

Bone Health Assessed by Calcaneal Quantitative Ultrasound among Cohort of Pregnant Egyptian Women

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Abstract

Aim: The aim was to assess the risk of osteopenia and osteoporosis and to identify possible risk factors affecting bone density (BD) during pregnancy as parity, body mass index (BMI), Vitamin D, and calcium supplementation using quantitative ultrasound (QUS) of the calcaneus among first- and third-trimester pregnant women. **Methods:** It is a case-control study conducted at Ain Shams Maternity Hospital, Egypt, from May 7 to December 14, 2015. One hundred and thirty-two women in the third trimester and 33 matched controls in the first trimester were screened for BD at the calcaneus by QUS. Stiffness index (SI), QUS-T, and Z scores were measured. **Results:** Comparing both the groups regarding QUS-T score, Z score, and SI showed a statistically significant difference between both groups. Third-trimester participants had lower scores (-0.72 ± 1.0 , -0.63 ± 0.99 , and 88.53 ± 14.81 , respectively) compared to their matched controls (1.05 ± 0.89 , 1.16 ± 0.91 , and 113.79 ± 12.49 , respectively). According to QUS-T scores, 82 women (62.1%) in the third-trimester group were assessed as having normal BD, whereas 47 women (35.6%) were at risk of being osteopenic and 3 women (2.3%) were at risk of being osteoporotic. All women of the first trimester were assessed as having normal BD. Logistic regression was performed to identify possible risk factors affecting BD among third-trimester patients. BMI was the only statistically significant predictor for changes in bone health in those women ($P = 0.001$, odds ratio: 0.857, 95% confidence interval: 0.786–0.936). **Conclusion:** With one-unit rise in BMI, a 14% reduction in risk of decreased bone health is obtained.

Keywords: Bone health, pregnancy, quantitative ultrasound, quantitative ultrasound-T score, stiffness index, Z score

INTRODUCTION

Pregnancy and breastfeeding influence several factors which, in turn, have an effect on bone mineral density (BMD). Some factors such as smoking and alcohol intake could decrease BMD.^[1,2] On the other hand, physical exercise, increased BMI, and anabolic hormones could increase BMD.^[3-5] Yet, the end result of pregnancy and lactation on BMD cannot be predicted. Various studies have been conducted, whether longitudinal or cross sectional case control, to analyze the effect of pregnancy and breastfeeding on BMD, showing that there is a reversible loss of BMD.^[6,7] Other studies have shown that women with higher parity and prolonged durations of breastfeeding do not necessarily have BMD any less than controls matched for age and BMI.^[5]

Osteoporosis is characterized by decreased bone mass and bone density (BD) leading to increased risk of bone fracture. It is assessed by measuring BMD using dual-energy X-ray

absorptiometry (DXA). The World Health Organization (WHO) has set levels of T scores obtained from DXA at the proximal femur and spine for diagnosis of osteoporosis. DXA is the gold standard for diagnosis of the condition, yet it is not feasible for mass screening. In addition, radiation produced by DXA scans is contraindicated during pregnancy.^[8] Quantitative ultrasound (QUS) was innovated to identify the risk of bone fractures in nonpregnant patients. High-frequency sound waves are emitted by QUS, passing through bone to assess the quality of bone. BMD is estimated by speed of sound (SOS) and broadband ultrasound attenuation (BUA).^[9,10]

To our knowledge, there are no studies evaluating the effect of pregnancy on bone health in Egyptian pregnant women using QUS; therefore, the aim of the current study was to assess the

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risk of osteopenia, osteoporosis and to identify possible risk factors affecting bone density during pregnancy as parity, body mass index (BMI), vitamin D and calcium supplementation using quantitative ultrasound (QUS) of calcaneus among 1st and 3rd trimester pregnant women.

METHODS

This was a case–control study carried out in Ain Shams Maternity Hospital, Cairo, Egypt, from May 7, 2015, to December 14, 2015. A cohort of 132 Egyptian pregnant women in their third trimester (36–41 weeks of gestation) and 33 matched controls (for age, parity, and BMI) in their first trimester (9–13 weeks of gestation) with singleton pregnancies were enrolled. Third-trimester participants were further categorized into primigravidas, low parity (1–3), and high parity (>3). Participants' ages were between 20 and 35 years. Women with secondary causes of bone loss such as hyperparathyroidism, comorbidities that interfered with bone metabolism as clinically significant liver or renal disease or medications known to affect bone-like steroid hormones and smokers were excluded. Furthermore, women with physical or orthopedic disabilities that limited the ability of the participant to perform QUS were excluded. This study conformed to the Declaration of Helsinki for ethical medical research. Institutional review and ethical board approval (May 4, 2015) were obtained, and all participants signed informed written consents.

Gestational age was calculated according to the 1st day of the last menstrual period by Naegele's rule and confirmed by ultrasound measurement of crown-rump length between 9 and 12 weeks for all participants. Body weight was measured and recorded using a weighing scale to the nearest 0.1 kg. Women were weighed partly dressed, and a correction of 0.5 kg was made for clothing. Standing height was measured and recorded to the nearest 0.5 cm without shoes. BMI was calculated from the weight and the height ($BMI = \text{weight in kg}/\text{height in m}^2$).^[6-8]

QUS was performed at the os calcis of the right foot for the women by Lunar Achilles Express ultrasonometer (GE Healthcare, Belgium). The device provided a combination of SOS and BUA, called stiffness index (SI) (expressed as SI with WHO graph) and Z score (expressed as Z score and percentage of age matched) with the associated QUS-T score (expressed as T score and percentage of young adult) of the calcaneus.^[9,10] The participant's result was expressed as a QUS-T score and compared to the reference population on the color-coded graph. QUS-T score < -2.5 is suggestive of osteoporosis, whereas a score of > -2.5 and < -1 is suggestive of osteopenia.^[11,12]

The participant's foot was exposed and evaluated for factors interfering with positioning of the ankle on the QUS unit such as edema or deformities. The participant's ankle was cleaned by 70% ethanol to remove material compromising the scan. The participant was encouraged to sit upright and still in an immobile chair throughout the scan. Scanning was done twice. The average was recorded.

Ten milliliters of venous blood samples was taken from all participants to measure serum calcium and alkaline phosphatase and analyzed on a COBAS INTEGRA® 400 plus analyzer (Roche Diagnostics Ltd., Switzerland).

The primary outcome was indices of pregnant women in their first and third trimester expressed as QUS-T score, Z score, and SI that was detectable by QUS at the os calcis. The secondary outcome was evaluation of risk factors affecting bone health during pregnancy, such as age, parity, BMI, Vitamin D, and calcium supplementation.

Sample size calculation

The sample size was calculated using data from a previous relevant study.^[13] Group sample sizes of at least 18 cases per group achieve 81% power to detect a difference in BMD of 0.015 g/cm² between the null hypothesis that both group means are 0.6 and the alternative hypothesis that the mean of Group 2 is 0.55 with estimated group standard deviations of 0.05 and 0.05 and with a significance level (alpha) of 0.05 using a two-sided two-sample *t*-test.

Data were statistically analyzed using SPSS® version 15 (SPSS inc, Chicago, IL, USA). Mean and standard deviation were used to present quantitative data. One-way ANOVA was used to compare means in the four groups, followed by Bonferroni *post hoc* pairwise comparisons. Pearson correlation coefficient was used to present the relationship between two quantitative data. Qualitative data were presented as count and proportion, and Chi-square test or Fisher's exact test was used to compare the proportions. *P* value was set at the level of ≤ 0.05 .

RESULTS

One hundred and thirty-seven participants were recruited in the third-trimester group. Five patients were excluded after enrollment; three of them had extensive foot edema and two patients refused the scan. Thirty-six patients were recruited in the first-trimester group. Three participants were excluded: one patient refused withdrawal of blood samples and two participants did not show up for their appointments.

The demographic data of participants are shown in Table 1. The mean age of the study groups showed no statistically significant difference ($P = 0.874$), so as were parity ($P = 0.391$) and BMI ($P = 0.616$). However, there was a statistically significant difference between both the groups regarding calcium and Vitamin D supplementation: a greater percentage of third-trimester women received supplementation ($P < 0.001$). A comparison of serum calcium level between both the groups was also statistically not significant ($P = 0.277$), yet serum alkaline phosphatase was statistically significantly higher in the study group (105.02 ± 38.96 IU) compared to the control group (61.70 ± 16.35 IU) ($P < 0.001$).

Comparing both the groups regarding QUS-T score, Z score, and SI showed a statistically significant difference between both the groups ($P < 0.001$). Third-trimester participants had lower scores (-0.72 ± 1.0 , -0.63 ± 0.99 , and 88.53 ± 14.81 ,

Table 1: Comparison of demographic data between the first- and third-trimester pregnant women

	Mean±SD		P
	First-trimester group (n=33)	Third-trimester group (n=132)	
Age (years) ^a	29.82±5.98	29.65±5.65	0.874
Parity ^a	1.94±1.34	1.69±1.48	0.391
BMI (kg/m ²) ^a	31.36±4.01	30.94±5.25	0.616
Calcium and Vitamin D Intake ^b , n (%)			
None	28 (84.8)	63 (47.7)	<0.001
1-2 months	5 (15.2)	20 (15.2)	
>2 months	0 (0.0)	49 (37.1)	
Serum calcium level (mg/dL) ^a	6.78±0.59	6.60±1.17	0.277
Serum alkaline phosphatase (U/L) ^a	61.70±16.35	105.02±38.96	<0.001

^aStudent's *t*-test, ^bFisher's exact test. SD: Standard deviation, BMI: Body mass index

respectively) compared to their matched controls (1.05 ± 0.89, 1.16 ± 0.91, and 113.79 ± 12.49, respectively) [Table 2].

According to QUS-T scores, 82 women (62.1%) in the third-trimester group were assessed as having normal bone health, whereas 47 women (35.6%) were suspected to be osteopenic and 3 women (2.3%) were suspected to be osteoporotic. On the other hand, all women of the first trimester had normal bone health [Table 3].

Further subgrouping of third-trimester women according to parity was done, and QUS-T score, Z score, and SI were compared between subgroups and first-trimester patients [Table 4], which showed a statistically significant difference between all the groups regarding all scores (*P* < 0.001). BD scores between the three subgroups of third-trimester participants were compared and showed no statistically significant difference (*P* = 1.000) [Table 5].

Logistic regression was performed to identify possible risk factors affecting BD among third-trimester patients [Table 6]. Age, parity, Vitamin D, and calcium intake did not show an effect on BD among third-trimester pregnant women, whereas BMI was the only statistically significant predictor for changes in BD in those women (*P* = 0.001, odds ratio: 0.857, 95% confidence interval: 0.786–0.936). With one-unit rise in BMI, a 14% reduction in risk of decreased BD was obtained.

DISCUSSION

A few studies have addressed decreased bone health during pregnancy. On the other hand, many trials have studied the long-term effect of pregnancy and lactation with conflicting results. The current study showed that third-trimester (between 36 and 41 weeks of gestation) Egyptian women had lower indices (QUS-T score, Z score, and SI) compared to the first-trimester (between 9 and 13 weeks of gestation) matched controls for age, parity, and BMI. Serum alkaline phosphatase levels were also higher in the third-trimester group but within the normal range for the third trimester in pregnancy, indicating that bone turnover was normal.^[14] The most important risk factor for low bone health among third-trimester women is

Table 2: Comparison of quantitative ultrasound-T, Z scores, and stiffness index between the first- and third-trimester pregnant women

	Mean±SD		P
	First-trimester group (n=33)	Third-trimester group (n=132)	
QUS-T score	1.05±0.89	-0.72±1.00	<0.001
Z score	1.16±0.91	-0.63±0.99	<0.001
Stiffness index	113.79±12.49	88.53±14.81	<0.001

QUS: Quantitative ultrasound, SD: Standard deviation

low BMI and not age, high parity, nor deficient Vitamin D and calcium supplementation. Therefore, pregnancy alone cannot be incriminated for decreased bone health.

Møller *et al.*^[6] measured bone mineral density in 92 women before and throughout pregnancy and up to 19 months postnatal in comparison to 75 nonpregnant-matched controls for age. In comparison to controls, BMD dropped significantly throughout pregnancy. At 19 months postnatal, BMD of breastfeeding women was similar to age-matched controls, hence concluding that pregnancy and lactation led to a temporary loss of BMD. They expressed their results as a percentage drop of BMD at different sites such as the lumbar spine and distal forearm. Most importantly, the authors have shown that calcium and Vitamin D supplementation by pregnant and breastfeeding women has not prevented the reversible BMD drop during pregnancy and postnatal. Javaid *et al.*^[11] studied several determinants for changes in calcaneal QUS of 307 pregnant women in their first and third trimesters. There was a decrease in calcaneal SOS by 0.5% and BUA by 3.2% during late pregnancy, which was statistically significant. These determinants were maternal fat stores, age, parity, milk ingestion, and physical activity, which affected the amount of decrease in calcaneal QUS values through pregnancy. They found that pregnant women with increased fat stores had a lower decrease in BUA during late pregnancy. In comparison to the current study, there was a drop of BD at os calcis by QUS where 36% were osteopenic, 2% were osteoporotic, and the rest had normal BD. In addition, the entire first-trimester group had

Table 3: Percentage of women in both groups assessed as having normal bone density, at risk of osteopenia, and at risk of osteoporosis according to quantitative ultrasound-T score

	First-trimester group (n=33), n (%)	Third-trimester group (n=132), n (%)	Fisher's exact test	P
Normal bone density	33 (100.0)	82 (62.1)	22.557	<0.001
Osteopenia	0 (0.0)	47 (35.6)		
Osteoporosis	0 (0.0)	3 (2.3)		

Table 4: Comparison of quantitative ultrasound-T, Z scores, and stiffness index between the three subgroups of the third-trimester pregnant women and first-trimester pregnant women

	n	Mean±SD	F ratio	P
QUS-T score				
First-trimester group all	33	1.05±0.89	29.097	<0.001
Third-trimester group primipara	35	-0.86±0.81		
Third-trimester group low parity 1-3	80	-0.64±1.04		
Third-trimester group high parity >3	17	-0.82±1.16		
Z score				
First-trimester group all	33	1.16±0.91	29.963	<0.001
Third-trimester group primipara	35	-0.81±0.81		
Third-trimester group low parity 1-3	80	-0.55±1.04		
Third-trimester group high parity >3	17	-0.62±1.11		
Stiffness index				
First-trimester group all	33	113.79±12.49	26.941	<0.001
Third-trimester group primipara	35	87.74±13.96		
Third-trimester group low parity 1-3	80	89.08±14.81		
Third-trimester group high parity >3	17	87.59±17.17		

QUS: Quantitative ultrasound

Table 5: Comparison between three subgroups of third trimester regarding Quantitative ultrasound-T, Z score and stiffness index

QUS scores	Patient subgroups	Mean difference	SE	P	95% CI	
					Lower limit	Upper limit
QUS-T score						
Third-trimester primipara	Third-trimester low parity 1-3	-0.221	0.199	1.000	-0.752	0.310
	Third-trimester high parity >3	-0.042	0.290	1.000	-0.817	0.732
Third-trimester parity 1-3	Third-trimester high parity >3	0.179	0.262	1.000	-0.521	0.879
Z score						
Third-trimester primipara	Third-trimester low parity 1-3	-0.257	0.198	1.000	-0.786	0.272
	Third-trimester high parity >3	-0.185	0.289	1.000	-0.957	0.587
Third-trimester parity 1-3	Third-trimester high parity >3	0.072	0.261	1.000	-0.625	0.769
SI						
Third-trimester primipara	Third-trimester low parity 1-3	-1.332	2.931	1.000	-9.161	6.497
	Third-trimester high parity >3	0.155	4.275	1.000	-11.265	11.575
Third-trimester parity 1-3	Third-trimester high parity >3	1.487	3.862	1.000	-8.830	11.803

Bonferroni pairwise *post hoc* test for comparison between subgroups of third-trimester participants was used. SI: Stiffness index, CI: Confidence interval, QUS: Quantitative ultrasound, SE: Standard error

normal BD. Decreased Vitamin D and calcium intake during pregnancy was not a risk factor for decreased BD in the study group, which is also shown by Møller *et al.*^[6]

De Laet *et al.*^[15] studied the effect of BMI on fracture risk in relation to age, gender and BMD, and collected data from 60,000 individuals from various studies all over the world.

Fracture risk adjusted for age was noticeably higher at lower BMI. Relationship of fracture risk and BMI was not linear, conferring that risk of fracture was much more at low BMI than at BMI above the median. They concluded that low BMI and low BMD posed risk for fracture regardless of age and gender. In the current study, one-unit rise of BMI decreased risk of decreased BD among third-trimester pregnant women by 14%.

Table 6: Results of logistic regression showing the effect of different risk factors on bone health among women in third-trimester group

	B	SE	Wald	df	P	OR	95% CI for OR	
							Lower limit	Upper limit
Age	-0.002	0.038	0.003	1	0.953	0.998	0.926	1.075
BMI	-0.154	0.044	11.958	1	0.001	0.857	0.786	0.936
Parity-primipara			4.003	2	0.135			
Parity-low	-0.22	0.458	0.231	1	0.631	0.802	0.327	1.97
Parity-high	1.05	0.722	2.116	1	0.146	2.857	0.694	11.758
Vitamin D and Calcium Intake	0.025	0.166	0.023	1	0.879	1.026	0.74	1.421
Constant	4.363	2.013	4.696	1	0.03	78.511		

B: Regression coefficient in the logistic regression, SE: Standard error of the regression coefficient, Wald: Test of significance of the regression coefficient, Df: Degree of freedom of the test, BMI: Body mass index, OR: Odds ratio

Hellmeyer *et al.*^[16] included 125 pregnant women, who underwent prenatal care, in their study. Ultrasound measurement of the calcaneus was performed in each trimester and then 6 weeks, 3 months, and 1 year postpartum. A complete panel of six measurements was acquired over the time period in 101 patients (80.8%). Forty-two percent of the included patients were primipara, whereas 58% had given birth to at least one child (47%) previously. There was a statistically significant change of the T score ($T = 2.14$, $P = 0.035$) and the SI ($tv = 2.46$, $P = 0.016$) from the second to the third trimester, followed by a plateau during lactation. Interestingly, the T score remained stable during lactation, regardless of the duration of lactation (<3 months, 3–6 months, and >6 months). The drop in Z score and SI score between first and third trimesters was far less than in our study, and this could be explained by the fact that the patients in that study had better nutrition, multivitamins, calcium supplementation, and access to routine antenatal care centers in addition a good number of those patients are doing regular sports compared to participants in our study.

There are several strengths in the current study. It is the only one to date studying the changes of BD in pregnant women, not only in Egypt but also in the Middle East and Africa. In addition, bone health was studied during and not after pregnancy using QUS rather than DXA scans; the latter is contraindicated during pregnancy due to radiation. Factors affecting bone health were also studied during pregnancy and not postnatal. Lunar Achilles Express ultrasonometer used in the current study is one of the most reliable machines used for this purpose,^[17] and QUS-T scores are comparable to T scores of DXA scan.

There are also a few limitations in the current study. Being a cross-sectional comparative study is one limitation as a longitudinal study with follow-up of bone health for the same participants from the first to the third trimester would have been more plausible. In addition, other risk factors should have been surveyed such as race, activity and exercise, alcohol intake, and nutritional status with emphasis on protein intake.

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Conflicts of interest

There are no conflicts of interest.

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