Changes in ultrasound shear wave elastography properties of normal breast during menstrual cycle

P. Rzymski[1], A. Skórzewska[2], T. Opala[1]

[1]*Department of Mother's and Child's Heath, University of Medical Science Poznan, Gynecologic and Obstetrical University Hospital,*
[2]*Department of Radiology, University of Medical Science Poznan, Gynecologic and Obstetrical University Hospital, Poznan (Poland)*

Summary

Elastography is a novel technique capable of noninvasively assessing the elastic properties of breast tissue. Because the risk factors for breast cancer include hormonal status and proliferation, the aim of our study was to estimate the intensity of sonoelastographic changes during the menstrual cycle. *Methods:* Eight women aged 20-23 years with regular menstrual cycles underwent B-mode sonography and sonoelastography (ShearWave on Aixplorer, France) on days 3, 10, 17 and 24. *Results:* Mean values of glandular and fat tissue elasticity did not change statistically significantly during the menstrual cycle as well as glandular to fat tissue ratio. During almost the whole cycle differences between outer and inner quadrants in glandular and fat tissue were statistically significant. The lowest values of elasticity occurred on the 10^{th} day and the highest on the 24^{th} of the menstrual cycle. There were statistically significant differences in elasticity between inner and outer quadrants of both breasts close to day 3 and 17 of the menstrual cycle.

Key words: Elastography; Breast; Menstrual cycle; Ultrasound.

Introduction

Breast cancer is a great cause of concern worldwide. The risk factors for this cancer include hormonal status and its implications: proliferation. Many data support the concept that the elevated risk early in reproductive age may be because of higher rates of proliferation. The reduced risk occurs in early pregnancy, when breast tissue differentiates [1, 2].

The breast is an organ which undergoes many physiological changes dependent on age, hormonal status, menstrual cycle and many others. It is well detectable and correlated with physiologic changes in mammography or magnetic resonance imaging [3]. Results from studies that correlated viscoelastic properties of breast tissue and physiologic or cancer risk factors are inconsistent [4]. Over 50% of women experience it as feeling of swelling before menstruation, some of them as cyclic or acyclic mastalgia [5]. The use of hormonal contraception, age, and pregnancy are also very important for histological changes in the breast, like fibroglandular proliferation and apoptosis [1, 2]. Various hypotheses have been developed to explain the observed variation of breast volume and hydratation during the menstrual cycle. The same process occurs during pregnancy and to a lesser degree every menstrual period. Especially pregnancy causes an increase in the hyperplasia of epithelial cells, their differentiation and organization into ductales, and the disappearance of connective tissue. The reverse occurs when lactation is interrupted, epithelial cells disappear and connective tissue goes hyperplasic changes. It has been suggested that the increase in the breast volume and hyperplasia about a week before menstruation may be the result of an increase in cell number, cell size and cell secretion. Another possible mechanism consists of an increase in extracellular water and tissue perfusion (blood vessel enlargement) [5]. All the above mentioned mechanisms depend on each other (i.e., breast volume from proliferation) and are potentially detectable when using B-mode sonography with sonoelastography and color Doppler imaging [1, 5, 6].

Elastography, both measured in ultrasonic systems and by magnetic resonance imaging (MRI), are novel techniques capable of noninvasively assessing the elastic properties of tissue [7, 8]. The modulus of elasticity is the relationship between the applied pressure (tension) needed to achieve a relative change of length (extension) [9]. It is supposed to provide more information about tissue lesions and seems to be ideally designed for diagnosis and differentiation of malignant and benign tumors. The literature about histological changes in the breast is relatively extensive, but little is known about hormonal-dependent breast physiology seen by imaging techniques like elastography. Especially when considering direct measurements, which are offered by MRI or ultrasound imaging. Generally breast cancer tissue is harder than adjacent normal glandular tissue, and this property serves as the basis of palpation examination. The palpation by ultrasound, called sonoelastography is based on the same properties. During elastography it is assumed that major displacement of tissue occurs in the longitudinal direction during compression [10, 11]. The other possibility is to measure the displacement generated by shear wave, which has been newly described [12]. The shear wave seems to be very promising, because the examination is relatively simple, requires only additional time when examining with B-mode ultrasound and could be more cost-effective and less time consuming than MRI. We

Revised manuscript accepted for publication December 16, 2010

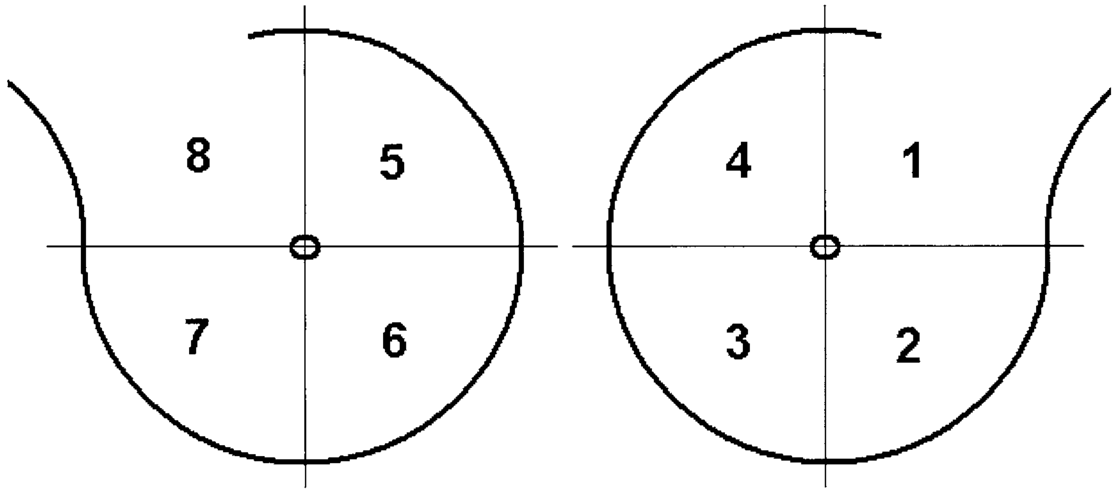

Figure 1. — Breast scans during the study.

tried as a part of planned more extensive research to estimate the intensity and importance of sonoelastographic changes during the menstrual cycle, which could be the right first step in understanding elastic properties.

Material and Methods

Eight healthy women aged 20-23 years with regular menstrual cycles every 28-30 days were invited for breast examination and sonoelastography measurements in our Department. The study was performed between November 2009 and January 2010. All patients had negative history concerning breast disease, all were nulliparous, not taking oral contraceptives and healthy. The examinations were scheduled for the third, tenth, 17^{th} and 24^{th} day of the menstrual cycle. All subjects filled in the questionnaire with general medical, obstetrical and breast history. They underwent B-mode breast sonography (Aixplorer Ultrasound System, SuperSonic Imagine SA, France), which yielded no abnormalities. The ultrasound examination as well as sonoelastography was performed by a gynecologist with seven years experience in breast ultrasound. The equipment enables normal ultrasound to be performed with a linear probe (15 MHz) and additionally real-time sonoelastography. The methodology consists of the generation of a remote radiation force by focused ultrasonic beams. Each pushing beam generates a remote vibration that results in the propagation of a transient shear wave. Several pushing beams transmitted at different depths generate a quasi-plane shear wave front which propagates through the whole imaging area. As a second part of the examination we divided the left and right breast into eight quadrants and acquired with elastography mode eight scans of both breasts in order as illustrated in Figure 1. Differences between inner and outer quadrants were calculated as the sum of scans 1,2,7 and 8 vs 3 to 6.

While acquiring a single scan the region of interest (ROI) was set to include subcutaneous fat at the top and margin of the pectoral muscle at the bottom. The best grayscale scan was used to identify glandular and fat tissue. All elastography scans included measurements with a 3 mm diameter Q-box (area of elasticity measurement in kPa) in glandular and fatty tissue. The chosen area was typical and representative for glandular and fatty tissue in grayscale ultrasound. Parameters included mean elasticity in Q-box, minimal and maximal elasticity in Q-box, and standard deviation (SD). One of the obtained scans is presented in Figure 2. From all eight patients 256 elastography scans were achieved from eight quadrants during the menstrual cycle. For analysis we calculated glandular to fatty tissue ratio and we also grouped breast quadrants into inner (scans 3,4,5 and 6) and outer (scans 1,2,7 and 8).

All data were stored in a Ms Excel calculation sheet (Microsoft Corp, USA) and analyzed with SigmaStat 3.1 (Jandel Corp, USA). For repeated measures of all data we used analysis of variance (ANOVA) after the normal distribution was confirmed by the Kolgomorov-Smirnoff test. Differences between glandular and fatty tissue on the same days of the menstrual cycle as well as in the whole material were analyzed with the paired t-Student test; p values less than 0.05 were considered significant. The study was approved by the local Bioethics committee at Poznań University of Medical Sciences and subjects gave informed written consent of participation in the study.

Results

We calculated the mean elasticity values of both breasts (quadrants 1 to 8) and the results are presented in Table 1. Mean values of glandular and fatty tissue did not change in a statistically significant manner during the menstrual cycle and the results are presented in Figure 2. The same refers to mean minimal and mean maximal values from all examinations, as well as glandular to fat-tissue ratio.

We also divided left and right breast into outer (scans 1,2,7 and 8) and inner quadrants (scans 3 to 6) and analyzed the whole material once again. There were no statistically significant changes during the menstrual cycle,

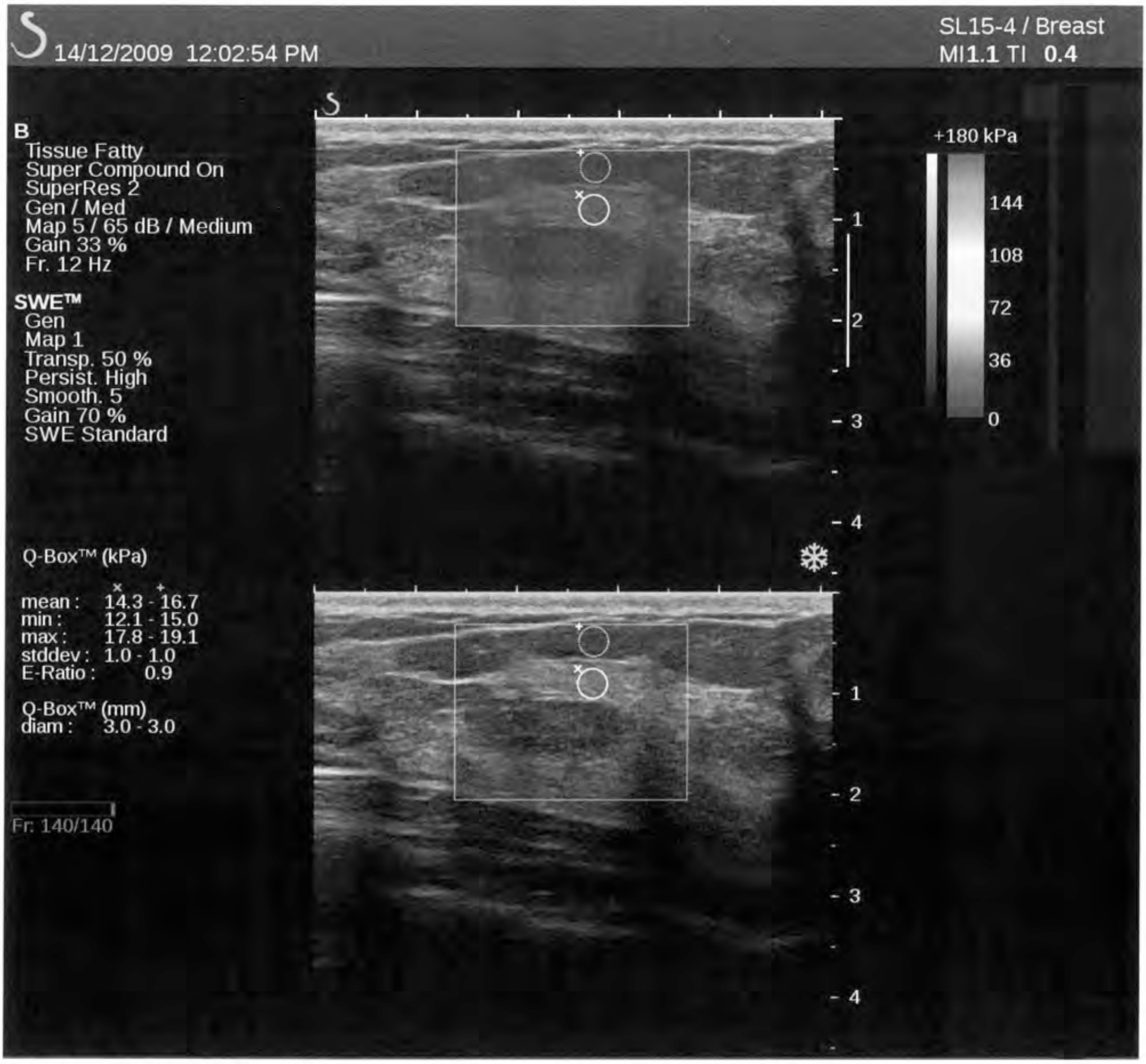

Figure 2. — Region of interest during measurement of breast sonoelasticity in one-quadrant scan.

but during almost the whole cycle differences between outer and inner quadrants in glandular and fatty tissue were statistically significant (Tables 2, 3, 4).

Discussion

The role of sonoelastography in diagnosis of benign and malignant tumors has been previously described [1, 8-12]. It has been proposed to use morphologic scoring of breast elasticity maps parallel to BI-RADS (Breast Imaging Reporting and Data System) classification. Many papers analyzed the possible use of the Matsumura elasticity scoring system in the differential diagnosis of breast tumors, with the power over 0.9 in area under the ROC curve and better sensitivity and specificity than B-mode ultrasound [7, 10]. In the major part of elastography studies the precise quantification of elasticity was not possible because the elasticity map represented relative values during freehand or somehow standardized breast compression [10, 11]. Using shear wave technology like in our study the exact quantification is possible. However little is known about other pathologic conditions and physiological processes [12]. In our opinion it is very important, because as many authors indicate, studies of elastography were set in referral centers with relatively few other than cancer patients [10, 11]. Additionally other properties of breast tissue are associated with diseased tissue, like water content, acoustic tissue scattering and density, and physiologic fluctuations [7]. The results of our examinations in normal breast tissue using supersonic shear imaging are similar to those described by Tanter *et al.* – in normal fat and glandular tissue a

Table 1. — *Analysis of changes in elasticity measured in both breasts (scans 1-8) during the menstrual cycle.*

Parameter	3rd day	10th day	17th day	24th day	ANOVA p
Glandular tissue mean elasticity (kPa)	8.41 ± 1.80	8.37 ± 2.28	8.62 ± 1.96	9.07 ± 3.37	p = 0.883
Glandular tissue mean elasticity (%)	100.0%	99.0%	103.8%	110.7%	p = 0.756
Glandular tissue min elasticity (kPa)	6.52 ± 1.51	6.60 ± 1.74	6.70 ± 1.56	7.26 ± 2.18	p = 0.787
Glandular tissue max elasticity (kPa)	10.36 ± 2.54	10.43 ± 3.01	10.81 ± 2.46	11.63 ±4.16	p = 0.714
Fat tissue mean elasticity (kPa)	8.12 ± 2.33	7.33 ± 2.56	8.01 ± 2.46	8.46± 3.29	p = 0.715
Fat tissue min elasticity (kPa)	6.05 ± 1.40	5.45 ± 1.74	6.03 ± 1.80	6.45 ± 3.31	p = 0.726
Fat tissue max elasticity (kPa)	10.73 ± 3.19	10.46 ± 3.58	11.31 ± 2.73	11.63 ± 4.72	p = 0.829
Glandular/Fat mean elasticity ratio	1.13 ± 0.17	1.27 ± 0.33	1.19 ± 0.28	1.23 ± 0.24	p = 0.372

Table 2. — *Analysis of changes in elasticity measured in outer quadrants (scans 1-2, 7-8) of both breasts during the menstrual cycle.*

Parameter	3rd day	10th day	17th day	24th day	ANOVA p
Glandular tissue mean elasticity (kPa)	7.35 ± 2.18	7.48 ± 2.85	7.17 ± 2.14	8.35 ± 3.38	p = 0.706
Glandular tissue min elasticity (kPa)	5.90 ± 2.12	5.84 ± 2.50	5.44 ± 1.71	6.79 ± 3.05	p = 0.524
Glandular tissue max elasticity (kPa)	8.98 ± 2.61	9.30 ± 3.37	9.11 ± 2.74	10.68 ± 3.99	p = 0.861
Fat tissue mean elasticity (kPa)	6.40 ± 2.18	6.17 ± 3.22	6.70 ± 2.05	7.12 ± 3.41	p = 0.851
Fat tissue min elasticity (kPa)	4.82 ± 1.49	4.61 ± 2.71	4.70 ± 1.40	5.43 ± 3.08	p = 0.831
Fat tissue max elasticity (kPa)	8.47 ± 31.8	9.46 ± 4.14	10.28 ± 3.14	9.61 ± 3.37	p = 0.656
Glandular/Fat mean elasticity ratio	1.25 ± 0.21	1.41 ± 0.59	1.29 ± 0.48	1.43 ± 0.31	p = 0.549

Table 3. — *Analysis of changes in elasticity measured in inner quadrants (scans 3-6) of both breasts during the menstrual cycle.*

Parameter	3rd day	10th day	17th day	24th day	ANOVA p
Glandular tissue mean elasticity (kPa)	9.48 ± 2.30	9.27 ± 2.58	10.07 ± 2.87	9.79 ± 4.20	p = 0.935
Glandular tissue min elasticity (kPa)	7.14 ± 1.78	7.36 ± 1.91	7.97 ± 2.31	7.73 ± 3.28	p = 0.865
Glandular tissue max elasticity (kPa)	11.74 ± 3.49	11.55 ± 3.44	12.50 ± 3.56	12.57 ± 5.33	p = 0.905
Fat tissue mean elasticity (kPa)	9.94 ± 3.76	8.48 ± 2.46	9.33 ± 3.27	9.79 ± 4.94	p = 0.684
Fat tissue min elasticity (kPa)	7.28 ± 2.26	6.30 ± 1.41	7.36 ± 2.68	7.47 ± 3.96	p = 0.699
Fat tissue max elasticity (kPa)	13.00 ± 4.66	11.47 ± 3.57	12.34 ± 4.24	13.65 ± 6.35	p = 0.671
Glandular/Fat mean elasticity ratio	1.06 ± 0.19	1.21 ± 0.28	1.16 ± 0.21	1.08 ± 0.22	p = 0.184

Table 4. — *Differences in mean elastic properties between outer (quadrants 1,2,7,8) and inner (quadrants 3-6) sides of breasts (values in Tables 2-3).*

Parameter	3rd day	10th day	17th day	24th day	ANOVA p
Glandular tissue mean elasticity (kPa) inner quadrants vs outer quadrants	p = 0.059	p = 0.13	p = 0.038*	p = 0.28	overall: p < 0.001*
Fat tissue mean elasticity (kPa) inner quadrants vs outer quadrants	p = 0.041*	p = 0.037*	p = 0.017*	p = 0.052	overall: p < 0.001*
Inner quadrants mean elasticity (kPa) Glandular tissue vs fat tissue	p = 0.55	p = 0.30	p = 0.089	p = 0.99	overall: p = 0.372
Outer quadrants mean elasticity (kPa) Glandular tissue vs fat tissue	p = 0.089	p = 0.088	p = 0.603	p = 0.012*	overall: p = 0.003*

* statistically significant.

Young's modulus ranged between 3kPa and 45 kPa. They also noticed smaller values of fatty tissue than glandular regions, but the difference in our study was smaller [12].

We observed a tendency in glandular tissue to decrease the elasticity between the 3rd and 10th day of the menstrual cycle, with successive increase in the next examinations. These small fluctuations were statistically insignificant, but are exactly imitate the significant pathologic changes observed by Going *et al.* [1]. They observed the same sinusoid variation, with the peak values of proliferation of glandular tissue on day 26. The minimal values of thymidine labeling index (TLI) fell on days 7 to 10. The same authors observed decreasing proliferative activity with age. The same team noticed that peak values of mitotic activity in multiparous women was close to the 26th day of the menstrual cycle, whereas in nulliparous subjects peak values were observed nearly on the 21st day. We also observed peak values of glandular tissue in central quadrants on day 17 in our exclusively nulliparous women. Our results are also in concordance with those by Potten *et al.* They observed the mitotic index and labeled cells to be the highest on day 20.8 of the menstrual cycle

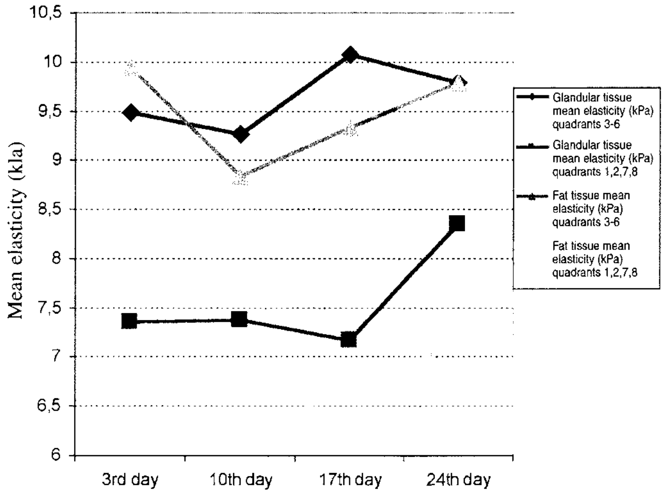

Figure 3. — Changes in mean elasticity during the menstrual cycle.

and the lowest on day 6.8. The changes were statistically significant when analyzed with ANOVA [2]. In another study of breast elasticity with MRI Lorenzen *et al.* observed five patients on a one-week basis. The tendency pattern was almost identical in all patients. They indicated decreasing elasticity on the 5th day of the menstrual cycle in fibroglandular tissue and increase after two weeks with the maximum values between day 11 and 23 (35% increase). Fatty tissue examination revealed only slight fluctuations [13]. All these data support, in our opinion, the need to perform ultrasound elastography examination within the late follicular phase of the menstrual cycle because the lowest elasticity values should sharpen the eventual differences, when a breast lesion is present.

In another interesting study estimating the changes of breast volume in MRI, Hussain *et al.* noticed the variation in average volume between the left and right breast. The breast volume also exhibited the same variation during the menstrual cycle, which is typical for proliferation activity. The minimum volume changed cyclically with a minimum around day 11 (just before ovulation which was monitored), and a maximum around day 20 (premenstrual phase). These fluctuations were respectively -5.5% than the volume during menses and +8.1% during the premenstrual days. The overall changes reached 13.6% [5]. Similar results, but not calculated, were also depicted in other papers [1, 2]. In our research fluctuations in breast elasticity did not exceed 11.8% and did not reach statistical significance. This could be due to analyses in raw data (not transformed) and a not numerous study group. However, interestingly, the insignificant tendency is consistent with other research [1, 2, 5]. Soman *et al.* and Fowler *et al.* reported that relative to menses, parenchymal water content and breast volume achieve minimal values between days 6 and 15, and the maximum after day 25 [14, 15]. Fowler *et al.* also estimated the volume of adipose tissue that decreased rather than increased during the menstrual cycle [14]. In our study adipose tissue changes were uncharacteristic.

Summarizing, the arrival of new shear wave technology, which is quantitative and enables precise quantification, requires also newly designed studies to obtain information about physiologic processes like aging, hormonal status, reproductive events, etc. This method could reach well known morphologic elasticity scoring thus adding new possibilities of diagnosis and differentiation. The qualitative evaluation could be supplemented with quantitative examination.

Conclusions

The lowest values of elasticity measured by shear wave ultrasound imaging during the menstrual cycle occurred on the 10th day and the highest on the 24th. However the differences were statistically insignificant.

There were statistically significant differences in elasticity measured by ultrasound between inner and outer quadrants of both breasts close to day 3 and 17 of the menstrual cycle.

References

[1] Going J.J., Anderson T.J., Battersby S., Macintyre C.C.A.: "Proliferative and secretory activity in human breast during natural and artificial menstrual cycle". *Am. J. Pathol.*, 1988, *130,* 193.

[2] Potten C.S., Watson R.J., Wiliams G.T., Tickle S., Roberts S.A., Harris M., Howell A.: "The effect of age and menstrual cycle upon proliferative activity of the normal human breast". *Br. J. Cancer,* 1988, *58,* 163.

[3] Boyd N., Martin L., Chavez S., Gunasekara A., Sellah A., Melnichouk O. *et al.*: "Breast-tissue composition and other risk factors for breast cancer in young women: a cross-sectional study". *Lancet Oncol.*, 2009, *10,* 596.

[4] Rzymski P., Skórzewska A., Skibińska-Zielińska M., Opala T.: "Factors influencing breast elasticity measured by the ultrasound Shear Wave elastography - preliminary results". *Arch. Med. Sci.*, 2010, *7,* 127.

[5] Hussain Z., Roberts N., Whitehouse G.H., Garcia-Finana M., Percy D.: "Estimation of breast volume and its variation during the menstrual cycle using MRI and stereology". *Br. J. Radiol.*, 1999, *72,* 236.

[6] Yakut Z.I., Kafali H., Karaoglanoglu M., Koktener A., Duvan C.I.: "A New radiological approach to cyclic mastalgia: venous Doppler ultrasound". *The Breast,* 2009, *18,* 123.

[7] Konofagou E.E.: "Quo vadis elasticity imaging?". *Ultrasonics,* 2004, *42,* 331.

[8] Sinkus R., Tanter M., Xydaes T., Catheline S., Bercoff J., Fink M.: "Viscoelastic shear properties of in vivo breast lesions measuered by MR elastography". *Magnetic Res. Imag.*, 2005, *23,* 159.

[9] Thomas A., Fischer T., Frey H., Ohlinger R., Grunwald S., Blohmer J.U. *et al.*: "Real-time elastography - an advanced method of ultrasound: first results in 108 patients with breast lesions". *Ultrasound Obstet. Gynecol.*, 2006, *28,* 335.

[10] Itoh A., Ueno E., Tohno E., Kamma H., Takahashi H., Shiina T. *et al.*: "Breast disease: clinical application of US elastography for diagnosis". *Radiology,* 2006, *239,* 341.

[11] Hiltawsky K.M., Kruger M., Starke C., Heuser L., Ermert H., Arne J.: "Freehand ultrasound elastography of breast lesions: clinical results". *Ultrasound Med. Biol.*, 2001, *27,* 1461.

[12] Tanter M., Bercoff J., Athanasiou A., Deffieux T., Gennisson J.L., Montaldo G. *et al.*: "Quantitative assessment of breast lesion viscoelasticity: initial clinical results using supersonic shear imaging". *Ultrasound Med. Biol.*, 2008, *9,* 1373.

[13] Lorenzen J., Sinkus R., Biesterfeldt M., Adam C.: "Menstrual-cycle dependence of breat elasticity: estimation with magnetic resonance elastography of breat tissue durnig the menstrual cycle". *Invest. Radiol.*, 2003, *38*, 236.
[14] Folwer P.A., Casey C.E., Cameron G.G., Foster M.A., Knight C.H.: "Cyclic changes in composition and volume of the breast during menstrual cycle measured by magnetic resonance imaging". *Br. J. Obstet. Gynaecol.*, 1990, *97*, 595.
[15] Soman S.D., Joseph K.T., Raut S.J., Mulay C.D., Parameshwaran M., Pandy V.K.: "Studies on major-trace element content in human tissues". *Health Phys.*, 1970, *19*, 641.

Address reprint requests to:
P. RZYMSKI, M.D, Ph.D.
Department of Mother's and Child's Heath
Gynecologic and Obstetrical University Hospital
Polna St 33, 60-535 (Poland)
e-mail: parzymsk@gpsk.am.poznan.pl

23rd Conference of the Society

Medical Innovation and Technology

Tel Aviv, Israel - September 13-16, 2011

Target Conferences: Tel. +972(3)5175150 - Fax +972(3)5175155
E-mail: smit2011@targetconf.com - Website: www.smit2011.org

Free of charge