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Original Research

Breast changes in pregnancy and lactation observed by ultrasonography

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Summary

Purpose of Investigation: To assess the ultrasound aspects of breasts and laser Doppler flow measurements of the internal mammary arteries (IMA) in pregnant, lactating, and non-pregnant (control) women. *Materials and Methods:* A cross-sectional observation study of 102 women, divided into three groups: control (CG), third trimester (G3), and lactation group (LG). The study variables were skin, subcutaneous adipose tissue, fibroglandular tissue, retromammary adipose tissue thickness, duct diameter, and pulsatility (PI) and resistance indices (RI) of the internal mammary arteries. Statistical analysis calculated the means and standard deviations, using two models Multivariate Analysis of Variance (MANOVA) models to assess the effect of groups on the mean values found and adjusted ANOVA models for individual means. The Tukey-Kramer multiple comparisons test was used to analyze intergroup. *Results:* There was no intergroup age difference (mean = 27 ± 4.76 years). A significant difference was observed between the G3/LG and the CG in terms of skin ($p = 0.001$), fibroglandular tissue thickness, duct diameter, and laser Doppler flow measurements of the IMA (all three with $p < 0.001$) and subcutaneous adipose tissue ($p = 0.045$). *Conclusion:* This study showed alterations in skin, subcutaneous adipose tissue, fibroglandular tissue, and duct diameter measurements, with a difference between pregnant/lactating women and the non-pregnant controls.

Key words: Pregnancy; Lactation; Breast ultrasound; Laser Doppler flowmetry.

Introduction

During pregnancy and breastfeeding, breasts undergo important physiological changes that are not fully known, but attributed to hormonal alterations that lead to vascular and lobular hyperplasia [1]. Increased serum estradiol, progesterone, and prolactin levels are primarily responsible for these changes, which occur in the first trimester of pregnancy [2].

The influence of estrogen in the first trimester results in the proliferation and branching of the ductal system, along with lobuloalveolar growth (mammogenesis), accompanied by an increase in vascularization and blood flow, as well as involution of fibro-fatty stroma [2, 3]. As pregnancy progresses, lobuloalveolar and ductal differentiation occurs [4], whereas progesterone induces continuous involution of fibro-fatty stroma [2, 4].

The action of prolactin, responsible for stimulating lactogenesis and galactopoiesis, is inhibited by high levels of estrogen and progesterone during pregnancy, which impedes full milk production. At the end of pregnancy, colostrum production increases in the alveolar cells [2, 3]. After delivery, lactation is stimulated and maintained by the end of hormone actions antagonistic to prolactin [2], via the continuous release of this hormone and oxytocin during nipple sucking [2, 3].

It is believed that mammary blood flow doubles during pregnancy [5] and is processed primarily by the branches of the internal mammary arteries (IMA) and the lateral thoracic artery (LTA), which supply 60-70% and 30% of mammary blood flow, respectively [5, 6]. However, the relationship between blood flow and milk production is not well understood, given that some animal studies show a positive correlation and others do not [5]. In humans there is insufficient data to establish this association [5, 7].

The physiological changes determined by pregnancy, such as an increase in volume, swelling, and hypernodularity [7], may hinder the diagnosis of some diseases such as cancer [4, 8, 9].

For an accurate diagnosis, imaging methods are indispensable in most breast diseases. Ultrasonography [7, 8, 10-14] has a sensitivity between 86.7% and 100% [4, 15], higher than the other methods [14] and, along with MRI [13], is the most appropriate to assess breast changes during pregnancy and lactation [13]. Although these methods do not increase the risk of fetal damage, it is recommended they be used with caution [13].

Despite the importance of the issue, the number of stud-

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ies on physiological breast changes during the pregnancy-postpartum cycle remains scarce [6, 16] and the results are inconsistent [10]. Moreover, studies on breasts during the pregnancy-postpartum cycle almost always focus on concomitant diseases [2, 4, 9, 17].

As described above, pregnancy and lactation determine the physiological and functional changes in breasts. Accordingly, the aim of this study was to assess breast ultrasound characteristics and laser Doppler flow measurements of the internal mammary arteries (IMA) in pregnant, breastfeeding, and non-pregnant women using breast ultrasonography and laser Doppler flow measurements of the internal mammary arteries.

Materials and Methods

This is a cross-sectional observational study conducted between August 2013 and August 2016. The study was approved by the Ethics Committee of the Federal University of Rio Grande do Norte (UFRN) under number 369.467 – CAAE: 17598813.4.0000.5292. All the participants gave their informed consent.

The study subjects were divided into three groups: control group (CG), composed of non-pregnant women, third trimester group (G3), and lactation group (LG). Included in the study were clinically normal women, aged between 19 and 35 years. The CG were in the middle follicular phase (7^{th} day of the menstrual cycle), the G3 in the third trimester of pregnancy, and the LG between the 10^{th} and 60^{th} day of lactation. Excluded were those with breast, endocrine, liver, kidney, or cardiovascular diseases, in addition to obese individuals and those who had undergone previous breast surgery. In the control (CG) and lactation (LG) groups, women who were taking hormonal medicine were also excluded. The exclusion of obese individuals was based on a body mass index (BMI > 30), but for the third trimester pregnant women (G3) this diagnosis was based on the table proposed by Atalah Sammur *et al.* [18].

The control (CG), third trimester (G3), and lactation (LG) groups are the independent variables. The measures of skin, subcutaneous adipose tissue, fibroglandular tissue, retromammary adipose tissue, duct diameter, as well as pulsatility index (PI) and resistance index (RI) of the internal mammary arteries (IMA), were considered dependent variables.

The women were submitted to breast ultrasonography and laser Doppler flow measurements of the internal mammary arteries by the same examiner, with a LOGIQ ultrasound machine in two-dimensional mode, using a linear probe at a frequency of 7- to 10-MHz, and adjusting the configurations to optimize the image and laser Doppler spectrum. The examination occurred at constant ambient temperature of 25 °C, with the woman in dorsal decubitus and hands behind her head, and the breasts examined from the parasternal line to the middle axillary line and from the clavicle to the inflammatory sulcus in the transverse, longitudinal, radial (transducer in a clockwise transverse and oblique cut) and antiradial planes (transducer in a counterclockwise transverse and oblique cut), as recommended in the literature [19]. The measures were taken in a longitudinal cut, using the average of three measurements in the upper quadrants and avoiding the inclusion of segments containing intermingled fat in the measure of fibroglandular tissue.

In this study, only the internal mammary arteries (IMA) were investigated since the lateral thoracic arteries (LTA) were absent in 18% of the women [17]. Internal mammary arteries (IMA) were identified based on a documented technique, positioning the transducer in the transverse plane, from the sternum, between the second and sixth intercostal spaces [16]. The lactating women were examined before breastfeeding or mammary expression, as recommended in the literature [4]. To test the reproducibility of the technique after assessment, 32 women were re-evaluated on the same day. Only the right breast was studied because literature data showed no significant differences between the breasts of a same woman, assessed at the same time [15, 19].

The statistical software program used was SPSS version 18. In statistical analysis, the results were presented as mean and standard deviation. To assess the effects of the groups (CG, G3, and LG) on the dependent variables (measures of breast tissues, duct diameter and PI and RI), MANOVA (Wilks' test) models were adjusted. Next, univariate ANOVA models were used for each dependent variable, given the differences between profiles. The Tukey-Kramer multiple comparisons test was applied when there was an intergroup difference in order to characterize each group. A 5% significance level was set for all the tests.

Results

A total of 102 women took part in the study: CG (n = 39), G3 (n = 30), and LG (n = 33). The mean age of the groups was 28.095 ± 4.93 (CG), 25.83 ± 4.79 (G3), and 26.030 ± 4.62 (LG) years, with an overall average of 27 ± 4.76 years. Of these, 32.7% were nulliparous.

Data analysis showed a significant difference between the groups (G3, LG, and CG) in relation to measures of skin and fibroglandular tissue thickness and duct diameter ($p < 0.001$), as well as subcutaneous adipose tissue thickness ($p = 0.045$) (Table 1). However, there was no significant difference between the three groups with respect to retromammary adipose tissue (Table 1).

The mean skin thickness was higher in the LG, followed by the G3 and CG. There was a significant difference between the CG and the other two groups, but not between the G3 and LG (Figure 1). By contrast, analysis of subcutaneous adipose tissue revealed that LG measurements were lower than those in the G3 (Figure 2). These differences were significant when the CG was compared with the other two groups, which, in turn, exhibited no significant intergroup differences.

With respect to measures of fibroglandular tissue (Figure 2) and duct diameter (Figure 1), it was found that the LG displayed higher values than those of the G3, which, in turn, were higher than those of the CG. The G3 and LG showed no significant intergroup differences, but were significantly different from the CG. Data analysis showed a significant difference between the groups (G3, LG and CG) in relation to measures of PI and RI ($p < 0.001$) (Table 2).

The laser Doppler flow index was higher in the CG group when compared to the G3 and LG groups, however there was no difference between the latter groups (Figure 3).

Table 1. — *Mean and standard deviation of the tissue thickness according to the groups.*

Groups		Skin		Subcutaneous fat		Fibroglandular		Ducts		Retromammary fat	
	N	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
CG	39	0.145	0.035	0.597	0.212	0.978	0.297	0.152	0.038	0.418	0.139
G3	30	0.171	0.028	0.716	0.273	1.473	0.338	0.294	0.045	0.443	0.113
LG	33	0.172	0.040	0.578	0.224	1.554	0.370	0.309	0.053	0.429	0.134
p-value*		0.001		0.045		< 0.001		< 0.001		0.741	

One Way ANOVA Test - comparing the means between groups.

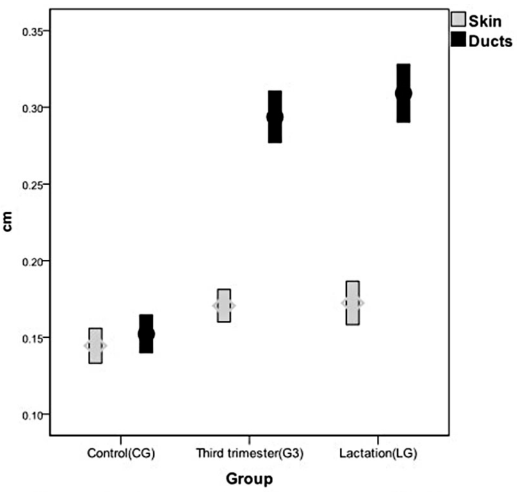

Figure 1. — Means and confidence intervals of skin and duct thickness.

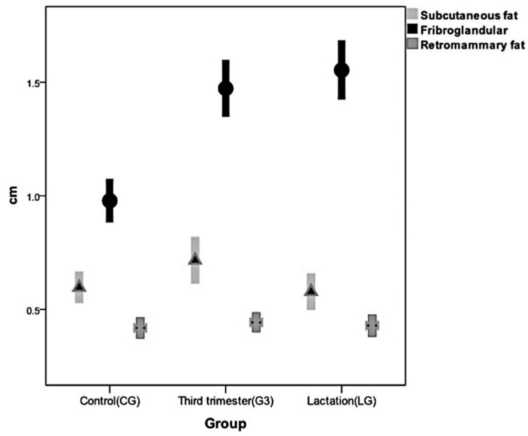

Figure 2. — Means and confidence intervals of subcutaneous, fibroglandular, and retromammary fat thicknesses.

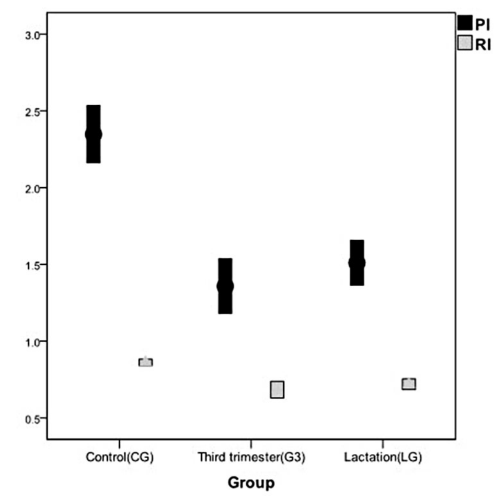

Figure 3. — Mean and confidence intervals of PI and RI according to group.

Table 2. — *Mean and standard deviation of the hermodynamic indices of internal mammary arteries according to group.*

Groups	N	PI		RI	
		Mean	Std. deviation	Mean	Std. deviation
Control (CG)	37	2.348	0.559	0.862	0.065
Third trimester (G3)	30	1.358	0.477	0.684	0.144
Lactation (LG)	33	1.51	0.411	0.72	0.099
p-value			< 0.001		< 0.001

Discussion

Ultrasound assessment of the breasts during pregnancy and lactation is a challenge for the doctor, largely due to the several physiological changes that make the examination more difficult, hindering a suitable interpretation of the findings [1, 2, 4] and possibly delaying the diagnosis of cancer [2].

Ultrasonography was used in the present investigation because it allows the study of small structures, such as the ductal and lobular system [5, 18]. There is also a need to better understand the characteristics of the image in the pregnancy-postpartum cycle [11, 20-22], as a way to facilitate diagnoses and establish an adequate approach for patients [4].

The composition of breast tissues has been the focus of a number of studies and recent data show that the amount of fibroglandular tissue in young women is influenced by prenatal factors, which may increase breast density and the risk of cancer in adulthood [23]. During pregnancy, these tissues undergo physiological changes to the detriment of endocrine, metabolic, and immunological diagnosis [20], increasing density and hindering diagnosis of the disease [4, 9].

With respect to skin, the literature reports that a number of changes occur, such as swelling, in 90% of pregnant women [24, 25]. In agreement with the literature, the present study revealed that the skin underwent important changes in the pregnancy-postpartum cycle, in terms of increased thickness.

In relation to subcutaneous adipose tissue, it is believed that it involutes concomitantly with ductal proliferation and to a lesser extent with lobular growth, which are determined by estrogen action in the first trimester [3]. As reported in the literature, this study found lower measures of subcutaneous adipose tissue in the LG compared to the G3. However, a cross-sectional study with breastfeeding women revealed significant differences between measures of adipose and fibroglandular tissue when the breasts of a same woman were compared, a finding also observed between different women [16].

As occurred in the subcutaneous adipose tissue, there was also a reduction in the measures of retromammary adipose tissue in the G3 compared to the LG, but this difference was not significant, even when compared to the CG.

In relation to fibroglandular tissue and duct diameter, higher measures were obtained in the LG than in the G3, both exhibiting larger values than those of the CG. On the other hand, the opposite occurred with subcutaneous adipose tissue. These data agree with the literature, where it is reported that during pregnancy and lactation, fibroglandular tissue growth is concomitant with the involution of fibroadipose tissue [6]. This growth intensifies from the second to the third trimester, due to the influence of progesterone [2, 3], although there are also reports of earlier occurrence, in the 22nd week of pregnancy [6].

Duct diameter increases in the pregnancy-postpartum cycle and is higher in lactation than during pregnancy [16], although non-significant ductal growth has also been observed during this period [6]. In the present study, the diameters recorded were 0.15, 0.29 and 0.30 mm, respectively, for the CG, G3 and LG, similar to the values reported in the literature, with a mean of 2.0 ± 0.8 mm [15].

The influence of estrogen during the first trimester of pregnancy results in intensified glandular vascularization [5], variation in mammary blood flow of different women [5], but no such variation when a same woman is assessed in different phases [5]. The number of studies is insufficient and it remains to be determined whether an increase in mammary blood flow interferes with lactation, as well as its percentage growth during pregnancy [5]. Despite the larger number of animal studies, data on the association with milk production have not been fully elucidated, since some of these obtained controversial results [5].

In the present study the PI and RI indices exhibited lower values in the G3, compared with the other groups. Literature data, where three phases of pregnancy were compared, report a decline in these values over pregnancy [19]. However, no studies assessing the pulsatility and resistance indices of IMA during lactation were found.

The results of the present study made it possible to use the ultrasound measures of breast tissues and laser Doppler flow measurements of the internal mammary arteries (IMA) to characterize the physiological changes in the third semester of pregnancy and lactation, compared with those of non-pregnant women.

These findings led the present authors to conclude that measures of skin, fibroglandular tissue, duct diameter, and PI and RI of IMA are influenced by the pregnancy-postpartum cycle, with lower values in the third trimester of pregnancy when compared to the lactation period. Measures of subcutaneous adipose tissue, on the other hand, exhibited opposite behavior, that is, lower lactation measures than at the end of pregnancy. These data allow greater understanding of physiological changes in the third trimester of pregnancy and lactation, serving as comparison parameters for women in the pregnancy-postpartum cycle undergoing breast ultrasound.

For clinical applicability of a study using this approach, it is suggested that the ultrasound and laser Doppler flow measurement aspects investigated be related to milk production in breastfeeding women.

References

[1] Boisserie-Lacroix M., Dos Santos E., Belléannée G., Bouzgarrou M., Galtier J-B., Trillaud H.: "Diagnostic difficulties in the pregnant woman". *Imagerie de la Femme*, 2004, *14,*145. [In French]

[2] Yu J.H., Kim M.J., Cho H., Liu H.J., Han S.J., Ahn T.G.: "Breast diseases during pregnancy and lactation". *Obstet. Gynecol. Sci*., 2013, *56,*143.

[3] Canoy J.M., Mithell G.S., Unold D., Miller V.: "A radiologic review of common breast disorders in pregnancy and the perinatal period". *Semin Ultrasound CT MR*., 2012, *33*, 78.

[4] Joshi S., Dialani V., Marotti J., Mehta T.S., Sianetz P.: "Breast disease in the pregnant and lactating patient: radiological-pathological correlation". *Insights Imaging*, 2013, *4,* 527.

[5] Gedds D., Aljazaf K.M., Kent J.C., Prime D.K., Spatz D.L., Garbin C.P., *et al.*: "Blood Flow characteristics of the Human Lactating Breast". *J. Hum. Lact*., 2012, *28,* 145..

[6] Geddes D.: "Inside the lactating breast: the latest anatomy research". *J. Midwives Healt.,* 2007, *52,* 556.

[7] Vashi R., Hooley R., Butler R., Geisel J., Philpotts L.: "Breast Imaging of the Pregnant and Lactating Patient: Imaging Modalities and Pregnancy-Associated Breast Cancer". *Am. J Roentgenol*., 2013, *200*, 321.

[8] Sebate J.M., Clotet M., Torrubia S., Gomez E.A., Guerrero R., De las Heras P., Lerma E.: "Radiologic evaluation of breast related to pregnancy and lactation". *Radiographics,* 2007, 27*,* 101.

[9] Langer A., Mohallem M., Chérel P.: "Pregnancy associated breast cancer: A review of the literature". *Imagerie de la femme*, 2013, *23*, 116. [In French]

[10] Geddes D.T.: "Ultrasound imaging of the lactating breast: methodology and application". *Int. Breastfeed J*., 2009, *4*, 4.

[11] Tomoyuki O., Okamoto K., Kanemaki Y., Tsujimoto F., Nakajima

Y., Fukuda M., Suka M.: ”Use of ultrasonography as an alternative modality as a first-line examination in detecting breast cancer in selected patients”. *Clin. Breast Cancer*, 2007, *7,* 624.

[12] Taylor D., Lazberger J., Ives A., Wylie E., Saunders C.: “Reducing delay in the diagnosis of pregnancy-associated breast cancer: how imaging can help us”. *J. Med. Imaging Radiat. Oncol.*, 2011, *55,* 33.

[13] Copel J., El-Sayed Y., Phillips Heine R., Wharton K.R.: “Guidelines for diagnostic imaging during pregnancy and lactation. Committee Opinion no 656”. American College of Obstetricians and Gynechologists”. *Obstet. Gynecol.*, 2016, *127*, e75.

[14] Lee S., Hartman H., Kuzmiak C., Crosby K.: “Management of breast symptoms in the pregnant and lactating patient”. *Curr. Obstet. Gynecol Rep*., 2013*, 2,* 53.

[15] Ezeonu P.O., Ajah L.O., Onoh R.C., Lawani L.O., Enemuo V.C., Agwu U.M.: “Evaluation of clinical breast examination and breast ultrasonography among pregnant women in Abakaliki, Nigeria”. *Onco. Targets Ther.*, 2015, *13,* 1025.

[16] Ramsay D.T., Kent J.C., Hartman R.A., Hartman P.E.: “Anatomy of the lactating human breast redefined with ultrasound imagining”. *J. Anat*., 2005, *206,* 523.

[17] Ulery M., Carter L., MCfarlin B.L., Giurgescu C.: “Pregnancy-associated breast cancer: significance of early detectetion”. *J. Midwifery Womens Health,* 2009, *54*, 357.

[18] Atalah-Samur E., Castillo-L.C., Castro-Santoro R., Aldea-P.A.: “Proposal of a new standard for the nutritional assessment of pregnant women”. *Ver. Méd. Chile*, 1997, *125,*1429. [In Spanish]

[19] Holanda A.A.R., Gonçalves A.K.S., Maranhão T.M.O.: “Breast ultrasonographic features and internal mammary artery hemodynamic indexes during normal pregnancy”. *Rev. Bras. Ginecol. Obstet*., 2015, *37,* 434. [In Portuguese]

[20] Zerouali A., Zaraa I., Trojjet S., El Euch D., Azeiez M.I., Mokni M., *et al.*: “Physiologic skin changes in pregnancy”. *Presse Med*., 2011, *40,* 17. [In French]

[21] Athanasiou A., Tardivon A., Ollivier L., Thibault F., El Khoury C., Neuenschwander S.: “How to optimize ultrasound”. *Eur. J. Radiol*., 2009, *69*, 6.

[22] Robbins J., Jeffries D., Roubidoux M., Helvie M.: “Accuracy of diagnostic mammography and breast ultrasound during pregnancy and lactation”. *Am. J. Roentgenol*., 2011, *196,* 716.

[23] Denholm R., De Stavola B., Hipwell J.D., Doran S.J., Busana M.C., Eng A., *et al.*: “Pre-natal exposures and breast tissue composition: findings from a British pre-birth cohort of young women and a systematic review”. *Breast Cancer Res.,* 2016, *18*, 102.

[24] Kar S., Krishnan A., Shivkumar P.: “Pregnancy and skin”. *J. Obstet Gynecol. India*. 2012, *62*, 268.

[25] Vora R.V., Gupta R., Mehta M.J., Chaudhari A.H., Pilani A.P., Patel N.: “Pregnancy and skin”. *J. Family Med. Prim. Care,* 2014, *3*, 318.

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