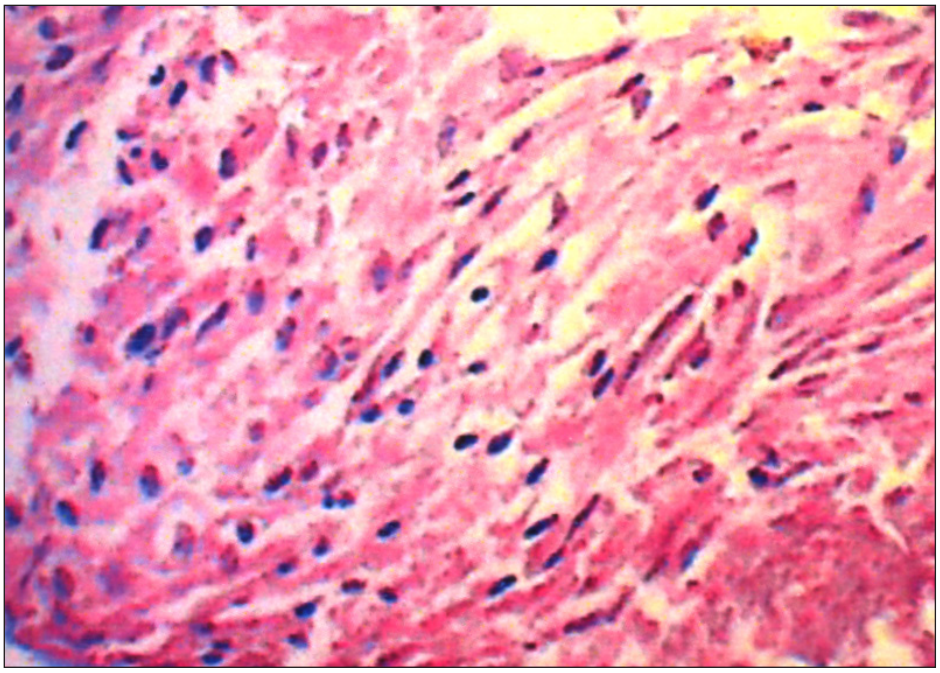

Fig. 4. Biopsy sample supravaginal part of the cervix (isthmus). Staining with hematoxylin and eosin. There is an increase in smooth muscle components over connective tissue components. Enlargment: oculus 15, lens 20.

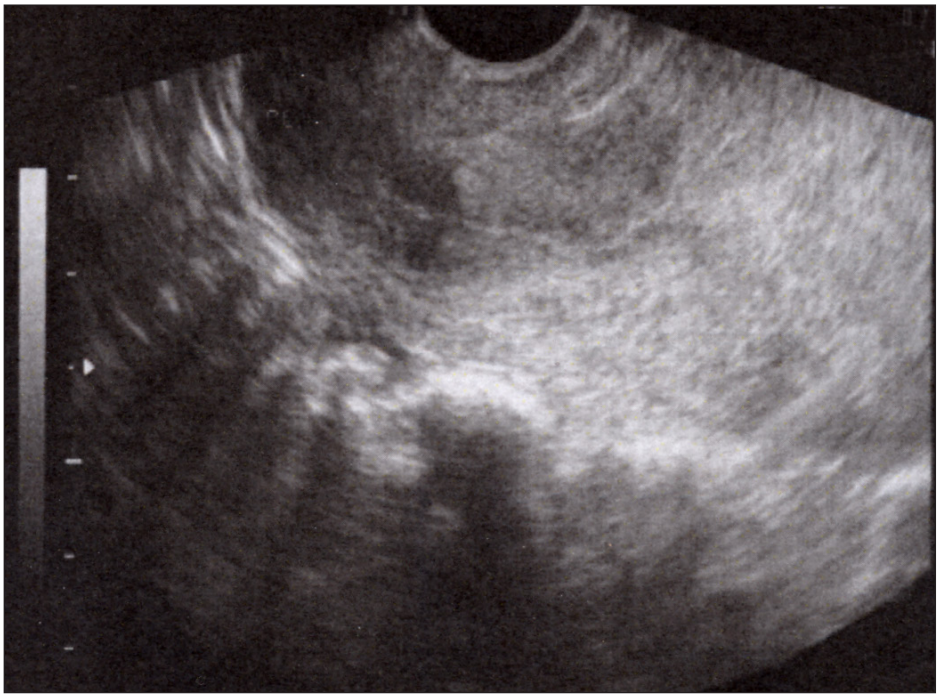

Fig. 5. Echograms of uterine leiomyoma . The echogenicity of the cervix is lower than the echogenicity of the uterine body.

Group I (n = 10) patients whose echogenicity of the cervix prevailed over the echogenicity of the uterine body;

Group II (n = 8), where the echogenicity of the cervix and uterine body coincided with each other;

Group III (n = 5), patients whose echogenicity of the cervix was lower than that of the body.

For the purpose of pathomorphological examination, a biopsy specimen was taken from the supravaginal part of the cervix from the removed uterus. The obtained material was fixed in a 10 percent solution of neutral buffered formalin (pH 7.9) for 24-36 hours, followed by embedding in paraffin blocks.

Features of the morphological structure of the uterine isthmus were studied in histological sections stained with hematoxylin and eosin depending on the echogenicity ratios of the cervix and uterine body in patients after hysterectomy. uterine leiomyomas . To assess the connective tissue component, sections were additionally stained according to Van Gieson and Masson (Trichrome Stain Kit).

RESULTS

In the first observation group with increased echogenicity of the cervix above the body of the uterus (Fig. 1), in hysterosalpingograms (Fig. 2) of the supravaginal part of the cervix, smooth muscle bundles were found in the form of a thin layer or individual cellular elements.

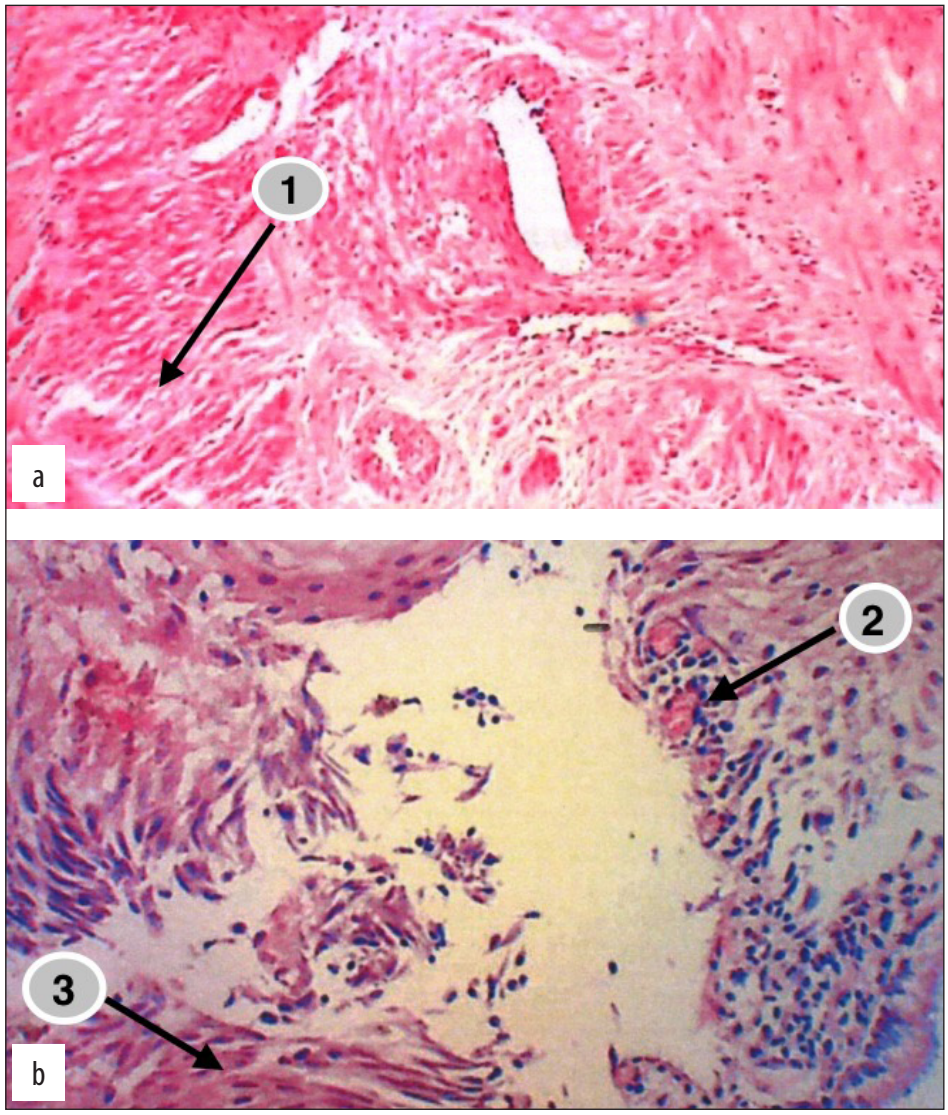

Fig. 6. a, b. Biopsy sample supravaginal part of the cervix with a violation of the morphological structure of the connective tissue in the form of an increase in the spaces between collagen fibers (1), hyperemia of the vessels of the connective tissue with the presence of foci of angiogenesis (2) and a significant number of smooth muscle fibers (3). Staining with hematoxylin and eosin. Enlargment: oculus 10, lens 20.

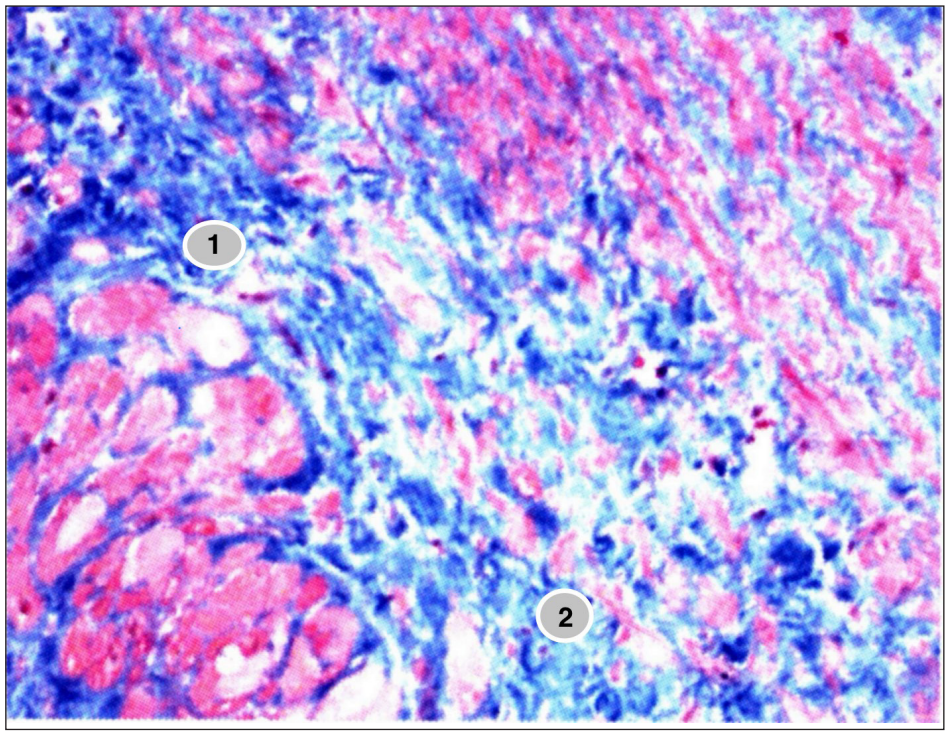

Fig. 7. Biopsy sample supravaginal part of the cervix from a multiparous patient . The histopathology shows a chaotic arrangement of connective tissue fibers with heterogeneous areas of hypochromia (1) and hyperchromia (2) and foci of degeneratively altered smooth muscle bundles. Staining according to Van Gieson and Masson. Enlargment: oculus 10, lens 20.

Smooth muscle bundles were separated by connective tissue fascia, where connective tissue elements predominated, creating a typical paravasal environment through which the functional activity of myocytes is ensured [10].

According to the results of the study, in the second group, both the cervix and the body of the uterus had the same echogenicity (Fig. 3).

Histomorphological data indicate a relative increase in the muscle component over the connective tissue component of collagen and elastic fibers, which predominated by 20-25% over smooth muscle bundles (Fig. 4).

In women of group III with echogenicity of the cervix less than the echogenicity of the uterine body (Fig. 5). on histological specimens. In the supravaginal part of the cervix, there is disorganization of the connective tissue with the presence of individual smooth muscle fibers, hyperemia of the connective tissue, and the presence of angiomatosis (Fig. 6).

In this case, the collagen tissue of the supravaginal part of the uterus, especially in multiparous patients, is stained heterogeneously with individual areas of hypo- and hyperchromia with the presence of foci of altered smooth muscle bundles (Fig. 7).

DISCUSSION

The results of our study indicate that in the supravaginal part of the cervix, when the echogenicity of the tissues of the cervix exceeds that of the body, the predominance of the muscular component over the connective tissue component is noted. In this case, the smooth muscle bundles are supported by connective tissue, which creates a typical paravasal environment between the muscle bundles, through which the functional activity of myocytes are ensured [10, 11].

In all women with the same echogenicity of the cervix relative to the body of the uterus or lower, disorganization of connective tissue was noted in histological preparations and dystrophic changes were observed in the cells of smooth muscle bundles, which changed the reflective activity of the echo signal by the structural elements of the cervix and body of the uterus and isthmus. The obtained data are consistent with the literature [11].

In some studies, there is evidence indicating that under conditions of chronic hypoxia, the processes of both collagenogenesis and lithogenesis are disrupted. Therefore, the disorganization of connective tissue and dystrophic changes in the cells of smooth muscle bundles that we have discovered, especially in multiparous patients, indicate the consequence of hypoxia in structural reorganization after traumatization of the lower uterine segment during childbirth.

In the literature there are some scientific works [11,12], which indicate that the intensity of collagen synthesis and the formation of collagen fibers occurs due to autoregulation of the processes of collagen synthesis and breakdown. This can be realized in two ways: pathological, when collagen fibers appear inside the cells in the cytoplasm of fibroblasts and myofibroblasts or by replacing damaged smooth muscle cells in bundles with connective tissue in case of impaired reparative processes [12], which is confirmed by histomorphological changes in histological specimens of multiparous women.

CONCLUSIONS

1. Comparative studies show that in cases of excess echogenicity of the cervix over the body of the uterus, pathomorphological changes in the supravaginal part of the cervix are not detected.
2. With the same or reduced echogenicity of the cervix compared to the body of the uterus, disorganization of connective tissue and dystrophic changes in the smooth muscle bundles of the supravaginal part of the cervix were observed in histological specimens.
3. A change in the ratio of echogenicity of the cervix to the body, which is closely related to the morphostructure of the isthmus of the uterus, can serve as one of the criteria for predicting the failure of the lower uterine segment in women.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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