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Maternal Vitamin D Concentration in Mid-pregnancy and Its Effect on Fetal Thymus Size: A Report from a Tertiary Center in Iran

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ABSTRACT

Background & Objective: The thymus gland significantly affects fetal immune system maturation. Additionally, there is a linear association between thymus gland size and its performance. Given the high prevalence of vitamin D deficiency in Iran and scarce studies with conflicting results, subjecting maternal vitamin D concentration effect on fetal thymus, we decided to investigate maternal vitamin D concentration and its relation to fetal thymus size in mid-gestation. This study also aimed to generate a race-specific reference range.

Materials & Methods: We performed a cross-sectional study of ultrasound measurements of the fetal thymus at 18-22 weeks of gestational age in 94 pregnant women and its correlation with maternal serum vitamin D levels from May to July 2021 at the tertiary center of Imam Khomeini Hospital in Tehran, Iran.

Results: The mean values of thymus perimeter, thymus-thoracic ratio, thymus transverse diameter, and thymus area in all participants were 4.18±0.56 cm, 0.37±0.04, 1.56±0.21 cm, and 1.11±0.76 cm^2, respectively. There was a trend toward decreased thymus perimeter and transverse thymus diameter with decreasing level of maternal vitamin D. There was also a significant correlation between thymus perimeter and transverse thymus diameter with fetal biometric indices and gestational age. Furthermore, a significant correlation was observed between the thymus perimeter and transverse thymus diameter.

Conclusion: We generated a race-specific nomogram for fetal thymus size in Iranian pregnant women. Moreover, the observed trend toward decreased fetal thymus size with decreasing maternal vitamin D levels requires further prospective investigations. A high prevalence of vitamin D deficiency and low compliance with daily vitamin D intake during pregnancy was also shown, which requires a solution.

Keywords: Pregnancy, Fetal Thymus, Thymus indices, Thymus Size, Vitamin D Deficiency

Introduction

The thymus gland, a bilobed organ located within the mediastinum between the sternum anteriorly and great vessels posteriorly, is an important part of the immune system and T-cell formation. In fact, maturation and activation of the T-cells occur preliminary inside the thymus gland. After that, mature immune-competent T cells are separated through the bloodstream and the lymphatic vessels and migrate into peripheral lymphoid organs like the spleen and lymph nodes. The thymus is responsible for modulating the entire immune system function and reaches its maximum size in the antenatal period. Not surprisingly, there is a linear association between thymus size and its performance. The thymus gland gradually decreases in

size after birth, which is considered a physiological involution. During this process, the thymus is less capable of regenerating the immune system although the remaining tissue can still produce new immunocompetent T cells during adolescence and even in old age **(1, 2)**.

As well, antigenic and environmental disturbances during fetal life may affect immune system programming. Conditions such as sepsis, trauma, and malnutrition can cause the gland's premature atrophy, which has been shown to be associated with immunodeficiency, autoimmune diseases, and cancers **(3)**. Additionally, the earlier the insult to the thymus gland occurs in the antenatal period, the more probably epigenetic environment changes will be induced. Moreover, these fetoplacental changes are reasonable explanations for the fetal origin of adult-onset diseases **(4)**. Recent studies have focused on thymus size as a non-invasive method to evaluate the prenatal performance inadequacy of the immune system **(5-8)** and even as a predictor of adverse pregnancy outcomes, such as gestational diabetes **(9)**.

To further clarify, any fetal thymus measurements out of the 5th to 95th percentile range in a gestational age-specific nomogram are considered inappropriate fetal thymus growth and might be a clue to the persistence of an abnormality in the fetus or the intrauterine environment, which requires further investigations. The data about thymus parameters have been collected mainly through ultrasound scans and less commonly by magnetic resonance imaging **(10-12)**. On the other hand, among all nutrients, vitamin D has been recognized as the primary modulator of immune and inflammatory system function, which has various significant effects on the innate and acquired immune system **(10-15)**. There is a significant emphasis on vitamin D and its effects on fetal gene regulation compared to other nutritional and environmental exposures. Vitamin D induced its biological effects through specific receptors in many human organs and tissues such as kidneys, the intestinal mucosa, osteocytes, thymus, T-cells, B-cells, and other immune system cells **(12, 16, 17)**. In general, 1,25(OH)vitamin D can enhance the innate immune response by stimulating cathelicidin, which per se is an important peptide in immune system defense against pathogenic organisms, whereas it can inhibit dendritic cells maturation, decrease proliferation of T-cells and also switch T-cell differentiation from T-helper1 toward T-helper2 pathway, so that, inhibiting the adaptive immune response **(18)**.

The Institute of Medicine (IOM) has defined Vitamin D deficiency as serum 25(OH) vitamin D level of less than 20 ng/mL **(19, 20)**. In agreement with IOM, The Endocrine Society's Practice Guidelines Committee also considers serum 25(OH) vitamin D concentration of 21–29 ng/mL as insufficient **(21)**.

Although few previous studies have focused on developing fetal thymus nomograms in different gestational ages, the data on fetal thymus biometry has high variation due to variation in the methodologies of different studies and various demographic parameters, such as racial, cultural, or nutritional **(22)**. There are also several reports in Iran that have shown a high prevalence of Vitamin D deficiency, especially among the pregnant population (ranging from 66 to 84%) **(23)**. Therefore, considering the high prevalence of vitamin D deficiency among the pregnant Iranian population and the insufficiency of articles about the association of maternal vitamin D level with fetal thymus size, even with conflicting results and different study designs and limitations **(24-26)**, a study was designed for the first time to assess the correlation between vitamin D level and fetal thymus gland size in the mid-gestation of Iranian pregnant women.

Methods

This cross-sectional study was conducted on pregnant women who were referred to undergo an anomaly scan of 18-22 weeks of gestational age at the tertiary center of Imam Khomeini Hospital Complex, Tehran, Iran, from May to July 2021, meeting our inclusion and exclusion criteria. Finally, 94 pregnant women were eligible to be included in our study.

The inclusion criteria were maternal age between 18 and 45, single spontaneous pregnancy, and patient desire to participate in the study. Those women who had a history of current pregnancy complications (e.g., gestational diabetes, hypertension, premature rupture of membranes, threatened abortions), evidence of fetal aneuploidy or fetal major structural malformations during the sonographic scan, or human immunodeficiency virus or hepatitis B/C infected patients or presence of any other active clinical infections, known drug or alcohol abuse, multiple pregnancies or pregnancies conceived after assisted reproductive technology, failure to get standard views of the fetal thymus, and patient's refusal to participate in the study were all considered as exclusion criteria.

This study was conducted in compliance with the Helsinki Declaration and approved by the Ethics Committee of Imam Khomeini Hospital Complex, affiliated with Tehran University of Medical Sciences (code: IR.TUMS.IKHC.REC.1400.116). All the participants signed the informed consent.

First, participants' demographic information was obtained, and then an anomaly scan was conducted by a single experienced fetomaternal subspecialist (i.e., the first author). All ultrasound measurements were performed using a PHILIPS Affiniti 70 ultrasound machine (PHILIPS Co., USA) equipped with a curvilinear transabdominal 6-9 MHz probe. The fetal thymus gland was assessed in a three-vessel-trachea view. The thymic-thoracic ratio (TTR), thymus perimeter, thymus area, and transverse thymus diameter were all measured three times, and the mean value for each parameter was recorded. The TTR was

calculated by dividing the anteroposterior diameter of the thymus by the anteroposterior diameter of the mediastinum at the three-vessel trachea view. The thymus perimeter was measured by the manual continuous tracing method, and the thymus area was auto-calculated during tracing. Thymus transverse diameter was measured as the diameter perpendicular to anteroposterior mediastinal diameter.

Then, all the subjects were requested to refer to the Hospital Laboratory to check their 25-hydroxy vitamin D level using a PGI ELISA kit (Padtan Gostar Isar Co., Iran). According to the Endocrine Society Practice Guideline on vitamin D status, deficiency, insufficiency, and sufficiency were defined as vitamin D < 20, within the range of 21-29, and at least 30 ng/mL **(27)**.

Sample Size Estimation

According to Bahar Gur *et al.*'s study (20), the correlation between thymus perimeter and vitamin D level was estimated at 0.4. Considering a confidence interval of 95% and power of 80%, and according to the sample size estimation formula (Figure 1), 70 participants were required for this study.

Statistical Analysis

All the statistical analyses were performed using SPSS software (version 24.0; IBM, New York, USA). Absolute and relative frequencies were reported for qualitative variables, and mean values were reported for quantitative variables. The Chi-Square and t-test (or Mann-Whitney U test, if the data were not normally distributed) were used to compare qualitative or quantitative variables, respectively. P-values lower than 0.05 were considered statistically significant.

Results

The mean age of the participants was 32.08±5.83 years (range: 18-45). The average women's body mass index (BMI) was 27.70±5.004 kg/m^2, and the mean gestational age of pregnant women was 18.7±0.89 weeks. Additionally, 38 (40.4%) and 56 (59.6%) fetuses were male and female, respectively.

The mean values of thymus perimeter, TTR, transverse thymus diameter, and thymus area in all the participants were 4.18±0.56 cm, 0.37±0.041, 1.56±0.21 cm, and 1.11±0.76 cm^2, respectively. Figure 2 shows different thymus measurements in four gestational age categories. The average serum vitamin D was 34.19±17.42 ng/mL (7.00-77.10). Furthermore, vitamin D deficiency was detected in 21.3% of the pregnant women; however, 23.3% of the women had insufficient vitamin D, and 55.4% had sufficient vitamin D concentration. Although it was statistically insignificant, maternal serum concentration decreased as gestational age progressed (35.55 ng/mL at the 19th week to 20.46 ng/mL at the 21st week).

This study evaluated the association between thymus biometry indices and maternal vitamin D concentration in mid-pregnancy. There was no significant correlation among these variables, even in subclasses of maternal vitamin D concentration analyses (i.e., deficient, insufficient, or sufficient). In addition, the association of thymus biometry indices with maternal BMI, fetus characteristics (e.g., biparietal diameter, head circumference, femur length, abdominal circumference, cerebellum size, and estimated fetal weight), and gestational age were evaluated in this study (Table 1).

Table1. The association between thymus biometry indices and maternal and fetus characteristics

Thymus biometry index		Maternal vitamin D	BMI	BPD	HC	FL	AC	Cerebellum	EFW	GA
Thymus perimeter	r*	0.066	0.087	0.517	0.500	0.453	0.349	0.337	0.460	0.406
	P**	0.528	0.402	<0.001	<0.001	<0.001	0.001	-0.001	<0.001	<0.001
TTR	r	-0.081	-0.163	-0.102	-0.042	-0.041	-0.049	0.011	-0.064	-0.066
	P	0.440	0.117	0.327	0.687	0.695	0.637	0.917	0.540	0.526
Thymus transverse diameter	r	-0.030	0.122	0.558	0.510	0.499	0.380	0.359	0.501	0.446
	P	0.771	0.240	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Thymus area	r	-0.019	-0.071	-0.007	0.016	0.048	-0.029	0.048	0.040	0.088
	P	0.858	0.495	0.947	0.879	0.646	0.779	0.647	0.699	0.400

*r: correlation coefficient, **p: P-value

The association evaluation analyses between thymus biometry indices showed a significant strong positive correlation between thymus perimeter and transverse thymus diameter (P<0.001). However, there were significant negative correlations between thymus perimeter and transverse thymus diameter with TTR (P<0.05) (Table 2).

Table 2. The association between thymus biometry indices

Thymus biometry index		Thymus perimeter	TTR	Thymus transverse diameter	Thymus area
Thymus perimeter	r*	1	-0.301	0.887	0.162
	P-value		0.003	<0.001	0.119
TTR	r	-0.301	1	-0.307	0.097
	P-value	0.003		0.003	0.350
Thymus transverse diameter	r	0.887	-0.307	1	0.176
	P-value	<0.001	0.003		0.089
Thymus area	r	0.162	0.097	0.176	1
	P-value	0.119	0.350	0.089	

*r: correlation coefficient

Discussion

Vitamin D deficiency is a common health problem throughout the world. Previous studies reported a vitamin D deficiency prevalence of 66-84% among Iranian pregnant women **(28, 29)**. In the present study, 45.6% of the pregnant women had vitamin D concentrations lower than the normal range. The causes for the lower prevalence of vitamin D deficiency might be more awareness of pregnant women regarding the importance of vitamin D intake, more regular prenatal visits, and coronavirus disease 2019 pandemic and its effects on social media commercials in the era of proper nutrition role in the prevention and treatment of this infection.

Asghar *et al.* **(22)** study, which estimated fetal thymus perimeter and weight during different gestational ages, reported fetal thymus perimeter and transverse thymus diameter as 32.21±14.33 and 6.87±3.23 mm at the gestational age of 16-20 weeks, respectively. In contrast to the results mentioned above, in the present study, fetal thymus perimeter and transverse thymus diameter were estimated at 41.8±5.6 and 15.6±2.11 mm at the gestational age of 18-22 weeks, respectively. As Asghar *et al.* studied postmortem fetuses, the results of the current study seem to be closer to the in-vivo conditions.

Harvey *et al.* **(25)**, in their study of vitamin D deficient rats, showed that maternal developmental vitamin D deficiency during the whole gestation could cause thymus hyperplasia in their offspring in adulthood; however, in this study, no correlation was observed between maternal serum vitamin D level and fetal thymus measurements in mid-pregnancy in humans.

Even the present study's findings are different from the findings of Gur et al.'s study **(24)** that measured maternal serum vitamin D level during 20-28 weeks of gestation, and fetal thymus measurements were carried out later at 37-40 weeks of gestation. Gur *et al.* observed a significant positive correlation between maternal vitamin D level and thymus perimeter. An explanation for the different results of the current study might be the different study designs and populations. The present study calculated fetal thymus biometry indices during mid-gestation while concomitantly measuring maternal vitamin D concentration.

Although this study reported no statistically significant correlation between maternal serum vitamin D concentration and fetal thymus biometry indices during mid-pregnancy, it was observed that thymus perimeter was lower in patients whose vitamin D concentrations were lower than 30 ng/mL, compared to that reported for the vitamin-D-sufficient patients (40.94 vs. 42.61 mm). Furthermore, this trend is similar to the findings obtained by Gur *et al.* **(24)**.

Selvi Gülaş *et al.* **(26)** also could not find any statistically significant correlation between neonatal thymus index and thymus weight index during the first 24 h of life with their vitamin D cord blood concentration. Similar to the current study design, they also concomitantly measured 25-hydroxy vitamin D cord blood, thymus index, and thymus weight index but immediately in the postnatal period and not during fetal life. According to the findings of Selvi Gülaş *et al.* and the mid-gestation observations in the present study, maternal vitamin D deficiency will not result in thymus growth disturbance during fetal life; however, any induced early or late functional impairment cannot be ruled out, and this issue requires further well-designed prospective investigations.

In addition, as Harvey *et al.* **(25)** observed, the rats exposed to a vitamin-D-deficient regimen during gestation had offspring with thymus hyperplasia in their adulthood; this may confirm induced thymus functional impairment caused by exposure to maternal vitamin D deficiency during the whole fetal period. On the other hand, Maghbuli *et al.* **(23)** confirmed a statistically significant association between maternal mid-gestational vitamin D levels and immediately postnatal vitamin D concentration in their neonates. Mohammadbeigi *et al.* also confirmed a positive

association between maternal vitamin D level at a delivery time with vitamin D concentration in cord blood **(30)**. By merging these aforementioned studies' results, it can be concluded that maternal vitamin D deficiency will lead to neonatal vitamin D deficiency but it takes time to affect any disturbance in fetal thymus size or performance. Furthermore, we declare that the lack of patients' follow-up to maintain neonatal vitamin D concentration and compare it with maternal vitamin D level was one of our main limitations in this current study. But, a significant percentage of our patients were referred from other centers just to do an anomaly scan and not willing to deliver at our institution and also due to time lack (as this paper is derived from a fellowship thesis results) and ethical issues regarding neonatal blood sampling, we could not design our study as a prospective cohort. But based on what mentioned before, we suggest providing pregnant women with adequate vitamin D intake and ensuring sufficient serum vitamin D concentration during gestation may prevent thymus function impairment in their offspring.

The national guidelines **(31)** on prenatal care emphasize a daily intake of 1000 IU of supplementary vitamin D and multivitamin tablets; however, only 35 pregnant women (39.3%) had regularly taken vitamin D (at least four times a week), and 43 patients (45.7%) never used vitamin D during their pregnancies. Moreover, 33% of the women had never used even multivitamin tablets during their gestations. Although it was statistically insignificant, as maternal serum vitamin D level in the present study rapidly dropped from a sufficient level at the 18th week to an insufficient level at the 21st week, it may be concluded that there is an immediate need to seek a solution for the enhancement of pregnant women's drug compliance to prevent any fetal or maternal short- and long-term consequences. Additionally, our national prenatal guidelines might be reasonable to make checking maternal serum vitamin D concentration during pregnancy mandatory. Moreover, it should be emphasized that this trend in our survey needs further prospective research to be confirmed.

In addition to the present study's novelty in evaluating a variety of thymus parameters at a specific time in the fetal period, this study could provide a race-specific reference range for various thymus measurements in mid-pregnancy at the time of an anomaly scan. The findings of this study can also help the National Office of Maternal Health to make some helpful changes in recommendations regarding maternal supplementary vitamin D intake or checking vitamin D concentration during pregnancy. Nevertheless, the limited sample size and lack of long-term follow-up during and after gestation are the main limitations of the current study. Therefore, larger sample-size, long-term, prospective, or case-control studies are essential to confirm the results of this study.

Conclusion

We have generated a race-specific nomogram for fetal thymus size for Iranian pregnant women; however, the trend seen toward decreased fetal thymus size with decreasing maternal vitamin D levels requires further investigation. Additionally, considering the high prevalence of vitamin D deficiency among our population, low compliance to the daily intake of vitamin D during pregnancy, and the potential long-term effect of maternal vitamin D deficiency on offspring's thymus function, it seems reasonable that obstetricians need to check pregnant women serum vitamin D level once or more during gestation to determine the required daily dose of vitamin D intake. This issue requires further investigations.

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Author's Contributions

All Authors conceived and designed the analysis, collected the data, contributed data or analysis tools, performed the analysis, and wrote and edited the final paper.

Conflict of Interest

The authors declared no conflict of interests.

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