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Fetal pulmonary artery Doppler blood flow velocity measures and early infant lung function. A prospective cohort study

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ABSTRACT

Background: Reduced lung function at birth has evident antenatal origins and is associated with an increased risk of wheezing and asthma later in life. Little is known about whether blood flow in the fetal pulmonary artery, may impact postnatal lung function.

Objective: Our primary aim was to investigate the potential associations between fetal Doppler blood flow velocity measures in the fetal branch pulmonary artery, and infant lung function by tidal flow-volume (TFV) loops at three months of age in a low-risk population. Our secondary aim was to explore the association between Doppler blood flow velocity measures in the umbilical and middle cerebral arteries, and the same lung function measures.

Methods: In 256 non-selected pregnancies from the birth cohort study Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) we performed fetal ultrasound examination with Doppler blood flow velocity measurements at 30 gestational weeks (GW). We recorded the pulsatility index, peak systolic velocity, time-averaged maximum velocity, acceleration time/ejection time ratio, and time velocity integral primarily in the proximal pulmonary artery close to the pulmonary bifurcation. The pulsatility index was measured in the umbilical and middle cerebral arteries and the peak systolic velocity in the middle cerebral artery. The cerebro-placental ratio (ratio between pulsatility index in the middle cerebral and umbilical arteries) was calculated. Infant lung function was assessed using TFV loops in awake, calmly breathing three months old infants. The outcome was the time to peak tidal expiratory flow to expiratory time ratio (t_{PTEF}/t_E), t_{PTEF}/t_E $<25^{th}$ percentile, and tidal volume per kg body weight (V_T/kg). Potential associations between fetal Doppler blood flow velocity measures and infant lung function were assessed using linear and logistic regressions.

Results: The infants were born at median (min - max) 40.3 (35.6 – 42.4) GW, with a mean (SD) birth weight of 3.52 (0.46) kg, and 49.4% were females. The mean (SD) t_{PTEF}/t_E was 0.39 (0.1) and the 25^{th} percentile was 0.33. Neither univariable nor multivariable regression models revealed any associations between fetal pulmonary blood flow velocity measures and t_{PTEF}/t_E, t_{PTEF}/t_E $<25^{th}$ percentile, or V_T/kg at three months of age. Similarly, we did not observe associations between Doppler blood flow velocity measures in the umbilical and middle cerebral arteries and infant lung function measures.

Conclusion: In a cohort of 256 infants from the general population, fetal third-trimester Doppler blood flow velocity measures in the branch pulmonary, umbilical, and middle cerebral arteries were not associated with infant lung function measures at three months of age.

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Introduction

Impaired lung function at the start of life is associated with respiratory morbidity, such as recurrent wheezing and asthma, and tends to track into adulthood [1,2]. Individuals born with a lower time to peak tidal expiratory flow to expiratory time ratio (t_{PTEF}/t_E) or lower maximal expiratory flow at functional residual capacity are at an increased risk of childhood asthma compared to those with higher values [3,4]. Shortly after birth, infants exposed to maternal smoking *in utero*, both healthy term infants and infants born preterm, were observed to have reduced lung function by tidal flow-volume (TFV) loops compared to infants of nonsmoking mothers [5–7]. However, limited knowledge exists on the aspects of fetal lung development that may lead to reduced lung function in early infancy, highlighting the need to explore the early origins of reduced lung function, within a general, low-risk population.

Lung development begins with the formation of airways, closely accompanied by the growth of pulmonary blood vessels [8]. Pulmonary blood circulation, together with fetal respiratory movements and amniotic fluid, is essential for lung growth and development. In a fetal sheep model, occlusion of one pulmonary artery (PA) branch impaired lung growth on the affected side [9]. Moreover, well-functioning fetoplacental blood flow is a general requirement for fetal growth and development [10].

Intrauterine growth restriction (IUGR) has been associated with reduced lung function in children [11–13]. Severe IUGR is accompanied by increased resistance in the placental and fetal pulmonary circulation [14] as well as a redistribution of fetal blood flow to maintain the oxygenation of the most vital organs [15]. Although the risk of asthma is increased in children born with low birth weight [16], most asthmatic children are appropriately sized at birth [17].

Therefore, to increase the understanding of the early origins of asthma, it is of interest to explore whether fetal blood flow measures are related to postnatal lung function in the general population of infants, without the presence of well-known risk factors of reduced lung function such as IUGR or prematurity [13]. A positive association between the pulsatility index (PI) in the middle cerebral artery (MCA) and childhood lung function was observed in a previous study [18]. A higher time velocity integral (TVI) in the main PA was found to be associated with an increased risk of childhood wheezing, but not with lung function [18]. Fetuses direct a larger proportion of the right ventricular cardiac output *via* the main PA and ductus arteriosus to the lower part of the body and placenta, whereas the rest of the blood is guided to the lungs through the pulmonary branches [19]. In fetuses with an increased risk of severe lung affection at birth, such as following preterm rupture of membranes or diaphragmatic hernia, higher branch PA PI, lower peak systolic velocity (PSV) and TVI [20], as well as shortened acceleration time/ejection time (AT/ET) ratio [21,22] were related to worsened postnatal respiratory outcomes. To our knowledge, no previous study has investigated whether there are associations between Doppler measures from branch PAs and postnatal lung function in the general pediatric population.

Our primary aim was to investigate whether third-trimester measures of fetal blood circulation in proximal PAs were associated with early infant lung function measured by TFV loops at three months of age in a general, low-risk population. Our secondary aim was to explore the possible associations between fetal Doppler blood flow velocity measures in the fetal umbilical artery (UA), MCA, and early infant lung function.

Materials and methods

Study population and study design

This prospective study included a subgroup of 256 infants from the mother-child birth cohort, Preventing Atopic Dermatitis, and ALLergies in Children (PreventADALL) study [23].

Figure 1 shows a flowchart of the 256 participants included in this study. Pregnant women from the general population were recruited during mid-pregnancy over a two-year period from December 2014 to October 2016. Participants with singleton pregnancies at the Oslo location were randomly selected for ultrasound examination at 30 gestational weeks (GW). Infants without severe disease or congenital anomalies born at 35.0 GW or later were enrolled after birth. Infant lung function was measured during the three-month postnatal follow-up. The study population included infants with available information on fetal Doppler blood flow velocity measures and lung function at three months of age.

Ultrasound data collection

Gestational age was determined from head circumference [24] measured during a routine ultrasound examination at approximately 18 GW. At 30 GW, ultrasound examinations were performed by a single operator (K.H.) on a GE Voluson E8 ultrasound system (GE Medical Systems, Zipf, Austria) using a 4-8 mHz

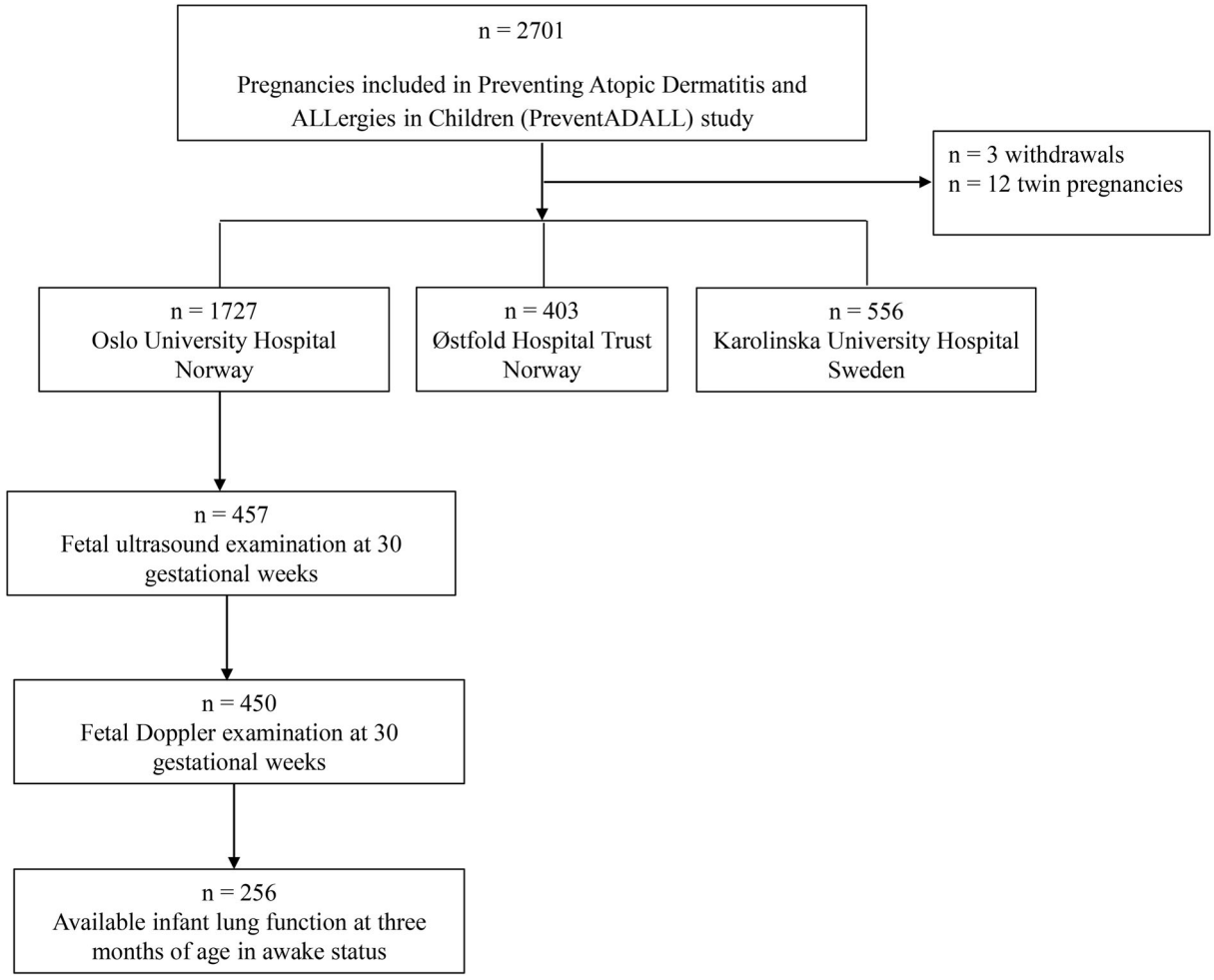

Figure 1. Flowchart of participants included in the study.

transducer. Fetal blood flow was measured using color-directed pulsed-wave Doppler in the absence of fetal respiratory movements, with the mothers lying in a semi-recumbent position. The insonation angle was kept as small as possible (always <25°). All blood flow variables are reported as the average value of three identical consecutive cardiac cycles. In the PA, we performed Doppler interrogation of the right or left proximal branches close to the pulmonary bifurcation. Pulsatility index, PSV, time-averaged maximum velocity, ET/AT ratio, and TVI were measured. Based on previous studies reporting similar blood flow velocity measures in the right and left proximal pulmonary branches [25–27], we sought to record these measures from at least one of the pulmonary branches. For statistical analyses, we used the right PA Doppler measures, if available ($n = 205$). Doppler measures from the left pulmonary branch were used for the remaining fetuses ($n = 8$). In the UA, we performed Doppler measurements in a free loop of the umbilical cord, and in the MCA in its proximal part. We measured the PI in the UA, and PI, and PSV in the MCA. The cerebro-placental ratio was calculated as the ratio of the MCA PI to the UA PI. Ultrasound examination at 30 GW included fetal thoracic circumference measurement by placing an ellipse around the bony thorax in the axial plane at the level of the four-chamber view of the heart parallel to the ribs, as previously described [28]. We estimated fetal weight using the Combs formula [29] from the head and abdominal circumference and femur length measured during the same ultrasound examination.

Infant lung function measurement

Infant lung function at three months of age was measured by TFV loops using an ultrasonic flow meter (Exhalyzer® D; ECO MEDICS AG, Switzerland) as previously described [30]. Trained study personnel measured infant lung function in awake, calmly breathing infants in the supine position. Post-processing analyses focused on the shape and reproducibility of TFV loops [30]. The primary outcome was t_{PTEF}/t_E as a continuous variable, and t_{PTEF}/t_E <25th percentile to specifically

explore infants with lung function in the lower range. The secondary outcome was tidal volume per kg body weight (V_T/kg). The infant weight was measured during the same visit.

Baseline data collection

We obtained baseline data and information on maternal and infant health from interviews and examinations at inclusion in the study, from electronic questionnaires (at 18 and 34 GW and three months after birth), and from obstetrical medical records.

Ethical approvals

The PreventADALL study was approved by the ethics committees of Norway (Regional Committee for Medical and Health Research Ethics in South-Eastern Norway; 2014/518) and Sweden (2014/2242–31/4) and registered at ClinicalTrials.gov (NCT02449850). Informed consent was obtained from all pregnant women at enrollment and from both parents at the time of newborn inclusion.

Statistical analyses

We present the baseline characteristics and descriptive data depending on the variable type and its distribution as means with standard deviation (SD), medians with the first and third quartiles, or numbers and percentages unless otherwise stated. Results from the regression analyses were presented as regression coefficients or odds ratios (OR) with 95% confidence intervals (CI). Group differences were analyzed using the Student's *t*-test, Mann-Whitney *U* test, and Chi-square test.

Linear and logistic regression analyses were used to analyze the associations between fetal Doppler variables and infant lung function. The exposure variables were Doppler measures from the PA, UA, and MCA, as well as the cerebro-placental ratio. The covariates used in the regression models were variables with a possible confounding effect: infant sex, maternal use of nicotine in pregnancy, and hypertension in pregnancy. Fetal size is related to both fetal Doppler measures [31] and childhood lung function [32,33]. Doppler measures in the PA were associated with a fetal thoracic circumference in our previous study [28]. As PA Doppler measures were our main exposure, we selected the fetal thoracic circumference at 30 GW as a covariate to adjust for fetal size. Owing to a slight difference in hemodynamic properties between the right and left PA [34], we adjusted the pulmonary Doppler variables for the sampling side.

To avoid losing track of cases with incomplete data, we imputed missing values for infant weight at three months of age ($n = 2$) and maternal nicotine use ($n = 2$) in the regression models. Missing infant weights were imputed using the mean value for each sex. Best-case imputation (no use) was applied when information on nicotine use during pregnancy was missing (87.9% reported no use of nicotine). Doppler blood velocity measures from the PA were missing for 35 (13.6%) fetuses and 23 (9%) from the MCA. Fetuses with missing pulmonary Doppler values had significantly more frequent long-lasting respiratory movements during ultrasound examination (77.4% vs. 25.8%, $p < .001$). Respiratory movements are frequent in the third trimester and occur 30% of the time at approximately 30 GW [35]. Therefore, we assumed that the missing values were random rather than selective. The distribution of the main outcome variables (t_{PTEF}/t_E and V_T/kg) was similar between infants with and without missing Doppler values (Supplementary Figure S1 showing plots of estimated density). Therefore, the missing variables should not be a substantial source of bias, and we opted not to impute the missing Doppler data.

We performed sensitivity analyses by excluding three infants born preterm (35.0 to 36.9 GW) and 26 infants born small for gestational age, defined as birth weight below the 10th percentile for the Norwegian population [36].

The statistical software IBM® SPSS® version 28.0 (SPSS Inc., Chicago, IL, U.S.A.) was used for the analyses, and statistical significance was determined by a *p*-value $<.05$.

Results

The infant population comprised 129 boys and 127 girls, born at a median age of 40.3 GW (min-max 35.9–42.4). Table 1 presents the baseline characteristics of the mothers and infants. The characteristics of the study population were largely comparable with those of the rest of the PreventADALL cohort, except for higher maternal age, higher prevalence of highly educated women, living in a densely populated area, nulliparity, and breastfeeding in the present study population (Supplementary Table S1). None of the pregnant women reported using nicotine products later than 10 GW. At the time of the ultrasound examination, the pregnant participants did not use any drugs known to modify the Doppler blood flow

Table 1. Maternal and infant baseline characteristics.

	N	Mean (SD) Median (Q1, Q3) *n* (%)
Maternal age (years)	256	33.2 (3.8)
Maternal pre-pregnancy BMI (kg/m^2)	252	22.0 (20.7, 24.2)
Nordic maternal origin, *n* (%)	228	206 (90.4)
Densely populated living area, *n* (%)	228	118 (51.5)
Nicotine use at any time in pregnancy, *n* (%)	254	31 (12.1)
Maternal higher education >4 years, *n* (%)	228	161 (70.6)
Nullipara, *n* (%)	256	170 (66.1)
Maternal asthma (doctor diagnosed), *n* (%)	228	36 (15.8)
Hypertensive disorders, *n* (%)	256	19 (7.4)
Preeclampsia, *n* (%)		6 (2.3)
Diabetes mellitus[a], *n* (%)	256	6 (2.3)
Gestational diabetes mellitus, *n* (%)		5 (2.0)
Estimated fetal weight at 30 GW (kg)	256	1.66 (0.15)
Gestational age at birth (weeks)	256	40.2 (39.3, 41.0)
Birth weight (kg)	256	3.52 (0.46)
Birth weight <10th percentile, *n* (%)	256	26 (10.1)
Caesarean delivery, *n* (%)	256	43 (16.8)
Apgar score at 1 min	252	9.0 (9.0, 9.0)
Apgar score at 5 min	252	10.0 (9.0, 10.0)
Female infant sex, *n* (%)	256	127 (49.6)
Respiratory distress or cough since birth	225	
Yes, once		8 (3.6)
Yes, more than once		3 (1.3)
Infant weight at 3 months of age (kg)	254	6.2 (0.8)
Infant length at 3 months of age (cm)	249	61.8 (2.2)
Breastfeeding at 3 months of age, *n* (%)	225	217 (96.4)

BMI, body mass index; GW, gestational weeks; Q, quartile; SD, standard deviation.
[a]Gestational diabetes mellitus was defined as a plasma glucose concentration ≥7.8 mmol/L 2 h after an oral glucose tolerance test of 75 g glucose.

velocity waveforms. Seven infants (2.3%) were admitted to the neonatal intensive care unit straight after birth, the median hospitalization length was 5 days (min-max 2–7 days). Three of these infants received respiratory support by Continuous Positive Airway Pressure for a short period (no longer than one day) and were discharged without the need for follow-up. Respiratory distress or cough between discharge from the hospital after birth and three months of age was reported in 11 infants from the study population, none of these were among infants hospitalized at the neonatal intensive care unit after birth.

The mean (SD) gestational age at ultrasound examination was 30.0 (0.5) GW, and the mean (SD) infant age at the time of lung function measurement was 92.7 (6.9) days. Mean (SD) deepest vertical amniotic fluid pocket and fetal thoracic circumference were 5.9 (1.02) cm and 20.9 (0.88) cm, respectively. Supplementary Table S2 presents the mean (SD) values of the Doppler blood flow velocity variables. Two fetuses had PI in the UA above the 90th percentile according to the reference charts [32]. The mean (SD) t_{PTEF}/t_E and V_T/kg were 0.39 (0.1) and 7.1 (2.0), respectively.

In both the univariable and multivariable regression models, Doppler variables from fetal PA were not associated with t_{PTEF}/t_E, t_{PTEF}/t_E <25th percentile, or V_T/kg. Similarly, we did not observe associations between UA and MCA Doppler variables and t_{PTEF}/t_E, t_{PTEF}/t_E <25th percentile (Tables 2,3), or V_T/kg (Supplementary Table S3).

Sensitivity analyses (excluding infants born preterm or small for gestational age) confirmed the results of the primary analysis, showing no associations between fetal Doppler blood flow velocity measures and infant lung function (t_{PTEF}/t_E, t_{PTEF}/t_E <25th percentile, or V_T/kg) (results not shown).

Discussion

In a cohort of 256 infants from the general, predominantly urban population, we found no associations between fetal Doppler blood flow velocity measures in the proximal pulmonary artery and infant tidal flow volume measures at three months of age. We did not find associations between Doppler blood flow velocity measures in the umbilical and middle cerebral arteries or cerebro-placental ratio and infant lung function.

To our knowledge, no previous studies have investigated the association between Doppler measures in fetal branch PAs and infant lung function. One study used prospectively measured TVI in the main stem of the PA at 30 GW in fetuses from the general population and, in line with our results, found no association with lung function in children aged 10 years [18].

Table 2. Results from the linear regression analyses with fetal Doppler blood flow velocity measures as exposure and infant t_{PTEF}/t_E at three months of age as outcome.

	Univariable		Multivariable	
Regression model	Coefficient (95% CI)	*p*–value	Coefficient (95% CI)	*p* - value
Pulmonary artery				
PI	0.02 (−0.01, 0.06)	.23	0.02 (−0.16, 0.06)	.28
PSV (m/s)	−0.03 (−0.12, 0.06)	.54	−0.03 (−0.12, 0.06)	.54
TAMX (m/s)	−0.12 (−0.39, 0.16)	.40	−0.12 (−0.39, 0.16)	.40
TVI (m)	−0.22 (−0.85, 0.40)	.49	−0.21 (−0.83, 0.41)	.51
AT/ET	−0.23 (−0.87, 0.40)	.47	− 0.09 (−0.72, 0.55)	.79
Umbilical- and middle cerebral artery				
Umbilical artery PI	0.02 (−0.06, 0.11)	.65	0.02 (−0.07, 0.11)	.68
Middle cerebral artery PI	−0.02 (−0,07, 0.03)	.41	−0.02 (−0.07, 0.03)	.38
Cerebro-placental ratio	−0.02 (−0.05, 0.01)	.17	−0.02 (−0.05, 0.01)	.17
Middle cerebral artery PSV (m/s)	0.008 (−0.15, 0.17)	.92	−0.01 (−0.17, 0.15)	0.90

AT/ET: acceleration time/ejection time ratio; PI: pulsatility index; PSV: peak systolic velocity; TAMX: time averaged maximum velocity; TVI: time velocity integral; t_{PTEF}/t_E: ratio of time to peak tidal expiratory flow to expiratory time. Multivariable models were adjusted for infant sex, fetal thoracic circumference at 30 gestational weeks, maternal use of nicotine in pregnancy, hypertension in pregnancy, and sampling side for models including blood flow variables from the pulmonary artery.

Table 3. Results from the logistic regression analyses with fetal Doppler blood flow velocity measures as exposures and t_{PTEF}/t_E at three months of age $<25^{th}$ percentile (t_{PTEF}/t_E <0.33) as outcome.

	Univariable		Multivariable	
Regression model	Odds ratio (95% CI)	*p* - value	Odds ratio (95% CI)	*p*–value
Pulmonary artery				
PI	0.83 (0.31, 2.20)	.71	0.94 (0.34, 2.58)	.90
PSV (cm/s)	1.00 (0.98, 1.03)	.75	1.01 (0.98, 1.03)	.71
TAMX (cm/s)	1.01 (0.94, 1.09)	.77	1.01 (0.93, 1.09)	.83
TVI (cm)	0.99 (0.84, 1.18)	.95	0.99 (0.83, 1.18)	.90
AT/ET Z-score[a]	1.13 (0.84, 1.54)	.42	1.09 (0.78, 1.52)	.63
Umbilical- and middle cerebral artery				
Umbilical artery PI	1.98 (0.18, 21.26)	.57	2.99 (0.24, 37.43)	.40
Middle cerebral artery PI	2.28 (0.63, 8.25)	.21	2.47 (0.66, 9.22)	.18
Cerebro-placental ratio	1.44 (0.62, 3.35)	.40	1.42 (0.59, 3.40)	.44
Middle cerebral artery PSV (cm/s)	1.01 (0.97, 165.45)	.71	1.01 (0.97, 1.06)	.57

AT/ET: acceleration time/ejection time ratio; PI: pulsatility index; PSV: peak systolic velocity; TAMX: (time averaged maximum velocity; TVI: time velocity integral; t_{PTEF}/t_E: ratio of time to peak tidal expiratory flow to expiratory time.
[a]The AT/ET ratio was converted to Z-score to improve the interpretability of the regression output. Multivariable models were adjusted for infant sex, fetal thoracic circumference at 30 gestational weeks, maternal use of nicotine in pregnancy, hypertension in pregnancy, and sampling side for models including blood flow variables from the pulmonary artery.

In agreement with our observations, two previous studies from the general population reported no association between third-trimester UA PI and childhood lung function [18,37]. In a study by Kooijman et al. a positive association between MCA PI at 30 GW in 903 fetuses from the general population and a ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) in children around 10 years of age was reported [18]. The different results obtained in our study may be attributable to the different methods and times of lung function measurement. While we measured TFV loops in early infancy, Kooijman et al. used lung function measures assessed using traditional spirometry, a method not suitable for early infancy [18].

The results of our study should be interpreted with caution, as our observations were restricted to lung function assessments in three months old infants. Although trajectories of lung function may seem to be at least partially established at birth [1,2] it will be of interest to further investigate whether fetal Doppler blood flow velocity measures in branch PAs are related to lung function measures and asthma-related symptoms in older age groups.

The main strength of our study is that all fetal ultrasound measurements were collected prospectively by the same, experienced, and dedicated operator within a period of two weeks at approximately 30 GW. Lung function was measured in early infancy using a standardized method [30]. The choice of TFV loops for lung function measurement might be considered as a possible limitation when compared to spirometry and its possibility to measure forced expiratory flow and perhaps more detailed outcomes. However, in our study, we aimed to investigate the origins of lung function in early infancy. In a larger epidemiological study such as the PreventADALL study, measuring TFV loops is a feasible method without the need for sedation, and t_{PTEF}/t_E correlates with forced expiratory measures in infants [4,38]. As previously shown, this method was

sufficiently sensitive to demonstrate improved lung function in the offspring of smoking mothers using vitamin C in pregnancy compared to those who used a placebo [7]. Most of the women in our study were highly educated, of Nordic origin, lived in urban areas, and did not use nicotine products during pregnancy. Therefore, the generalizability of our results to other populations is limited.

Conclusion

In this study from the general population, we observed no associations between third-trimester fetal Doppler blood flow velocity measures in the pulmonary, umbilical, and middle cerebral arteries, as well as the cerebro-placental ratio and lung function in healthy infants at three months of age. Future studies should investigate the relationship between blood flow in branch PAs, spirometry measurements, and symptoms of obstructive respiratory disease in older children.

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