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Correlation between Pulmonary Artery Doppler with Neonatal Outcome in Patients with Placenta Accreta Spectrum Disorders

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Abstract

***Objective**: The purpose of this study was to correlate fetal main pulmonary artery (PA) Doppler indices with the neonatal outcome in the late preterm and early term pregnancies in placenta accreta spectrum (PAS) patients **Methods**: A prospective cross-sectional study was conducted on 71 patients with PAS disorders singleton pregnancies undergoing elective or emergency termination of pregnancy under general anesthesia at or after 34 weeks. A full obstetrics ultrasound scan was performed within 24 hours before delivery and after corticosteroids administration to confirm the eligibility criteria and to measure PA Doppler indices in the main PA (pulsatility index (PI), resistance index (RI), systolic to diastolic (S/D) ratio, peak systolic velocity (PSV) and acceleration to ejection time (At/Et) ratio). **Results**: Twenty-three neonates needed respiratory support and neonatal intensive care unit (NICU) admission. Fetuses that needed respiratory support had a significantly lower gestational age at delivery (36±1.2 versus 36.8±0.5), lower estimated fetal weight (EFW) (2770±475 versus 3096±328), lower birth weight (2782±595 versus 3152±337) and also lower Apgar score than those who did not need. None of the PA Doppler parameters correlated with the neonatal need for respiratory support. The need for respiratory support was more in the neonates who were terminated on emergency basis (39.1% versus 60.9%). The depth of placental invasion correlated with maternal morbidity. **Conclusions**: PA Doppler parameters do not correlate with the need for respiratory support in patient with PAS disorders.*

Keywords: *Placenta accreta spectrum disorders, Pulmonary artery Doppler, Respiratory support*

1. Introduction

The incidence of PAS has risen dramatically over the last three or four decades owing to the increase in incidence of cesarean delivery (CD) (1, 2). PAS is associated with various maternal and neonatal morbidities and mortalities. This is due to the massive blood loss either antepartum, intrapartum (with manual separation of the placenta) or even postpartum if conservative management was chosen, the need for peripartum hysterectomy, massive blood transfusion, associated organ injuries and maternal intensive care unit (ICU) admission (1). These morbidities are lower in elective than emergency termination **.(3)**

Therefore, management options balance maternal antepartum bleeding and fetal prematurity. This has led to scheduling of termination of pregnancy in PAS as late preterm (34-36 weeks) and early term (37 weeks) to avoid the need for emergency surgery (4). Presence of signs of fetal lung maturity in routine antenatal ultrasound can aid the obstetrician to the accurate timing of termination especially in low-income countries with limited access to NICUs**.**

Several studies have addressed the role of fetal PA Doppler in detecting fetal lung maturity for example it has been evaluated in diabetics where they found that the fetal PA At/Et ratio was elevated in those who developed respiratory distress syndrome (RDS) (5). On the other hand, fetal PA At/Et ratio was lower in small for gestational age and was inversely correlated with transient tachypnea of newborn

(TTN) (6). Most have agreed that a cut off value of 0.3 for fetal PA At/Et could predict the development of RDS (7). None has investigated its role in cases with PAS with its different placental shunts and lacunae that affects fetoplacental circulation resistance. The aim of our work was to detect whether the fetal PA Doppler could predict the need for neonatal respiratory support or not.

2. Materials and Methods

This prospective cross-sectional study was performed at the obstetrics and gynecology department faculty of medicine Cairo University from August 15, 2021 to September 1, 2022 after approval of the institutional ethical committee (MD-20-2021) and the Clinicaltrials.gov (NCT04911322). We recruited 71 pregnant women diagnosed with PAS disorders preoperatively according to Jauniaux et al., (8), Jauniaux et al. (9) who had completed the course of antenatal corticosteroids according to RCOG (10) with age ranging from 18 to 42 years old and gestational age 34 0/7 – 38 6/7 weeks undergoing either elective or emergency termination of pregnancy under general anesthesia. We excluded multifetal pregnancy, intrauterine fetal death, intrauterine growth restriction, medical disorders with pregnancy as diabetes or pregnancy induced hypertension, premature rupture of membranes (PROM), body mass index (BMI) above 40 (due to technical difficulties to obtain accurate measures), narcotic usage during anesthesia before fetal delivery, major congenital fetal anomalies (whether diagnosed before or after delivery), maternal fever more than 37.4 degree, emergent cases presenting with fetal distress and intraoperative spontaneous separation of the placenta .

After obtaining an informed written consent, the gestational age was calculated (based on the first trimester crown to rump length or an accurate last menstrual period) .

A full obstetrics ultrasound scan using GE Voluson → E10, GE Medical System, Zipf, Austria was performed within 24 hours before delivery to assess signs of placental invasion, to document fetal biometry and to measure the fetal PA Doppler parameters.

To assess signs of placental invasion, transabdominal ultrasound using RAB6-D probe with a 2-8 MHz curved array was performed in a supine position with full bladder then the patient was asked to evacuate her bladder and a transvaginal RIC5-9-D probe with 4-9 MHz was performed in a stretcher with stirrups to confirm signs of placental invasion.

Fetal Echo was performed to all participants and this included structural fetal heart examination (4 chamber view, three vessel view, outflow tracts and aortic arch view). The fetal PA Doppler parameters were measured in the main PA midway between the pulmonary valve and bifurcation of the right and left branches with angle of insonation within 15 degrees with the fetus at rest without gross movements or breathing. Doppler gain and scale were adjusted for optimal velocity waveform that clearly display the PSV and early diastolic notch. Three consecutive measures were taken and the results were reported as average of these three measures. The PA Doppler parameters included PI, RI, S/D ratio, PSV and at/Et ratio. The At/Et ratio was obtained through dividing the time interval from the beginning of the systole to the peak velocity of ventricular systole (At) by time interval from the beginning to the end of the ventricular systole (Et).*(11)*

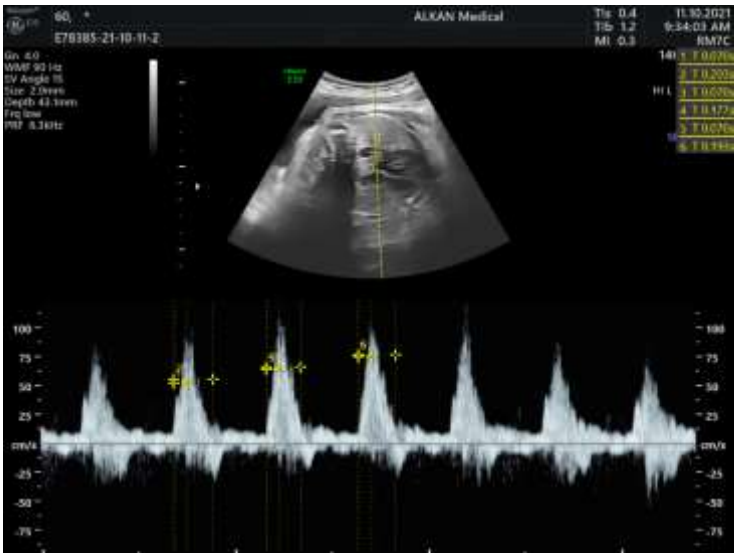

Figure 1: Measurement of blood flow velocity waveform through the main PA (adapted from our patients)

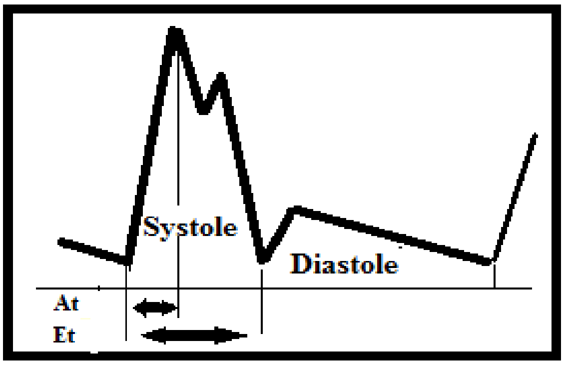

Figure 2: Schematic representation of the fetal PA Doppler waveform. Abbreviations: At: acceleration time, time interval from the beginning of ventricular systole to the peak of systole. Et: ejection time, time interval from the beginning to the end of ventricular systole.

Termination of pregnancy was performed by a specialized team in our department who were in charge of all PAS cases. Intraoperative confirmation of diagnosis was according to Jauniaux et al. (12) The following operative details were recorded: time from anesthesia till delivery (cord clamping) in minutes (we approximated to the nearest minute), time from skin incision to delivery, elective or emergency termination, upper segment versus lower segment CD, cesarean hysterectomy, organ injuries, need for blood and blood products transfusion and the number of units transfused .

Following fetal delivery, Apgar score was assessed at 1 and 5 minutes. The need for respiratory support (whether nasal, continuous positive airway pressure (CPAP) or ventilation) and NICU admission were recorded. Also, the neonatal birth weight was recorded.

The neonates were grouped according to the need for respiratory support (poor neonatal outcome) and no need for respiratory support (good neonatal outcome).

Outcome measures:

Primary outcome:

-At/Et ratio of fetal PA Doppler in neonates with good and poor outcome.

Secondary outcome:

-The rest of the aforementioned PA Doppler parameters in good and poor neonates.

-Percent of women who undergone cesarean hysterectomy versus conservative management

-The need for blood transfusion

-Maternal morbidity and mortality rate

Sample size calculation statistical statement:

Sample size calculation was done using the comparison of Doppler-measured At/Et in fetal PA between fetuses with poor outcome and those with good outcome. As reported in previous publication (13), the mean ± SD of At/Et in cases with neonatal RDS was approximately 0.209 ± 0.054, while in good outcome group it was approximately 0.332 ± 0.066. Assuming that the prevalence of poor neonatal outcome in similar population is approximately 20% (14), we need to study at least 48 participants to be able to reject the null hypothesis with 80% power at $\alpha = 0.05$ level using Student's t test for independent samples. Sample size calculation was done using PS Power and Sample Size Calculations software, version 3.0.11 for MS Windows (William D. Dupont and Walton D., Vanderbilt University, Nashville, Tennessee, USA).

However, due to our wide inclusion criteria, we considered performing more cases to search for correlation between different variables of inclusions.

Statistical Analysis: Data were statistically described in terms of mean □ standard deviation (□ SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using Student t test for independent samples in comparing normally distributed data and Mann Whitney U test for independent samples for comparing not-normal data. For comparing categorical data, Chi-square (□2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Pearson moment correlation equation for linear relation of normally distributed variables and Spearman rank correlation equation for non-normal variables/non-linear monotonic relation. Multivariate logistic regression analysis was used to test for the preferential effect of the independent variable(s) on predicting the need of respiratory support with presenting the regression equation. Two-sided p values less than 0.05 was considered statistically significant. IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows was used for all statistical analyses.

3. Results and Discussion

We approached 103 patients and 32 patients were excluded .

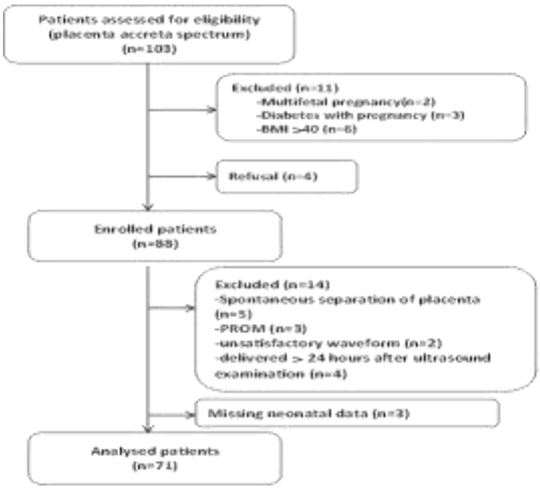

Figure 3: Patient enrollment chart.

We thus analyzed 71 patients (33 cases acreta, 34 cases increta and 4 cases percreta) including 58 elective and 13 emergency cases. There were 23 neonates who needed respiratory support and NICU admission (13 neonates needed nasal flow oxygen, 10 cases needed CPAP, 0 cases needed ventilation). Thirty-one women (43.7%) underwent cesarean hysterectomy and other 40 women (56.3%) had conservative management. Forty-eight women (67%) needed blood transfusion with the average number of packed RBCs units transfused 2 ± 1.05 and fresh blood 1.56 ± 0.52. Thirteen women (18.3%) needed fresh frozen plasma transfusion with the average number of units transfused 1.92 ± 1.44. Six patients had organ injuries in the form of bladder, ureteric and serosal intestinal injuries. No cases of maternal ICU admission or mortality .

There was no statistically significant difference between both groups in the need for respiratory support as regards the maternal age, parity, BMI, procedure done whether conservative or cesarean hysterectomy, uterine incision (vertical upper segment or lower transverse incision), need for blood transfusion, placental invasion and neonatal sex. On the other hand, the neonates who needed respiratory support were those with lower gestational age, lower EFW, who were terminated on emergency basis, with longer time from anesthesia till delivery, longer time from skin incision till delivery, lower Apgar score at 1 and 5 minutes and lower neonatal birth weight.

Table 1: Correlation between the studied variables and the need for respiratory support.

Variable	Need respiratory support (n=23)	No need for respiratory support (n=48)	P-value
Age (years)	33 ± 4.6	31.1 ± 5.3	0.147
Parity	3 (1-7)	3 (1-8)	0.135
Gestational age (weeks)	36 ± 1.2	36.8 ± 0.5	<0.001*
BMI (Kg/m^2)	29.4 ± 4.2	30.1 ± 4.04	0.46
Estimated fetal weight (g.)	2770 ± 475	3096± 328	0.001*
Termination urgency			0.003
Elective	14 (60.9%)	44 (91.7%)	
Emergency	9 (39.1%) (GA <37 weeks in 8 out 9)	4 (8.3%) (2 out of 4)	
Procedure			0.624

Conservative	12 (52.2%)	28 (58.3%)	
Cesarean hysterectomy	11 (47.8%)	20 (41.7%)	
Uterine incision			0.313
Vertical upper segment	13 (56.5%)	21 (43.8%)	
Lower transverse incision	10 (43.5%)	27 (56.3%)	
Time from anesthesia till fetal delivery (min.)	43.5 ± 9.3	37.9 ± 6.4	0.004
Time from skin incision till fetal delivery (min.)	32 ± 9.8	27.1 ± 7	0.02
Need for blood transfusion	17 (73%)	31 (64%)	0.43
Placental invasion			0.35
Acreta	8 (34%)	25 (52.1%)	
Increta	13 (56.5%)	21 (43.8%)	
Percreta	2 (8.7%)	2 (4.2%)	
APGAR score at 1 min.	4 (2-7)	7 (2-8)	<0.001
APGAR score at 5 min.	7 (4-10)	9 (7-10)	< 0.001
NBW (g.)	2782 ± 595	3152 ± 337	0.001
Neonatal sex			0.607
Male	13 (56.5%)	24 (50%)	
Female	10 (43.5%)	24 (50%)	

Abbreviation: BMI: Body mass index, g: grams, GA: gestational age, min: minutes, NBW: neonatal birth weight, IQR: Interquartile range, SD: standard deviation
p-value>0.05 NS
Values are given as mean± SD or Median (IQR) or number (percentage)

When we correlated the fetal PA Doppler parameters with the need for respiratory support, none was statistically significant.

Table 2: Correlation between PA Doppler data and the need for respiratory support**.**

Variable	Need respiratory support (n=23)	No need for respiratory support (n=48)	P-value
PA PI	2.33 ± 0.3	2.35± 0.4	0.79
PA RI	0.84± 0.04	0.84± 0.04	0.84
PA S/D	6.8± 2	6.5± 1.7	0.49
PA PSV	68.1 ± 20.5	67.9 ± 18.4	0.96
PA At/Et	0.337 ± 0.051	0.34 ± 0.051	0.82
PA At	57.34 ± 17.54	55.33 ± 11.4	0.566
PA Et	173.64 ± 58.1	164.76 ± 39.02	0.449

Abbreviation: PA: pulmonary artery, PI: pulsatility index, RI: resistance index, S/D: systolic to diastolic ratio, PSV: peak systolic velocity, At/Et: acceleration time to ejection time ratio
p-value>0.05 NS
Values are given as mean ± SD

As regards the maternal morbidity, there were no statistically significant difference between both groups in maternal age, parity, gestational age, procedure done, elective or emergency termination, uterine incision, time from anesthesia till delivery and the need for blood transfusion. However, the gravidity and the extent of placental invasion correlated with the maternal morbidity.

Table 1: Correlation between the studied variables and the maternal morbidity.

Variable	Maternal morbidity (n=6)	No maternal morbidity (n=65)	P-value
Age	36.17 ± 5.345	31.4 ± 4.977	0.029
Gravidity	5 (3-10)	3 (1-10)	0.046
Parity	4 (3-7)	3 (1-8)	0.076
Gestational age (weeks)	36.81 ± 0.42	36.5 ± 0.93	0.704
Procedure			0.235
Conservative	2 (33.3%)	38 (58.5%)	
Cesarean hysterectomy	4 (66.7%)	27 (41.5%)	
Termination urgency			0.226
Elective	6 (100%)	52 (80%)	
Emergency	0	13 (20%)	
Uterine incision			0.069
Vertical upper segment	5 (83.3%)	29 (44.6%)	
Lower transverse incision	1 (16.7%)	36 (55.4%)	
Time from anesthesia till fetal delivery (min.)	40 ± 11.4	39.7 ± 7.6	0.958

Need for blood transfusion	4 (66.7%)	44 (67.7%)	0.959
Placental invasion			0.006
Acreta	1 (16.7%)	32 (49.2)	
Increta	3 (50%)	31 (47.7%)	
Percreta	2 (33.3%)	2 (3.1%)	

Abbreviation: min: minutes, IQR: Interquartile range
p-value>0.05 NS
Values are given as mean± SD or Median (IQR) or n (%)

PAS management starts from prenatal diagnosis that allows reasonable risk stratification, surgical planning and team mobilization. Prenatal diagnosis depends mainly on ultrasonography which is not without limitations; being operator dependent and depend on several factors as elevated BMI, posterior placentation, angle of insonation and equipment settings. Moreover, we are lacking of standardized definitions of PAS markers and recent studies have found these markers in women with low risk of PAS. On the other hand, the absence of these markers does not exclude the diagnosis of PAS .(15)

One should not forget the antenatal assessment for the possibility of respiratory distress in neonates is of important clinical significance as more than three quarters of premature babies can be saved with timely feasible, cost-effective care especially in setting with poor neonatal facilities Therefore, interventions should begin from the antenatal period and extend to the postnatal period. It remains challenging for the obstetrician to balance the risks of continuing the pregnancy versus the risk of delivery before term.

Early attempts have been made to predict fetal maturity based on antenatal ultrasound parameters including lung characteristics, bowel pattern, placental grading (which cannot be relied upon in patients with PAS), the presence or absence of intra-amniotic particles (vernix caseosa) and the epiphyseal ossification centers (16). However, none of these has proven to be accurate for use in clinical practice. Recently, fetal PA Doppler has been used to predict neonatal RDS (17) However to the best of our knowledge no one has correlated PA Doppler indices with the neonatal outcome in the late preterm and early term neonates in PAS patients.

In the present study, the maternal obstetrics and demographic data did not affect the neonatal need for respiratory support and the studied PA Doppler parameters, did not correlate with the need for respiratory support.

Kim et al. (11) did not agree with this and found elevated fetal PA At/Et ratio in preterm infants who developed RDS and Mohamed et al. (5) who also found elevated fetal PA At/Et ratio in fetuses of diabetic mothers who developed RDS. However, our results agreed with their results in that no correlation was found between PA S/D, PSV, At, RI, PI and the neonatal need for respiratory support.

Our results also contradicted Moety et al. (13) who found At/Et ratio was decreased, main PA PI was increased, and the PSV was decreased in fetuses that developed RDS and Sahin et al. (6) who found that At/Et was inversely correlated with TTN. Also, Abdel Hamid et al. (7) found that At/Et ratio was lower in those fetuses who developed RDS and that there were no difference in PI and RI between both groups. Duncan et al. (18) found lower At/Et ratio in fetuses of mothers with PROM who developed respiratory complications .

Our results agreed with Borna et al. (19) who found no difference in PA PI fetuses of mothers with PROM who developed respiratory complications. Similar results were obtained by many authors who hypothesized that the vasculature of preterm lungs has high resistance and pressure. (Aafreen et al. (20), Guan et al. (21), Khanipouyani et al. (22), Buke et al. (14) , Buke and Akkaya. (23) , Khalil et al. (24). Aafreen et al. (20) In cases of pulmonary hypertension, the time taken to reach the peak (At) is shortened, resulting in reduced time interval to complete the systole. As a result, the At/Et ratio is decreased in preterm lung as compared to term fetus. Therefore, an inverse correlation exists between At/Et ratio and occurrence of respiratory distress.

One should note that none of the previous studies clearly stated whether the fetal PA Doppler indices were measured before or after steroid administration for lung maturity. This is important because Vafaei et al. (17) studied the impact of betamethasone on fetal pulmonary, umbilical and middle cerebral artery Doppler velocimetry and its relationship with neonatal RDS. They concluded that maternal antenatal betamethasone administration reduced the fetal PA resistance among fetuses with RDS. In addition, among fetuses with RDS, significant decrease in PA At was found and no differences were observed in the PA At/Et ratios, PI, RI, and ET.

Our results were in agreement with Lindsley et al. (25) who studied the effect of maternal corticosteroids administration on fetal PA blood flow in women at risk of preterm labour and found no differences in fetal PA PSV, S/D ratio, PI, and RI, AT, At/Et ratio of preterm newborns with RDS versus those without RDS. Gungor et al. (26) also found no statistically significant differences in pulmonary blood flow (PI and RI) between fetuses who developed RDS and those who did not .

The results of this study showed that fetuses that needed respiratory support had a significantly lower gestational age at delivery, lower EFW, lower birth weight and also lower Apgar score than those whose did not need. These results are in agreement with several authors. Kim et al . (11), Guan et al. (21) , Moety et al. (13) Gungor et al. (26), Buke et al. (14) , Khalil et al. (24), Abdel Hamid et al. (7), Duncan et al. (18) and Aafreen et al. (20). However, these results are not in agreement with Buke and Akkaya. (23) Also, Vafaei et al. (17) found no difference in neonatal weight between fetuses who developed RDS and who did not.

Our results showed no difference in fetal gender between fetuses that needed respiratory support and who did not, however, Moety et al. (13) stated that RDS was more commonly encountered in male fetuses.

Our results showed that the depth of placental invasion correlated with maternal morbidity. However, the maternal outcome was not affected by the gestational age at termination even those that needed emergent delivery did not have more morbidities or complications. These results agree with Allen et al. (27) and Cali et al. (28). The latter studied 259 pregnant women with placenta previa and PAS disorders. They found that the increasing severity of PAS disorders was associated with increase in surgical complications, longer operative time and longer hospital stay. Their results are not in agreement with ours in that increasing severity of PAS disorders is associated with more blood loss, higher need for blood transfusion and ICU admission. Similar results were obtained by Dall'Asta et al. (29) when they evaluated 43 cases of placenta previa and PAS disorders.

Our results agree with Flores-Mendoza et al. (30) who studied 125 patients with PAS disorders who were scheduled for elective or emergency termination. They found that emergency birth was associated with lower gestational age at termination. Contrary to our results, they reported that emergency termination was associated with higher surgical complications, maternal blood loss, coagulopathy and blood transfusion this may be due to lack of standardized management protocols between elective and emergency termination in their setting

Our results also agreed with Morlando et al. (31) who studied 356 women with PAS disorders and found that no significant differences in terms of blood loss, transfusion rates or major maternal morbidity between planned and emergency deliveries. Regarding the neonatal outcome, emergency termination was associated with lower gestational age at delivery, with better neonatal outcomes for higher gestational ages. Similarly, Huang et al. (31) studied 225 patients with PAS disorders and found that planned delivery was associated with higher neonatal birth weight and lower rate of preterm delivery compared with emergency delivery.

Conclusion

We believe that the strength of this study lies in its novality, prospective design, sample size calculation, single sonographer with no interobserver variation, and prenatal administration of maternal steroids to all cases. However, no study is without limitation. We acknowledge that we need a larger sample size, a wider range in gestational age and to study the effect of steroids on fetal PA Doppler velocimetry. Additionally, Doppler is a difficult technique, heavily operator dependent and requires a great deal of experience. Inter and intra observer variation was not assessed in this study.

To conclude PA Doppler parameters do not correlate with the need for respiratory support in patient with PAS disorders, yet further studies are needed to verify such findings in different clinical settings.

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