The Fetal Airway Parameters: Potential Diagnostic and Prognostic Markers of Intrathoracic Lesions

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Running title: THE FETAL AIRWAYS PARAMETERS

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We declare that we have no conflict of interest.

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what's already known about this topic?

The diagnostic and prognostic indicators of fetal intrathoracic lesions still have some limitations.

what does this study add?

The fetal airway paraments may play a role in diagnosis and prognosis of fetal intrathoracic lesions.

Data availability statement

The data that support the findings of this study are openly available in [repository name e.g "figshare"] at http://doi.org/[doi], reference number [reference number].

Abstract:

Objective: Aim to study the fetal airway parameters in normal fetuses and fetuses with intrathoracic lesions. **Methods:** This was an observational case–control study. In the control group, 77 women were screened at 20-24 weeks gestational age, 12 were screened at 24-28 weeks gestational age, and 23 were screened at 28-34 weeks gestational age. In the case group, 41 cases were enrolled (6 cases of intrathoracic bronchopulmonary sequestration, 22 cases of congenital pulmonary airway malformations, and 13 cases of congenital diaphragmatic hernia). Fetal airway parameters (tracheal width, the narrowest lumen width, width of subglottic cavity and laryngeal vestibule) were measured. The correlations between fetal airway parameters and gestational age were analyzed. The fetal airway parameter differences between the control group and the case group were analyzed. **Results:** Fetal airway parameters of both groups were increased and had association with gestational age. Fetal airway parameters of the case group were smaller than the control group. The tracheal width in fetuses with congenital diaphragmatic hernia was the smallest in the cases studied. **Conclusion:** Fetal airway parameters are expected to provide a novel diagnostic and prognostic method for intrathoracic lesions.

Key words: Fetus; Airway; Congenital pulmonary airway malformation; Bronchopulmonary sequestration; Congenital diaphragmatic hernia

Introduction:

Biomechanics and lung luminal fluid are key to fetal lung development [1]. The development and morphology of animal airway are influenced by pressure [2]. Mechanics is believed to play a significant role in lung development [3]. Cilley RE et al. found lung development impaired without airway pressure, whereas with airway pressure, the development gene expression was enhanced [4]. Fetal airway liquid is a major determinant of development and morphology of the fetal airway [5]. The liquid is a delivery media of pressure. Fetal lung growth depends on the degree distended by luminal liquid [6]. The pulmonary epithelium secretes liquid that distends the airways and plays a key role in normal lung growth and development [7]. The changes of luminal pressure and biomechanics could lead to changes in production and secretion of lung fluid [8].

The trachea and bronchi are mainly composed of cartilage and smooth muscle; the development of those two components influenced each other [9]. The smooth muscle is the major component from trachea to lung [10, 11]. Transmural pressure could promote growth of smooth muscles in the airway [2, 11].

Epithelial development of the airway wall is influenced by pressure such as shear stress [12]. The principle is that pressure changes gene expression, promotes the release of growth factors, and leads to changes in cell morphology and growth patterns [2, 13]. Those factors could influence growth of the lung and trachea.

Severe congenital thoracic lesions can cause fetal pulmonary hypoplasia, cardiovascular collapse and death [14]. In fetuses with intrathoracic lesions, pulmonary volumes and capacities were decreased [14]. The liquid through airway lumen was decreased, and the liquid secreted by pulmonary epithelium was also decreased. Therefore, the pressure and expansion effect from the liquid was decreased. The effect of mechanical stimulus, such as shear stress and transmural pressure, decreased with the reduction of liquids too. Therefore, the thoracic lesions might affect the development of the trachea, and the parameters of the trachea might play a potential diagnostic, prognostic role on fetal thoracic lesion diseases. The normal fetal trachea development, normal fetal trachea parameters, and fetal thoracic lesion diseases merits further research.

Prenatal imaging and experimental models have provided a comprehensive understanding of intrathoracic lesions [15]. Using fetal ultrasonography, fetal malformations were able to be directly identified [16] and the development of the fetal airway was also able to be identified [17]. The larynx, a well-defined anatomical site, continues into the inferior trachea and forms the inlet of the fetal airway [18]. A deeper study of normal anatomy is the basis for prenatally detected structure deformities [19]. With the measurements results affected by different sample preparations, there are several limitations to airway studies on specimens [20, 21]. The ultrasonography is thought to be the preferred option to study living fetal trachea [22]. The aim of this study is to use ultrasound to observe fetal airway parameters' growth with gestation age and compare them with the airway parameters of fetuses with intrathoracic lesions.

Methods:

This was a single-center (Beijing Obstetrics and Gynecology Hospital, Beijing, China), prospective, case-controlled, observational study performed December 2020 to June 2021. This study was approved by the Institutional Review Boards/Ethics Committees of Beijing Obstetrics and Gynecology Hospital. The entry criteria of control group were normal singleton fetus with known gestational age (by dates or by early ultrasound exam) and followed up through September 2021 without gross malformations. The entry criteria of case group were singleton fetuses with an intrathoracic lesion without associated genetic or major anomalies. Exclusion criteria: 1. Patients with discomfort who could not tolerate sonography examinations. 2. The obtained images were not satisfactory for maternal and/or fetal reasons. Finally, 112 controls were enrolled. 77 were screened at 20-24 weeks gestational age, 12 were screened at 24-28 weeks gestational age, and 23 were screened at 28-34 weeks gestational age. 41 cases were enrolled (22 cases of CPAMs, 6 cases of BPS, and 13 cases of CDH). 14 were screened at 20-24 weeks gestational age, 16 were screened at 24-28 weeks gestational age, and 11 were screened at 28-34 weeks gestational age. CPAMs and BPS were confirmed by ultrasonography. CDH was confirmed by prenatal MR, newborn surgery or fetal autopsy. Examinations were performed by two sonographers in our center. Measurements were obtained using ultrasound equipment (WS80A, Samsung Medison Co., Ltd., Seoul, South Korea) with a CV1-8A probe. To calculate intra-observer variation, measurements were repeated at a different time and under the same conditions using 10 randomly selected fetuses. The differences between the repeated measurements were evaluated by the intraclass correlation coefficient (ICC).

All the gravidas signed informed consent forms. All airway parameters were measured during fetal apnea. Airway parameters included: traches width (TW), subglottic cavity width (SW), narrowest lumen width (NW), and laryngeal vestibule width (LW). All airway parameters were measured in all cases.

The results differed as a result of the different methods of assessing tracheal parameters in present studies [23]. Within the current study, we took the following simple approach to standardized measurements. The tracheal ring is composed of a “C” type cartilage ring, with the free ends of cartilages at the posterior border bridged by smooth muscle [24]. On the coronal plane, the diameter between the hyperechoic lines at the edge of the tracheal lumen is tracheal width. The tracheal width was measured 0.5-1 cm distal to the cricoid cartilage, make sure the trachea wall was clearly displayed, both sides of the wall were hyperechoic, and the body of tracheal cartilage was anechoic. The width of laryngeal vestibule was measured when the thickness and length of cricoid cartilage on both sides were equaled. In this plane (Figure 1), the area of piriformis fossa on both sides were also equal. The width of subglottic cavity was measured at the level of mid-point of the cricoid cartilage. The value of the narrowest width in this lumen, often close to the level of the upper border of the cricoid cartilage, was recorded [20]. Each observer made measurements independently.

Data was analyzed with Statistical Product and Service Solutions ® (SPSS®) software (version 26.0). The Kolmogorov-Smirnov test was performed on all measured parameters to assess whether they followed a normal distribution. Non-parametric test was performed when data did not follow a normal distribution and when the variance was not homogeneous. The correlation between airway parameters and gestational age was analyzed. The fitted growth curves of the airway parameters were obtained. Independent samples t-tests were applied to calculate group differences. Intra- and inter-observer reproducibility were assessed by analyzing the difference between the values of 10 randomly-selected fetuses.

Two trachea specimens of fetuses with the same gestation age were applied, one fetus with CDH and pulmonary dysplasia (GW: 23W3D, BPD = 5.8 cm, HC = 20.7 cm, AC = 20.3 cm, FL = 3.8 cm), and another fetus with a single ventricle and normal lung development (GW: 23W4D, BPD = 6 cm, HC = 22.5 cm, AC = 18.9 cm, FL = 3.9 cm).

Results:

Airway paraments of the two groups with different gestational ages are shown in Table 1. Airway parameters of the control group were expressed by the functions: TW = -0.033 + 0.748 × GW (R2 = 0.559, $p < 0.001$). NW = -0.073 + 0.723 × GW (R2 = 0.523, $p < 0.001$), SW = -0.077 ± 0.728 × GW (R2 = 0.533, $p < 0.001$), LW = -0.031 + 0.636 × GW (R2 = 0.405, $p < 0.001$) ; case group TW R2 = 0.474, NW R2 = 0.425, SW R2 = 0.623, LW R2 = 0.347.

Airway parameters in the case group were smaller than those in the control group, and showed a statistical difference ($p < 0.01$) (Table 1). The gestational age of two groups showed no statistically significant differences (p=0.40), and the gestational age of different case groups showed no statistically significant differences (p=0.085) too. Airway parameters of the two groups increased with gestational age and correlated well (Figure 4). The width of trachea in the CDH group had a better correlation of gestational age than the other groups and was minimal in all groups (Figure 2). Inter-observer variability was not significantly different (TW p = 0.913, SW p = 0.468, NW p = 0.413, LW p = 0.991). The ICC values show the intra-operator reproducibility at TW

(ICC = 0.958), SW (ICC = 0.966), NW (ICC = 0.805), LW (ICC = 0.848).

Gross specimens of lungs were shown in Figure 3. Trachea of fetus with single ventricle but normal development lung was wider than fetus with pulmonary dysplasia which was caused by CDH.

Discussions:

During the embryonic phase, fetal lungs begin as two outpouchings of the foregut which will eventually form the trachea and esophagus[1]. Biomechanics and liquids are important determinants of fetal lung development [5, 8]. Biomechanics are mainly influenced by fetal breath movement and transpulmonary pressures caused by lung liquid [25, 26]. Fetal lung liquids and expansion are medias of pressure. Lung liquid maintains fetal lung expansion and is produced by lung epithelial cells [1]. At the same time, fetal lung liquid production and secretion are enhanced by intra-amniotic pressure and fetal breath movement [8].

Gene and growth impactor expression are enhanced by pressure and liquids [4]. Airway morphology and development are influenced by pressure and liquids. Fetal breath movement enhance lung growth and airway expansion [27]. Development of components of the airway wall (smooth muscle, cartilage, and epithelial) are adjusted by pressure and liquid [13]. Additionally, they are influenced by each other [9]. The airway smooth muscle (ASM) plays an important role in promoting lung growth during gestation. Growth of the nerve follows the ASM which can spontaneously narrow and relax the airways [28]. Production of neurotrophic factor is initiated by stretch-induced signals [11].

When the larynx is closed, the laryngeal vestibule, trachea cavity and subglottic cavity compose an intact lumen and withstands extrusion from the same pressure transmitted by liquids. Lateral walls of laryngeal vestibule are composed of upright aryepiglottic folds [29]. The distance inside the aryepiglottic folds is the inner diameter of the laryngeal vestibule. The width of subglottic larynx is measured at the cricoid cartilage level [30]. The width of the narrowest cervical airway lumen is also measured. Artifacts such as the partial volume effect may affect the accuracy of image quantification [31]. Angle of insonation is an important condition to assure the sonographic image quality to avoid artifacts [32]. Cartilage is the main component of the tracheal wall [9]. With the development of ultrasonic technology, the accuracy of fetal sonography has improved. Fetal cartilage demonstrates an anechoic body and a hyperechoic edge [19]. The diameter between the hyperechoic lines of the inner edges of both sides of the tracheal wall may reflect the true internal diameter. Szpinda et al. found in fetal specimens, the trachea was almost circular at 14-18 weeks gestational age and more D-shaped at 21-25weeks gestational age [21], therefore, the change in the tracheal width may be more pronounced.

Tracheal width in this study was similar to the results of Kalache et al. (from 20-38 weeks gestational age from 2.14 ± 0.40 to 4.32 ± 0.89) [33], and slightly different from Richards et al. s（from 2.4 mm at 18 weeks gestational age to 4.6 mm at 38 weeks gestational age and Can et al. (from 1.8 mm at 20 weeks gestational age to 4.7 mm at 40 weeks gestational age) [17, 34].

Consistent with previous findings, this study demonstrated a correlation between gestational age and airway paraments in control group [17, 33, 34]. In contrast to the study of Michał Szpinda et al., our correlation was smaller ($R2 = 0.56$ VS $R2 = 0.81$) [21]. This may have been a result of using two observers to perform the measurements in this study. This may have produced observer bias to some extent, although there was no significant interobserver difference. In the case group, airway paraments were positively associated with gestational age too. The airway parameters in the control group were larger than in the case group. The results validated our hypothesis that intrathoracic lesions might impede airway development. The correlations of gestational age with TW and SW were better than with NW and LW. Firstly, because of the cartilage, it provides mechanical support to wall of trachea and subglottal cavities. Secondly, the movement of the wall of the laryngeal vestibule and the narrowest lumen might affect measuring stability. The airway parameters in the CDH group had a better correlation of gestational age than other groups and were minimal in all groups. Intrathoracic lesions in the fetus could lead to lung hypoplasia [1]. Both CPAMs and BPS have decreased fetal lung volume and reduced fetal lung liquid secretion. CDH is caused by insufficiency of the diaphragm, potentially leading to pulmonary hypoplasia [35], which could impede movement of diaphragm and deceased fetal lung volume. Pressure caused by diaphragm movement and lung liquids secretion was also decreased, explaining why the width of trachea in CDH group was minimum. BPS is a congenital pulmonary malformation separated from the normal tracheobronchial tree; lesions are composed by nonfunctioning lung tissue with blood supplied from systemic arterial [14]. Most BPS are intrathoracic lesions that can be divided into two categories: intralobar (15%) and extralobar sequestrations (85%) [36]. Similar to CPAMs cases, BPS cases are comprised of non-functioning lung tissue, may form hybrid lesions with CPAMs [37]. BPS also shared the same prognosis predictors with CPAMs [38].

The CPAMs volume ratio (CVR) is a measurement of the tumor normalized for gestational age. The assumption is the shape of the CPAMs are roughly the approximated shape of an ellipse. The volumes are calculated with the formula length $\times$ height $\times$ width $\times$ 0.52 [39].

The existence of CDH will interfere with normal fetal lung development in intrauterine life which leads to decrease bronchiolar branching, small lung size and hypoplasia [40]. Prenatal diagnosis of CDH is based on ultrasound. Sometimes CDH is hard to diagnose because the herniated liver and lung have the same sonographic characteristics [40]. As prognostic predictors for CDH, the Lung to Head circumference Ratio (LHR) and observed/expected LHR still are controversial and have some limitations [40, 41]. There were some limitations on sonographic characteristics assessment of severity of the fetal intrathoracic lesions. First, fetal position and thorax may impede proper measurement for lesion diameters. Second, the shape of lesion is always irregular, therefore, the results obtained by the above formula might be different with the true volume. Thus, structure characteristics outside of thoracic trachea may provide new diagnostic value. Relatively speaking, airway examinations, especially the cervical trachea, are less affected by fetal position and thorax parameters. A fetus with suspected congenital esophageal hiatal hernia in the other center accepted ultrasound examination at 37W5D in our center, had a 0.37 cm tracheal width. Based on the normal tracheal width, we excluded the suspected diagnosed above. Ectopic kidney was diagnosed by later MR examination. Proved that the airway parameters may have some diagnostic value in fetuses with intrathoracic lesion.

Lung function is not only linked to its volume, but also to its biomechanics [42]. Volume parameters can only reflect the change of lung volume. The airway parameters influenced by biomechanics and lung liquid, might reflect relatively true lung function. The LHR only has prognostic value in left-sided CDH [40]. The airway parameters may be associated with overall lung development, have a potential prognostic value for all types of CDH.

The tracheal diameter in fetuses with laryngeal atresia was significantly higher than normal fetuses [33]. As observed in this study, airway parameters in fetuses with intrathoracic lesion are smaller than normal fetuses. Therefore, when applying the airway parameters for diagnosis and treatment, such as for fetal endoscopic tracheal occlusion on fetus and neonate, suitable instruments selection should be carefully considered.

Limitations and further research:

We were unable to assess the change of airway parameters in many kinds of diseases as the sample size was not sufficient to make such an analysis.

Different stages of lung development are influenced by different kinds of factors [1]; pressure and liquid may play different roles in different stages of lung development. As lesion's size changed with gestational age, characteristics of airway changing mode might be different. Therefore, further investigation on airway growth influenced by kinds of disease, volume change of lesions, change of gestational age is needed. We are in the process of collecting more intrathoracic lesions cases to analyze the correlation between airway parameters and CVR and LHR. In our further study, the value of airway parameters as a predictor of prognosis should be assessed. With volume of lesions would decrease in approximately 15% of CPAMs and 68% of BPS [14], the airway development might have changed accordingly. A fetus with CPAMs was examined by ultrasound in our study, the tracheal width was 0.33 cm and the CVR was 2.38 at 23W6D gestational age, the tracheal width was 0.35 cm and the CVR was 0.38 at 31W6D gestational age. Support our speculation that the airway parameters may have some prognostic value in fetuses with intrathoracic lesion. However, due to small sample size for sequential observation, the correlation between the airway parameters and change of lesions size changes during gestational needs to be further researched.

Conclusions:

Airway diameters increased with gestational age. In fetuses with intrathoracic lesions, the airway diameters are often decreased as compared to normal fetuses. Fetuses with CDH had the smallest trachea diameters in the case group. Airway parameters, especially the tracheal width, is expected to provide a novel diagnostic and prognostic method for intrathoracic lesions.

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	Gestational weeks		TW	SW	NW	LW
Control group	2024	N	77	77	77	77
		Mean	.2606	.1838	.1387	.2749
		Std. Deviation	.03176	.02390	.02035	.04444
	2428	N	12	12	12	12
		Mean	.2825	.2067	.1617	.3133
		Std. Deviation	.02417	.03229	.02038	.05051
	2834	N	23	23	23	23
		Mean	.3483	.2626	.2039	.3678
		Std. Deviation	.05123	.05404	.04418	.06281
Case group	2024	N	14	14	14	14
		Mean	.1786	.1386	.1114	.2321
		Std. Deviation	.03134	.02282	.02381	.04726
	2428	N	16	16	16	16
		Mean	.2338	.1794	.1494	.2744
		Std. Deviation	.04544	.03065	.03473	.04647
	2834	N	11	11	11	11
		Mean	.2800	.2327	.1845	.3236
		Std. Deviation	.03873	.04101	.04083	.04843

Table 1 Airway paraments of the control and the case groups with different gestational ages. (TW: tracheal width, SW: width of subglottic cavity, NW: the narrowest lumen width, LW: width of laryngeal vestibule, GW, gestational weeks)

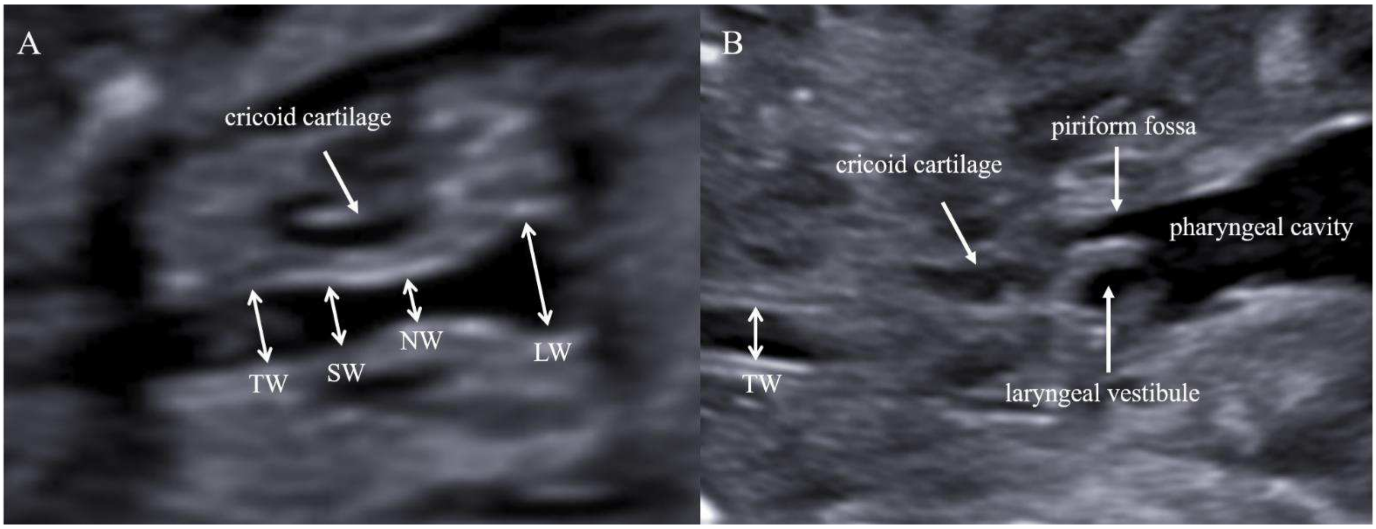

Figure 1 A The opening of the laryngeal lumen, B The closing of the laryngeal lumen. (TW: tracheal width, SW: width of subglottic cavity, NW: the narrowest lumen width, LW: width of laryngeal vestibule)

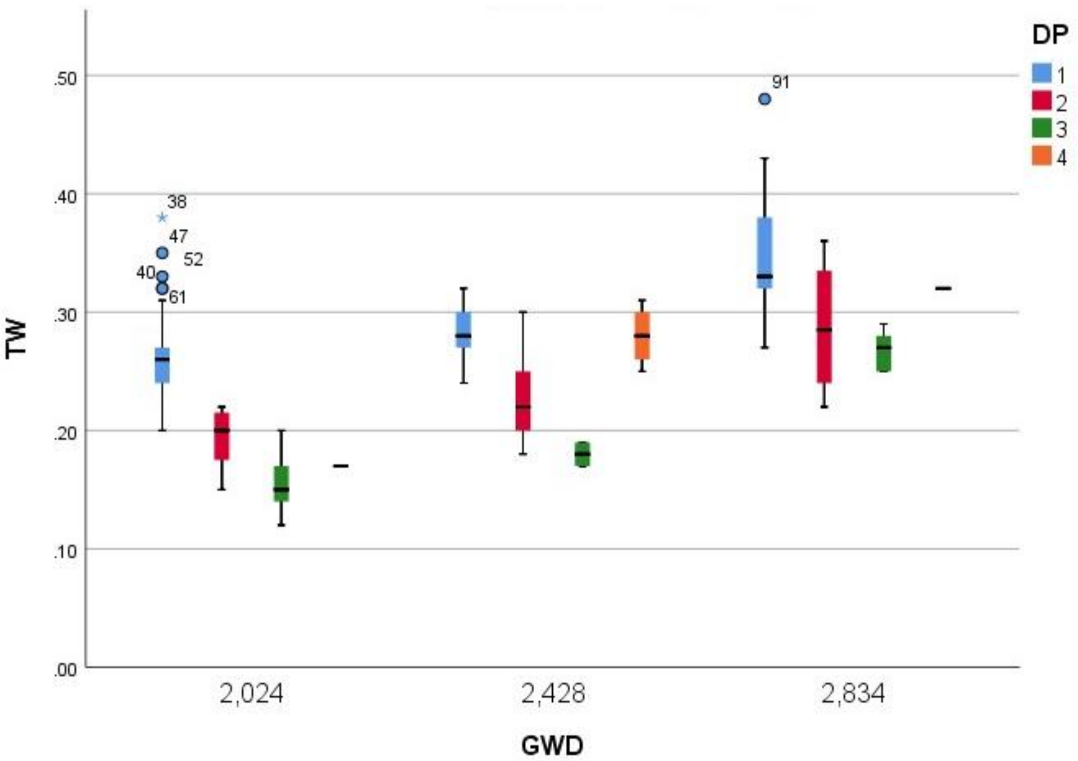

Figure 2 Width of trachea in CDH were minimal than other groups. (DP1: control group, DP2: CPAM group, DP3: CDH group, DP4: BPS group, GWD, gestational weeks)

Figure 3 With the same gestation age, trachea of fetus with normal developed lung (right) was wider than fetus with pulmonary dysplasia which was caused by CDH (left).

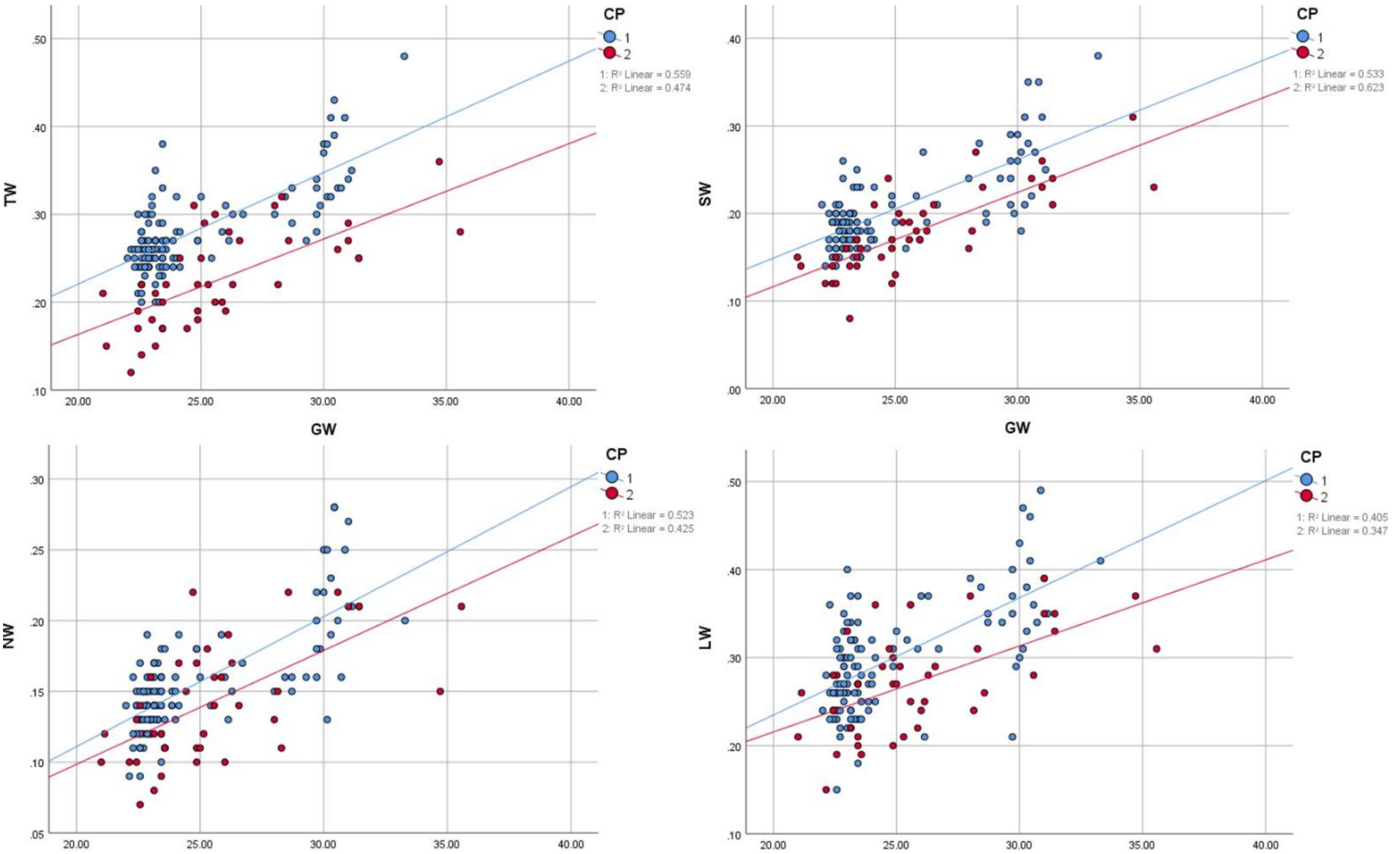

Figure 4 Fetal airway parameters of two groups increased with gestational age. (CP1: control group, CP2: case group, TW: tracheal width, SW: width of subglottic cavity, NW: the narrowest lumen width, LW: width of laryngeal vestibule, GW, gestational weeks)