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Normal Ranges of Fetal Adrenal Gland at 25-37 weeks of Gestation

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ABSTRACT

Objectives: To identify the average measurements for the fetal adrenal gland and examine the relationship between the fetal adrenal gland sizes at different gestational ages between 25 and 37 weeks of gestation.

Materials and Methods: A prospective cohort study conducted at the antenatal care unit of Rajavithi hospital from October 2018 to August 2019. The singleton pregnant woman at the gestational age of 25 to 37 weeks is of interest. Two-dimensional transabdominal ultrasound measurements of the whole fetal adrenal gland and fetal zone was performed in the transverse and sagittal planes to establish the correlation with gestational age. All participants were followed until delivery.

Results: A total of 286 participants had ultrasounds performed. A linear correlation between the whole fetal adrenal gland and the gestational age (GA) for the variables of length = 15.3 + 1.08 × GA(weeks) ($R^2 = 0.856$, $p < 0.001$), width = -3.69 + 0.24 × GA(weeks) ($R^2 = 0.699$, $p < 0.001$) and depth = -3.05 + 0.29 × GA(weeks) ($R^2 = 0.651$, $p < 0.001$) was found. Meanwhile, a correlation between the fetal zone and gestational age in term of length = -14.21 + 0.86 × GA(weeks) ($R^2 = 0.801$, $p < 0.001$), width = -1.33 + 0.09 × GA(weeks) ($R^2 = 0.497$, $p < 0.001$) and depth = -1.95 + 0.14 × GA(weeks) ($R^2 = 0.506$, $p < 0.001$) was also found.

Conclusion: The whole fetal adrenal gland and the fetal zone were enlarged correspondingly with GA and was visible and measurable in all planes during the prenatal period between 25 and 37 weeks of gestation when using a two-dimensional ultrasound. The normal values of the fetal adrenal gland may be useful in the prediction and management of complications during pregnancy in the future.

Keywords: fetal adrenal gland, adrenal fetal zone, normal range, 2-D ultrasound.

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ค่าปกติของต่อมหมวกไตของทารกในครรภ์ในช่วงอายุครรภ์ 25-37 สัปดาห์

นุชนารถ พัฒนาปัญญาสัตย์, เด่นนพพร สุดใจ, ลัลธพร พัฒนาวิจารย์

บทคัดย่อ

วัตถุประสงค์: *เพื่อหาค่าเฉลี่ยของขนาดต่อมหมวกไตของทารกในครรภ์และหาความสัมพันธ์ระหว่างขนาดของต่อมหมวกไตของทารกในครรภ์และอายุครรภ์ในช่วงอายุครรภ์ระหว่าง 25 ถึง 37 สัปดาห์ของการตั้งครรภ์*

วัสดุและวิธีการ: *รูปแบบการศึกษาเป็นการศึกษาแบบไปข้างหน้า โดยทำการศึกษา ณ แผนกฝากครรภ์ โรงพยาบาลราชวิถี ระหว่างเดือนตุลาคม พ.ศ. 2561 ถึงเดือนสิงหาคม พ.ศ. 2562 โดยกลุ่มตัวอย่างคือ สตรีตั้งครรภ์ที่มีอายุครรภ์ระหว่าง 25 ถึง 37 สัปดาห์จำนวน 286 คน มาเข้ารับการตรวจอัลตราซาวน์แบบ 2 มิติ เพื่อวัดขนาดของต่อมหมวกไตของทารกในครรภ์ทั้ง 2 ส่วน คือ ส่วนต่อมหมวกไตทั้งหมดและต่อมหมวกไตส่วนด้านใน และวัดใน 2 ระนาบคือ ระนาบตัดขวางและระนาบตัดแนวยาว หลังจากนั้นจึงนำขนาดของต่อมหมวกไตไปหาความสัมพันธ์กับอายุครรภ์ต่างๆ โดยมีการติดตามผลระยะยาวจนถึงหลังคลอด*

ผลการศึกษา: *จากผู้เข้าร่วมทั้งหมด 286 คน ที่ได้รับการตรวจอัลตราซาวน์ พบความสัมพันธ์ระหว่างขนาดต่อมหมวกไตทั้งหมดของทารกในครรภ์และอายุครรภ์แบบเส้นตรง ดังนี้ ความยาว = 15.3 + 1.08 × GA(สัปดาห์) (R^2 = 0.856, $p < 0.001$), ความกว้าง = -3.69 + 0.24 × GA(สัปดาห์) (R^2 = 0.699, $p < 0.001$) และความหนา = -3.05 + 0.29 × GA(สัปดาห์) (R^2 = 0.651, $p < 0.001$) ตามลำดับ และพบความสัมพันธ์ระหว่างขนาดต่อมหมวกไตส่วนด้านในของทารกในครรภ์กับอายุครรภ์แบบเส้นตรงเช่นกัน ดังนี้ ความยาว = -14.21 + 0.86 × GA(สัปดาห์) (R^2 = 0.801, $p < 0.001$), ความกว้าง = -1.33 + 0.09 × GA(สัปดาห์) (R^2 = 0.497, $p < 0.001$) และความหนา = -1.95 + 0.14 × GA(สัปดาห์) (R^2 = 0.506, $p < 0.001$)*

สรุป: *ขนาดของต่อมหมวกไตของทารกในครรภ์ทั้ง 2 ส่วน มีความสัมพันธ์กับอายุครรภ์ที่มากขึ้น เมื่อได้ค่าปกติของขนาดต่อมหมวกไตของทารกในครรภ์ที่อายุครรภ์ 25-37 สัปดาห์ อาจนำมาซึ่งการใช้ประโยชน์ในการทำนายและดูแลรักษาภาวะแทรกซ้อนที่สำคัญของการตั้งครรภ์ต่อไปในอนาคต*

คำสำคัญ: *ต่อมหมวกไตของทารกในครรภ์, ต่อมหมวกไตส่วนด้านใน, ค่าปกติ, อัลตราซาวน์แบบ 2 มิติ*

Introduction

The fetal adrenal gland is one of the most important glands in the body system because it is dedicated to the production of neuroendocrine hormones. The two main parts of the adrenal gland have different roles. The outside adrenal cortex, the definitive zone, produces multiple glucocorticoid hormones including cortisol that regulates the blood glucose and plays a role in fetal metabolism. The inside core, known as the fetal zone, produces dehydroepiandrosterone sulfate (DHEAS) which stimulates maternal parturition[1].

Several studies have attempted to measure the normal size of the adrenal gland in utero and the correlation with gestational age. Further, previous studies have shown that the whole fetal adrenal gland, fetal zone size, and volume increase during gestation are related in some way. Moreover, the evidence suggest that an enlargement of the fetal adrenal gland can be used to predict complications during pregnancy including preterm birth (PTB), gestational diabetes mellitus (GDM) and intrauterine growth restriction (IUGR)[2-6].

However, in Thailand, there has been no research on the interaction of the fetal adrenal gland level at the end of the second and third trimesters. Therefore, the purpose of the present study was to identify the average measurements for the fetal adrenal gland and the relationship between fetal adrenal sizes at different gestational ages between 25 and 37 weeks of gestation.

Materials and Methods

The present study was a prospective cohort study conducted at the antenatal care unit of Rajavithi hospital from October 2018 to August 2019. The study was approved by the Ethical Review Committee in Medical Research Involving Human Subjects and all participants were offered and signed the consent form before starting the procedure. The singleton pregnant woman at gestational age 25 to 37 weeks was of interest. Gestational age (GA) was calculated from the last menstrual period and confirmed by the first and/or second-trimester ultrasonography[7]. The inclusion criteria were singleton pregnant women without fetal anomalies in the ultrasound screening during the second trimester, no chromosomal abnormalities in case of amniocentesis or cordocentesis was performed, normal amniotic fluid index and no maternal underlying diseases that might affect fetal growth including chronic hypertension, pre-gestational diabetes mellitus or thyroid disease. Exclusion criteria were pregnant women who had a history of previous preterm births, pre-pregnancy body mass index (BMI) > 30 kg/m^2 and pregnancy with conditions of intrauterine growth restriction (IUGR), large for gestational age (LGA), preterm labor (PTL), or stillbirths. Additionally, the fetal adrenal glands that could not be measured due to improper fetal position were excluded from the present study.

After enrollment, all pregnant women underwent a two-dimensional ultrasound using a Voluson E8 (GE Healthcare, USA) with a probe of 2-5 MHz frequency. All examinations were performed by one operator, and each participant was measured only once during pregnancy. An ultrasound was generally performed to measure standard biometry for fetal growth and fetal adrenal gland size in two parts; the whole fetal adrenal gland and fetal zone. The estimated fetal weight was calculated using the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). The method for measuring the fetal adrenal gland was based on a previous study[2,5]. The measurement was initiated by the identification of fetal kidney. The adrenal gland was then identified superior and medial to the kidney as a pyramidal or triangular structure in coronal or sagittal planes and an oval shape in cross section with an echogenic core and anechoic periphery[8]. Then, the picture was magnified to approximately 75% of the image. The fetus was resting during measurement. The length, width, and depth of the whole fetal adrenal gland and fetal zone were then measured on the same side. The right and left sides were not classified because there was no difference in size between the right and left in the previous study[9]. Therefore, the fetal adrenal gland

nearest to the probe side was identified. The whole fetal adrenal gland and fetal zone were identified in the transverse and the sagittal plane. Length and width were then measured in the transverse plane, while depth was measured in the sagittal plane. A caliper was placed from the outer border to the outer border (Fig. 1.), and all parts of the whole fetal adrenal gland and fetal zone were measured three times at each examination. The mean of the values recorded in millimeters was then used for the analysis, and intra-observer variability was calculated. As the examiner performed three measurements for each plane of adrenal gland of 15 random participants, the intraclass correlation coefficient was 0.70 the value referred to a moderate correlation. All participants were followed until delivery. Moreover, complications during antenatal care were looked for including that of preterm labor (PTL), GDM, and fetal growth disorder. Finally, when the child was delivered, the weight, Apgar score and admission in neonatal intensive care unit (NICU) data were recorded.

The sample size was calculated based on previous study[10] by using the below formula

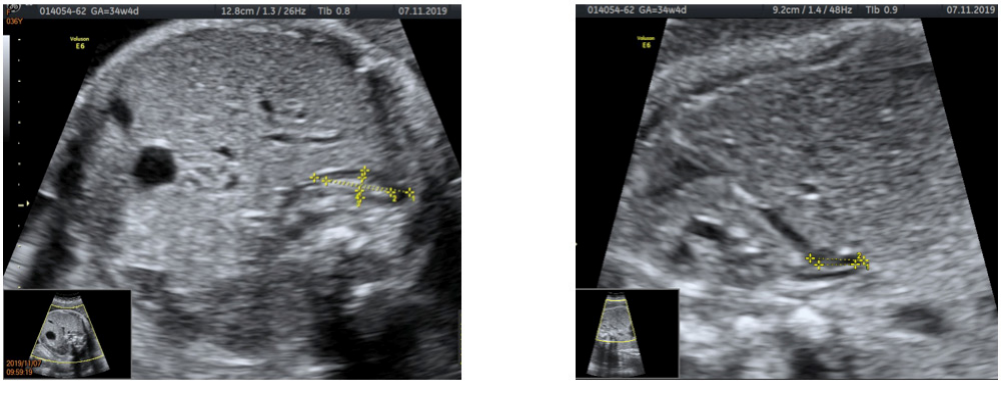
$$N/group = (Z\alpha/2)^2 \times (SD)^2/d^2$$

N = sample size, $\alpha = 0.05$

$Z\alpha/2 = 1.96$, SD = 2.14

d = 1

As a result, the participants were 18 per group. With the addition of 20% of drop-out rate, the total number of participants was 22 per group. The data were analyzed by SPSS version 22. The demographic data of maternal age, pre-pregnancy BMI, GA at delivery and birthweight were reported as mean ± standard deviation (SD). The size of the fetal adrenal glands in each plane and GA was reported as mean ± SD and percentile at 5th, 50th, 95th, and the relationship between the sizes of the fetal adrenal gland and GA was reported using regression analysis.



A) Transverse plane —length and width

B) Sagittal plane —depth

Fig. 1. . Diagram for measurement of fetal adrenal gland in three planes: (A) transverse plane —length and width B) sagittal plane —depth

Results

Of the 286 participants who had ultrasounds performed, eight fetuses were excluded—five were due to PTB, and three were large for GA. This left 278 participants remaining for the final analysis. No abnormalities were found on postnatal examination screening, and all participants were able to follow-up until delivery. The mean maternal age was 27.62 ± 5.50 years, mean pre-pregnancy BMI was 21.57 ± 3.00 kg/m^2, mean GA at delivery was 38.5 ± 1.00 weeks and mean birthweight was 2982.08 ± 355.09 grams. The size of the fetal adrenal gland was shown in two parts: the whole fetal adrenal gland and the fetal zone of each GA (Tables 1-6).

Table 1. The length of the whole fetal adrenal gland (mm.).

Gestational age (weeks)	N	Mean ± SD	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile
25	22	11.54 ± 1.69	8.88	9.54	11.00	14.12	15.36
26	20	11.95 ± 1.70	9.37	10.07	11.62	14.87	15.76
27	21	14.06 ± 1.95	10.22	10.86	14.57	16.58	16.60
28	21	14.95 ± 1.63	12.36	12.58	14.83	17.21	17.56
29	20	15.61 ± 1.38	13.37	13.40	15.63	17.44	17.59
30	22	17.48 ± 1.48	14.38	15.40	18.00	18.91	19.16
31	21	18.29 ± 1.81	15.34	15.78	18.30	21.04	21.44
32	21	19.65 ± 1.64	17.44	17.60	18.73	21.97	22.54
33	22	21.00 ± 1.71	17.59	18.40	21.12	23.32	23.69
34	22	21.26 ± 1.36	19.34	19.56	21.13	23.64	24.21
35	22	22.43 ± 1.69	20.42	20.53	22.33	24.69	25.75
36	22	22.90 ± 1.66	20.91	20.94	22.45	25.54	26.80
37	22	24.28 ± 1.58	22.12	22.21	24.45	26.79	26.94

Table 2. The width of the whole fetal adrenal gland (mm.)

Gestational age (weeks)	N	Mean ± SD	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile
25	22	2.48 ± 0.51	1.66	1.86	2.55	3.29	3.39
26	20	2.67 ± 0.45	1.88	2.17	2.65	3.32	3.56
27	21	3.00 ± 0.56	1.99	2.31	3.00	3.72	3.85
28	21	3.19 ± 0.52	2.45	2.57	3.13	3.97	4.36
29	20	3.32 ± 0.41	2.77	2.80	3.32	3.97	4.38
30	22	3.62 ± 0.48	2.84	3.04	3.67	4.29	4.42
31	21	3.69 ± 0.39	3.00	3.08	3.68	4.39	4.43
32	21	3.93 ± 0.59	3.12	3.19	3.77	4.83	4.92
33	22	4.07 ± 0.47	3.45	3.55	4.00	4.93	5.17
34	22	4.48 ± 0.56	3.84	3.91	4.38	5.54	5.97
35	22	4.84 ± 0.86	3.91	3.95	4.50	6.33	6.55
36	22	5.36 ± 0.92	3.95	4.11	5.18	6.49	6.70
37	22	5.45 ± 0.70	4.37	4.63	5.30	6.57	6.78

Table 3. The depth of the whole fetal adrenal gland (mm.).

Gestational age (weeks)	N	Mean ± SD	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile
25	22	4.41 ± 0.80	3.35	3.45	4.45	5.72	5.97
26	20	4.72 ± 0.74	3.42	3.87	4.82	5.80	6.03
27	21	4.92 ± 0.65	4.07	4.10	4.93	5.90	6.31
28	21	5.03 ± 0.77	4.14	4.21	4.98	6.52	6.88
29	20	5.50 ± 0.74	4.15	4.43	5.47	6.68	6.90
30	22	5.80 ± 0.93	4.28	4.47	6.13	6.92	6.97
31	21	5.94 ± 0.62	4.46	4.99	6.00	6.76	6.95
32	21	6.36 ± 0.61	5.13	5.41	6.37	7.17	7.38
33	22	6.57 ± 0.76	5.33	5.48	6.48	7.55	8.43
34	22	6.70 ± 0.85	5.47	5.59	6.60	8.05	8.64
35	22	7.48 ± 0.90	6.23	6.24	7.35	8.74	8.82
36	22	7.54 ± 0.99	6.41	6.45	7.41	9.09	9.63
37	22	7.98 ± 1.07	6.90	6.91	7.85	9.81	9.99

Table 4. The length of the fetal zone of the fetal adrenal gland (mm.).

Gestational age (weeks)	N	Mean ± SD	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile
25	22	6.97 ± 1.44	5.00	5.01	7.00	9.26	9.97
26	20	7.45 ± 1.40	5.02	5.49	7.30	9.48	10.20
27	21	9.40 ± 1.53	6.01	7.63	9.83	11.43	12.23
28	21	10.39 ± 2.03	7.80	8.06	9.93	13.49	14.34
29	20	10.57 ± 1.56	8.05	8.91	10.47	13.78	14.47
30	22	11.94 ± 1.75	8.24	9.19	12.17	14.20	14.49
31	21	12.36 ± 1.38	10.40	10.41	12.43	14.85	15.11
32	21	13.57 ± 1.72	11.20	11.27	13.30	16.31	16.46
33	22	15.01 ± 1.14	12.68	13.08	15.37	16.34	16.51
34	22	15.30 ± 1.46	13.19	13.56	15.58	17.47	18.17
35	22	15.89 ± 1.66	13.59	13.80	15.87	18.25	18.68
36	22	16.09 ± 1.40	14.07	14.11	16.03	18.37	18.94
37	22	17.42 ± 1.94	14.17	14.42	17.63	20.13	20.55

Table 5. The width of the fetal zone of the fetal adrenal gland (mm.).

Gestational age (weeks)	N	Mean ± SD	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile
25	22	0.98 ± 0.20	0.55	0.70	0.97	1.22	1.23
26	20	1.04 ± 0.22	0.64	0.74	0.98	1.42	1.47
27	21	1.18 ± 0.26	0.80	0.81	1.13	1.53	1.77
28	21	1.24 ± 0.27	0.80	0.83	1.23	1.56	1.82
29	20	1.26 ± 0.29	0.87	0.90	1.30	1.57	2.01
30	22	1.37 ± 0.33	0.97	0.98	1.37	1.78	2.23
31	21	1.50 ± 0.30	1.01	1.05	1.50	1.83	2.25
32	21	1.57 ± 0.33	1.10	1.15	1.57	2.11	2.28
33	22	1.63 ± 0.34	1.13	1.27	1.62	2.26	2.33
34	22	1.69 ± 0.31	1.16	1.33	1.67	2.26	2.39
35	22	1.82 ± 0.45	1.20	1.34	1.68	2.61	2.66
36	22	2.07 ± 0.55	1.24	1.39	1.97	2.87	2.92
37	22	2.08 ± 0.47	1.64	1.66	1.88	2.89	3.30

Table 6. The depth of the fetal zone of the fetal adrenal gland (mm.).

Gestational age (weeks)	N	Mean ± SD	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile
25	22	1.69 ± 0.41	1.04	1.24	1.63	2.33	2.53
26	20	1.77 ± 0.39	1.14	1.27	1.73	2.49	2.60
27	21	1.93 ± 0.41	1.21	1.37	1.93	2.52	2.77
28	21	1.98 ± 0.45	1.41	1.47	2.01	2.70	2.89
29	20	2.25 ± 0.37	1.61	1.72	2.22	2.97	3.01
30	22	2.45 ± 0.56	1.70	1.73	2.40	3.11	3.53
31	21	2.48 ± 0.56	1.80	1.90	2.47	3.52	3.97
32	21	2.65 ± 0.60	1.83	1.90	2.53	3.57	4.05
33	22	2.76 ± 0.60	1.87	2.10	2.62	3.72	4.06
34	22	2.84 ± 0.65	1.93	2.14	2.65	3.95	4.28
35	22	3.15 ± 0.55	2.17	2.57	3.07	4.13	4.30
36	22	3.29 ± 0.73	2.37	2.58	3.11	4.40	4.49
37	22	3.35 ± 0.61	2.57	2.65	3.22	4.57	4.83

The correlation between the whole fetal adrenal gland and GA for the variables of length = 15.3 + 1.08 × GA(weeks) (R^2 = 0.856, p < 0.001), width = -3.69 + 0.24 × GA(weeks) (R^2 = 0.699, p < 0.001) and depth = -3.05 + 0.29 × GA(weeks) (R^2 = 0.651, p < 0.001) is shown in Fig. 2. Meanwhile, the correlation between the fetal zone and GA were length = -14.21 + 0.86 × GA(weeks) (R^2 = 0.801, p < 0.001), width = -1.33 + 0.09 × GA(weeks) (R^2 = 0.497, p < 0.001) and depth = -1.95 + 0.14 × GA(weeks) (R^2 = 0.506, p < 0.001) as shown in Fig. 3.

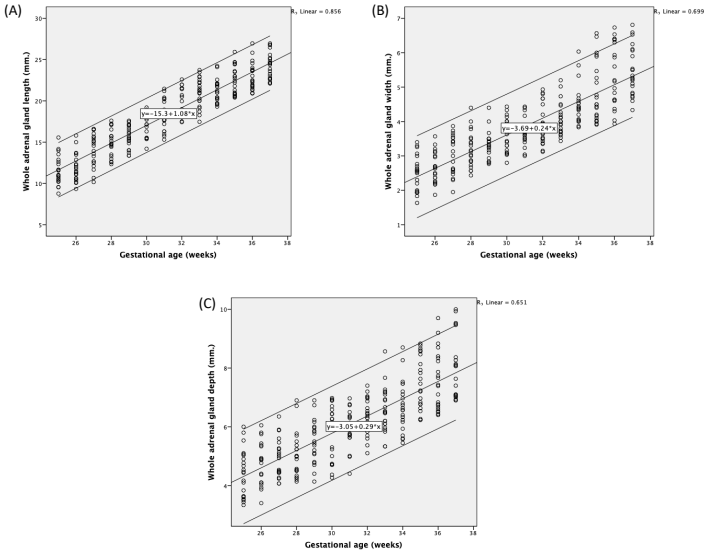


Fig. 2. The correlation between the whole fetal adrenal gland and GA: (A) the length of the whole fetal adrenal gland, (B) the width of the whole fetal adrenal gland, and (C) the depth of the whole fetal adrenal gland. The upper and lower lines indicate the 95th and 5th percentiles.

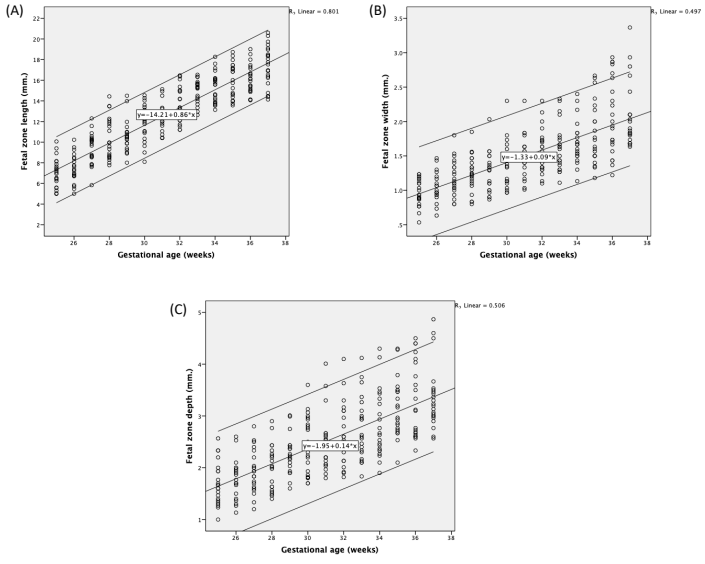


Fig. 3. The correlation between the fetal zone and GA: (A) the length of the fetal zone, (B) the width of the fetal zone, and (C) the depth of the fetal zone. The upper and lower lines indicate the 95th and 5th percentiles.

Discussion

In the present study, the whole fetal adrenal gland and the fetal zone in correlation with GA in a linear pattern were significantly enlarged. In this context, there have been many studies about the normal values of the size and volume of the fetal adrenal gland[10-14]. For example, Lewis et al presented the normal fetal adrenal gland after 30 weeks of GA. The authors found that the long axis of the fetal adrenal gland in the transverse view had a range of 14 to 22 mm., but only one view of the fetal adrenal gland was measured in this study[11]. Further, the study by Van Vuuren et al reviewed the nomograms for the fetal kidney dimension and volume, renal pelvis dimension, and adrenal gland length from 15 weeks of GA until delivery. The length of the fetal adrenal gland was measured by the total kidney length, including the adrenal gland subtracted from kidney length in the sagittal plane of the fetus[12]. Additionally, there was also a study conducted in Thailand by Jamigorn and Phupong, in which the whole fetal adrenal gland and the fetal zone between 16 to 24 weeks of GA were measured in three planes of the fetus: transverse plane (length), coronal plane (width), and sagittal plane (depth). The correlation between size and GA was then reported[10].

However, the measurement of the fetal adrenal gland in two parts in many studies had different results. This includes the present study that found it to be relatively smaller than previous studies due to the varying techniques for measurement and the operator's expertise. Nevertheless, the correlation between the size of fetal adrenal gland and GA was strongly consistent in all studies. Moreover, the variation of measurement was related to different GA. Rosenberg, et al[8] reported that the fetal adrenal gland was recognized sonographically in only 12% of fetuses at less than 26 weeks of GA and 90% of fetuses at more than 26 weeks. The authors found that, in early gestation, the fetal adrenal gland was visualized as just an anechoic area in the expected location of the gland, while the pattern of an anechoic limb with an echogenic core was identified more distinctly beyond 32 weeks of GA.

Moreover, the studies on normal-sized fetal adrenal glands in normal fetuses of varying GA are beneficial for assessing the correlation between the fetal adrenal gland and high-risk complications including PTB and IUGR. For example, Turan et al measured the fetal adrenal gland volume and fetal zone enlargement for the prediction of preterm births and found that the fetal zone enlargement in 2D ultrasonography was superior to cervical length for predicting the risk of a preterm birth within seven days[2]. Further, Sage et al evaluated the fetal adrenal gland volume as a useful screening tool for spontaneous PTB in low-risk pregnancies between 24 to 36 weeks of GA. The authors found that the fetal adrenal gland was significantly smaller for those delivering preterm[3]. In addition, Santipap and Phupong measured the combination of the fetal adrenal gland volume enlargement, fetal zone enlargement and cervicovaginal placental alpha macroglobulin-1 (PAMG-1). These measurements increased sensitivity for delivery timing prediction within seven days in pregnant women presenting with threatened PTL and PTL[6]. Additionally, Mohajeri et al found that the fetal adrenal gland volume in the IUGR group was larger than the control group, while a smaller fetal zone volume in the IUGR group was comparable to the fetuses in the control groups[4]. Therefore, the evidence that recorded references, in Thailand, of the fetal adrenal gland in the early second trimester (16 to 24 weeks)10 and additional data from the present study that started from 25 to 37 weeks of GA can be helpful for further studies in predicting complications in pregnancy.

The strength of the present study was that it covered multiple gestational ages from 25 to 37 weeks, and this was important in terms of keeping track of many complications that occurred in second and third trimester. Further, the fact that all participants were followed until delivery was also a strength. However, the weakness of the current study was that the measurements were taken by one operator. Additionally, there was a relatively small number of participants, and the data were not collected longitudinally.

Conclusion

In conclusion, the whole fetal adrenal gland and the fetal zone were enlarged with GA correspondingly and were visible and measurable in all planes during the prenatal period at the end of the second and third trimesters using a two-dimensional ultrasound. Further, the normal values of the fetal adrenal gland may be useful in predicting and managing complications during pregnancy in the future.

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Potential conflicts of interest

The authors declare no conflict of interest.

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