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Shear-wave elastography evaluation of adrenal glands in healthy newborns: a preliminary study

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SUMMARY

OBJECTIVES: Establishing standard shear-wave elastography (SWE) values for healthy newborns can help distinguish normal conditions of the adrenal gland (AG) from pathological conditions. We aimed to establish a reference data set for AG stiffness values using SWE in healthy newborns.

METHODS: The quantitative stiffness of the AG was measured in the coronal plane in kilopascal (kPa). The quantitative descriptive statistics were presented as mean with standard deviation and median with range. The relationship between the quantitative variables was calculated using "Spearman's rank correlation coefficient test." The intraclass correlation coefficient (ICC) test was used to analyze intraobserver reliability. A p-value <0.05 was considered statistically significant.

RESULTS: A total of 120 AGs of 60 healthy newborns (30 females and 30 males) was examined. The mean stiffness values of the right AG for the first and second visits were 7.51±2.45 and 7.54±2.49 kPa, respectively, and those of the left AG for the first and second visits were 7.60±2.03 and 7.42±1.97 kPa, respectively. There was no statistically significant difference between the mean values of adrenal stiffness and the length and width of AG and weight, height, and age (p>0.05). The ICC values for mean stiffness values of each AG were >0.80–0.90, indicating good intraobserver agreement.

CONCLUSIONS: This study is the first SWE study to evaluate the AG in healthy newborns. Our study's data can be used as a reference for future research.

KEYWORDS: Adrenal gland. Newborn. Reference data. Sonoelastography. Stiffness.

INTRODUCTION

Adrenal glands (AGs) are organs with an endocrine function that are located retroperitoneally in the abdomen. Unlike adults, the AG is easier to examine in newborns due to its large size and low amount of retroperitoneal fat. With the introduction of ultrasound (US), several studies have researched the sonographic appearance and measurement of the typical AG in neonates[1-4]. The AG size is a harbinger of preterm labor in fetal life and a predictor of postpartum glucocorticoid-responsive circulatory collapse in neonates[5-7]. The AGs may show involvement secondary to diseases such as bleeding, hyperplasia, and tumor in the newborn, as well as due to storage diseases such as Wolman's disease[8,9].

The stiffness of tissues can be measured quantitatively using the shear-wave elastography (SWE) technique. With the stiffness changes in the tissues, the SWE can help diagnose diseases; however, to compare with pathological tissues, normal values must first be determined. There exists no

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research on the normal stiffness of the AG in the literature. In this study, we aimed to determine normal values of adrenal stiffness in term newborns and their relationship with age, height, and weight.

METHODS

Study population and design

A total of 60 healthy newborns were included in this prospective study conducted between October and December 2020. An SWE for the right AG (RAG) and left AG (LAG) was performed on newborns between 0 and 28 days who came for routine control US. Babies with adrenal thickening, difficult labor history, and abnormal metabolic laboratory parameters were excluded from this study. In addition, crying or very mobile babies could not be included in this study, since only respiratory movements were accepted during the SWE examination. Premature babies were included in this study, considering their corrected ages. All subjects were noted for age in days, gender, height, and weight. This study was approved by the Local Ethics Committee and complied with the Helsinki Declaration (2019-1901). Informed consent was obtained from parents of newborns before the SWE examinations.

US and SWE imaging

All US and SWE examinations were performed via a digital US device (LOGIQ P9, GE Healthcare, Chicago, IL, USA) and a 9-MHz frequency linear transducer. This study involved a single observer (IA with 11 years of experience in abdominal radiology). The examinations were first started using the grayscale US. Both AGs were evaluated for mass, contour irregularity, hyperplasia, and echogenicity abnormality. The length of the AG was defined as the maximum cephalocaudal dimension. The width was defined as the maximum thickness of one of the limbs. Both AGs were observed as triangular structures near the superior and medial sides of the kidneys. The grayscale US and SWE examinations were performed with the same probe in the same session. In the meantime, care was taken that the baby is as immobile as possible. Images were retaken until they were acquired without artifacts. The evaluation of the stiffness of both AGs was also performed in the coronal plane (Figure 1). A 2–4 mm region of interest was placed in both AGs with minimal pressure on the skin to avoid external compression. The stiffness measurements were obtained in kilopascal (kPa). The examiner assessed the adrenal stiffness values five times and obtained the median of these consecutive measurements on the same SWE images in kPa. All subjects were examined consecutively

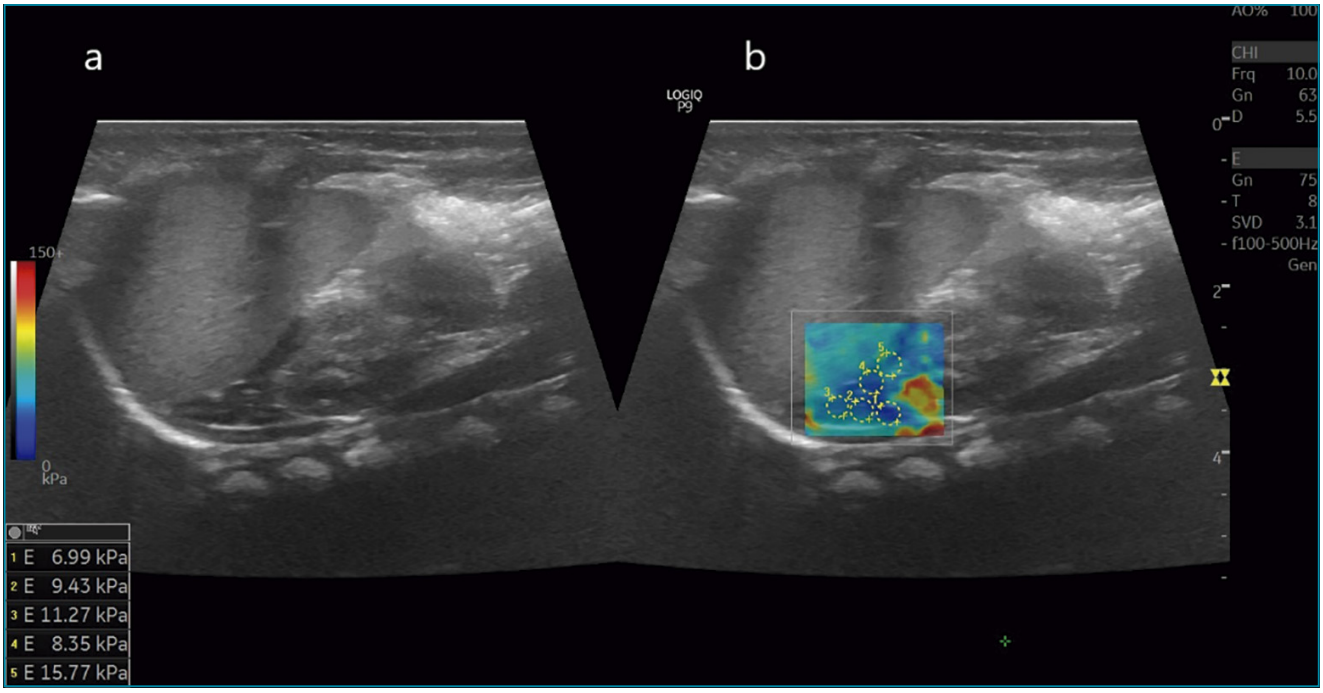

Figure 1. A 14-day-old male healthy newborn. Normal right adrenal gland was shown in B-mode ultrasound (a) and standard shear-wave elastography (b) imaging, superomedial to the kidney and inferior to the liver. (a) B-mode ultrasound: triangular shape right adrenal gland is depicted, and (b) standard shear-wave elastography imaging: a square region of interest with a color elastogram map is depicted along with the smaller circular region of interest with elastogram measurements.

by the examiner during the same visit. For intraobserver reliability, two measurements were made by the examiner at 1-h intervals in two separate settings.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 22 package program. The quantitative descriptive statistics were presented as mean with standard deviation (SD) and median with range. The distribution of data was analyzed using the Kolmogorov-Smirnov test. A nonparametric test (Mann-Whitney U test) was used to evaluate the relationship between the mean stiffness, length, and width measurements of the AG and gender. In addition, the Mann-Whitney U test was used to assess the differences between the mean elasticity of the RAG and LAG.

The relationship between the mean stiffness and length and width measurements versus age, height, and weight was calculated using the "Spearman's rank correlation coefficient test." The intraclass correlation coefficient (ICC) test was used to analyze intraobserver reliability with their 95% confidence intervals (CI) of repeated measurements in the absolute-agreement, two-way mixed-effect model. The ICC was defined as follows: values less than 0.5 indicate poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values higher than 0.90 indicate excellent reliability. A p-value <0.05 was considered statistically significant.

RESULTS

In this study, 70 participants (140 AGs) were initially recruited, and 10 patients were eventually excluded (4 participants with adrenal thickening, 4 participants had insufficient SWE evaluation due to inadaptability, and 2 participants with a difficult labor history). As a result, a total of 60 subjects (120 AGs; 30 males and 30 females; age range: 1–28 days) were included in this study. Thus, the success rate of performing SWE was 85.7% (60/70). The demographic data of the subjects are presented in Table 1.

There was no statistically significant relationship between the mean stiffness, length, and width measurements of both AG and gender (p>0.05). We also measured the mean stiffness and length and width of AG on the right and left sides of each subject and found no statistically significant differences (p=0.544). There was no correlation between length and width measurements and stiffness values of AG (p>0.05). The mean stiffness values of the RAG for the first and second visits were 7.51±2.45 and 7.54±2.49 kPa, respectively, and those of the LAG for the first and second visits were 7.60±2.03 and 7.42±1.97 kPa, respectively. The mean stiffness of AG and the length and width of each AG during the two visits are given as mean and SD in Table 2.

The ICC for intraobserver reliability of mean stiffness values of RAG and LAG was 0.898 (0.838–0.930) and 0.897 (0.863–0.918), respectively, at a 95% CI. The ICC values for mean stiffness values of each AG were >0.80–0.90, indicating good intraobserver agreement (Table 3).

Table 1. Descriptive statistics for age, height, weight, and gender distributions of all subjects.

Clinical characteristic	Total (n=60)
Age (in days)	15.03±9.04 (1–28)
Height (cm)	51.5±5.11 (49–56)
Weight (g)	3509.63±482,65 (2480–4450)
Gender (M/F)	30/30

Data are expressed as n (number) or the mean± standard deviation (range). F: female, M: male.

Table 2. Measurements of adrenal gland's stiffness and length and width.

Parameters	First visit	Second visit
RAG		
Mean±SD (range)	7.51±2.45 kPa (4.44–12.71)	7.54±2.49 kPa (4.52–12.82)
Median	6.76 kPa	6.84 kPa
RAGL and RAGW	17.48±3.58 mm and 2.98±0.52	17.16±3.52 mm and 2.96±0.50
LAG		
Mean±SD (range)	7.60±2.03 kPa (4.49–11.72)	7.42±1.97 kPa (4.34–10.94)
Median	7.19 kPa	7.08 kPa
LAGL and LAGW	17.13±2.83 mm and 3.03±0.47	17.18±2.85 mm and 3.05±0.48

RAG: right adrenal gland; RAGL: right adrenal gland length, RAGW: right adrenal gland width, LAG: left adrenal gland; LAGL: left adrenal gland length, LAGW: left adrenal gland width.

Table 3. Intraclass correlation coefficient for intraobserver measurement of adrenal gland mean stiffness values.

	ICC value	95%CI	p-value
RAG	0.898	(0.838–0.930)	<0.001*
LAG	0.897	(0.863–0.918)	<0.001*

RAG: right adrenal gland, LAG: left adrenal gland, ICC: intraclass correlation coefficient; CI: confidence interval. *p-value significant at 0.05.

There was no statistically significant difference between the mean values of adrenal stiffness and the length and width of AG and weight, height, and age (p>0.05). In addition, there was no statistically significant correlation between mean length and width of AG and mean stiffness values of AG (p>0.05).

DISCUSSION

The US is the ideal modality for the initial evaluation and follow-up of newborns because it is accessible, rapid, safe, noninvasive, and free of ionizing radiation. Computed tomography and magnetic resonance imaging are useful for the evaluation of the AGs. However, these imaging modalities do not provide information about quantitative mechanical properties, such as tissue stiffness.

Elastography is a noninvasive technique used to determine the stiffness or elasticity of the tissue in a specific area. Strain elastography and SWE are the two types of elastography methods[10]. The SWE provides real-time quantitative information on tissue elasticity in kilopascals (kPa). Operator independence, repeatability, and quantitative analysis are the advantages of SWE. As a result, SWE outperforms strain elastography in terms of repeatability, objectivity, and quantification[11].

Normative measurements of adrenal elasticity in newborns may facilitate the early detection of the adrenal abnormalities mentioned above. In addition, it may be beneficial to use standardized stiffness values to distinguish ectopic or accessory adrenal tissue from other tissues[12-15]. We believe that the results of this preliminary study will facilitate the characterization of adrenal tissue, especially in cases of aberrant localization.

In this study, 120 AGs from 60 healthy newborns were assessed with SWE. The preliminary results show the elasticity of the adrenal tissue and give information about the average stiffness of the AGs. The relationships between elasticity and height, weight, and gender were also studied.

In the literature, there are grayscale US studies of the AGs in newborns rather than SWE studies. In their study of 156 healthy newborns, Karagüzel et al.[16] determined the length of the RAG to be 17.6±3.6 mm and its width to be 2.1±0.5 mm, and the length of the LAG to be 16.8±3.1 mm and its width to be 2.1±0.5 mm[16]. In a study of 39 diabetic pregnant women conducted by Garcia-Flores et al.[17], a statistically significant correlation was observed between birth weight and adrenal length. In a study conducted by Karsli et al.[1] on 99 infants, AG volume was found to be significantly related to prenatal factors and postnatal outcomes.

SWE values for the AGs in normal newborns are needed as reference data, and to the best of our knowledge, this study is the first report on this topic. Fernandez et al.[18] conducted an acoustic radiation force impulse study of adrenal elastography in 30 healthy dogs and found no significant relationship between RAG and LAG sheer velocity values. In an adrenal SWE study, Slapa et al. measured the elasticity values of 16 nonmalignant adrenal lesions in 13 patients. According to the results, no statistically significant difference was found between the stiffness of adenomas and hyperplastic nodules, whereas nonmalignant neoplastic myelolipomas were found to be harder than adenomas[19]. In another study, Slapa et al.[2] demonstrated the importance of US and SWE in the evaluation of the AGs. In this study, the mean stiffness values of the RAG for the first and second visits were 7.51±2.45 and 7.54±2.49 kPa, respectively. For LAG for the first and second visits, the mean stiffness values were 7.60±2.03 and 7.42±1.97 kPa, respectively. There were no significant differences between the absolute values of the intraobserver measurements. This significant intraobserver agreement suggests that SWE is a repeatable method for assessing the elasticity of AG and that the stiffness values from normal AG can be used as reference data to distinguish between different pathological conditions.

This study has several limitations. First, we did not assess interobserver reproducibility because all repeated measurements were performed by a single observer. Second, it is a single-center study. Third, this study had a relatively small number of subjects. Fourth, although SWE measurements were taken using the breath-holding technique in adult studies, we were only able to measure the resting breathing position for newborns. Finally, repeated follow-up measurements should be performed with the same machine to avoid reference value discrepancies between different elastography machines.

CONCLUSIONS

There are some SWE studies on intra-abdominal organs in the newborn age group in the literature, yet there are no SWE studies on the AG. This study is the first SWE study to assess AG in healthy newborns. We described the SWE method and reported normal values for AG in healthy newborns. Establishing standard SWE values for healthy newborns can help distinguish normal conditions of AG from pathological conditions. The data from our study can be used as a reference for future research. Multicenter and prospective studies with a larger number of subjects are needed to establish the reference values and repeatability of this imaging technique.

ETHICAL APPROVAL

This study was approved by the Local Ethics Committee (2019-1901). All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Verbal and written informed consent was obtained from the parents of patient.

AUTHORS' CONTRIBUTIONS

EG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration. **İA:** Data curation, Investigation, Methodology, Project administration.

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