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RESEARCH

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Validity of ductus arteriosus indices added to other ultrasound and Doppler parameters as markers of fetal lung maturity in pregnancy-induced hypertension

Safia Badr Sayed[1*], Soha Talaat Hamed[1], Hassan Mostafa Gaafar[2], Kareman Hamza Ibrahim[1] and Mariam Raafat Louis[1]

Abstract

Aim of work To determine the relationship between the gestational age and the (PSV, RI and PI) of the ductus arteriosus and lung maturity and to determine the effect of pregnancy-induced hypertension on these parameters.

Material and methods A prospective cohort study was carried out, in which 90 pregnant women at gestational age 34–40 weeks were selected, 50 as a control and 40 with pregnancy-induced hypertension (PIH). They underwent measurement of ductus arteriosus (DA) (PSV, RI and PI) and observing the percentage of the development of neonatal RDS in control and PIH cases.

Results There was a direct correlation between the PSV, PI, RI of ductus arteriosus and development of neonatal RDS. A cutoff value for GA, PSV, RI and PI for prediction of the subsequent development of RDS was determined in control ((35.7, 89.9, 0.80, 2.14), with sensitivity (71.4, 100, 85.7, 85.7%) and specificity (93, 97.7, 97.7, 93%), respectively), and PIH (35.7, 91.1, 0.80, 2.14), with sensitivity (71.4, 100, 85.7, 100%) and specificity (71.7, 100, 85.7, 100%), respectively).

Conclusions We concluded from our study that for the detection of fetal lung maturity in fetuses of GA from 34 to 40 weeks, it is better to combine GA, PSV, RI and PI of DA to detect lung maturity in control and PIH groups to get more accurate results.

Keywords Respiratory distress syndrome, Doppler ultrasound, Ductus arteriosus, Fetal lung maturity

Background

Respiratory distress syndrome (RDS) is the most common cause of respiratory distress in premature infants. Incidence and severity are inversely related to GA. It affects up to 92% of neonates born at 24–25 weeks, with incidence decreasing to 57% at 30–31 weeks [2].

Hypertension associated with pregnancy is a common condition which affects more than 5—8% of all pregnancies. It is one of the main causes of maternal, fetal and neonatal mortality and morbidity; 5–22% of all pregnancies may suffer any of medical problem due to hypertension such as eclampsia, placental abruption, HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count), preterm delivery, or even fetal or maternal death. The probability of adverse perinatal outcome increases with lower gestational age [6].

*Correspondence:
Safia Badr Sayed
drsafiabadr@yahoo.com
[1] Radiology Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[2] Obstetrics and Gynecology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

Biochemical, biological and physical tests of amniotic fluid have been developed to determine the risk of neonatal RDS and help obstetricians to decide when to terminate pregnancy [5]. However, amniotic fluid can only be tested after amniocentesis which is an invasive procedure that presents potential hazards for pregnancy, such as feto-maternal hemorrhage, placental rupture, premature rupture of the membranes, neonatal sepsis, fetal injury and even fetal death [1].

Therefore, a non-invasive test to assess fetal lung maturity is a more acceptable option for pregnant women. Fetal lung maturity can be assessed by ultrasonic evaluation of gross morphology and the use of Doppler indices which are the assessment of the fetal ductus arteriosus (PSV, RI, PI) to predict neonatal RDS [7].

Methods

This prospective study was done on 90 pregnant females in the child-bearing period aged 19–40 years with gestational age between 32 and 40 weeks, 50 as control and 40 with PIH who came to Fetal Medicine Unit between June 2019 and May 2022, admitted during labor or elective CS 24 h before labor. All of the study participants gave informed written consent to the study.

Inclusion criteria: In the control group: medically free women with singleton pregnancy at gestational age 32–40 weeks. In hypertensive group: persistent high blood pressure that developed during pregnancy and associated with proteinuria or the new development of decreased blood platelets, renal or hepatic troubles, fluid in the lungs, or CNS symptoms such as seizures and/or visual disturbances.

Exclusion criteria: Multiple pregnancies–fetal growth less than the 10th percentile or greater than the 95th percentile for gestational age, chromosomal/structural abnormalities. Known, pre-existing medical conditions (e.g., diabetes, nephropathy, and cholestasis).

All patients were subjected to

a. Thorough clinical examination with history taking and gynecological examination.

b. Ultrasonographic assessment &PSV, PI,RA of DA.

Obstetric ultrasonography was performed on admission within 24 h before labor by the same operator using the Voluson E10 (General Electric Healthcare) using 3–5-MHz multifrequency convex trans-abdominal transducer. The women were placed in the supine position, with head to 35°; obstetric ultrasound examinations were performed in all cases including fetal biometry, placental site, amniotic fluid index, excluding gross fetal anomalies.

c. Doppler study of PSV, RI, PI of ductus arteriosus (DA).

Doppler measurements were obtained at a physiologic fetal heart rate of 120–160 beats/min in the absence of maternal or fetal body and breathing movements. The fetal heart is examined in a systematic manner (the four-chamber view, the outflow tracts and the three-vessel view) to exclude important structural cardiac defect. Then, an axial plane was used through the fetal chest to achieve the vision of 4 chambers of the heart. Measurements of PSV, RI, PI of DA were taken place within the proximal portion of the ductal arch in a longitudinal section of the fetus from which the ductal arch can be appreciated. Color Doppler was used to adjust the ideal Doppler parameters (i.e., scale, color gain, filter) and then turned off as it causes blue and red overlapping colors, which would obscure the ductus vision, then pulsed Doppler was introduced, and the sample volume was focused on the DA. The sample volume was placed over the ductus directly depending on the sonographic anatomy, the sample volume was adjusted to 3 mm, and the insonation angle was remained at 15°.

Statistical analysis and sample size

Data were coded and entered using the Statistical Package for the Social Sciences (SPSS), version 28 (IBM Corp., Armonk, NY, USA). Data were summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were made using unpaired t test. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. ROC curve was constructed with area under curve analysis performed to detect best cut-off value of significant parameters for detection of need of ICU. Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic efficacy were calculated. *P* values less than 0.05 were considered as statistically significant. The calculated sample size is 90 fetuses, 50 as control and 40 being mother with pregnancy-induced hypertension, examined to detect DA PSV, RI, PI within 24 h of delivery.

Follow-up after delivery and diagnosis of RDS

Upon delivery, the route of delivery, GA, neonatal birth weight (NBW) were recorded. The diagnosis of RDS was based on clinical signs of respiratory distress (Figs. 1, 2, 3 and 4).

Results

A total of 90 fetuses were examined, 50 as control and 40 being mother with pregnancy-induced hypertension, examined to detect DA PSV, RI, PI within 24 h of

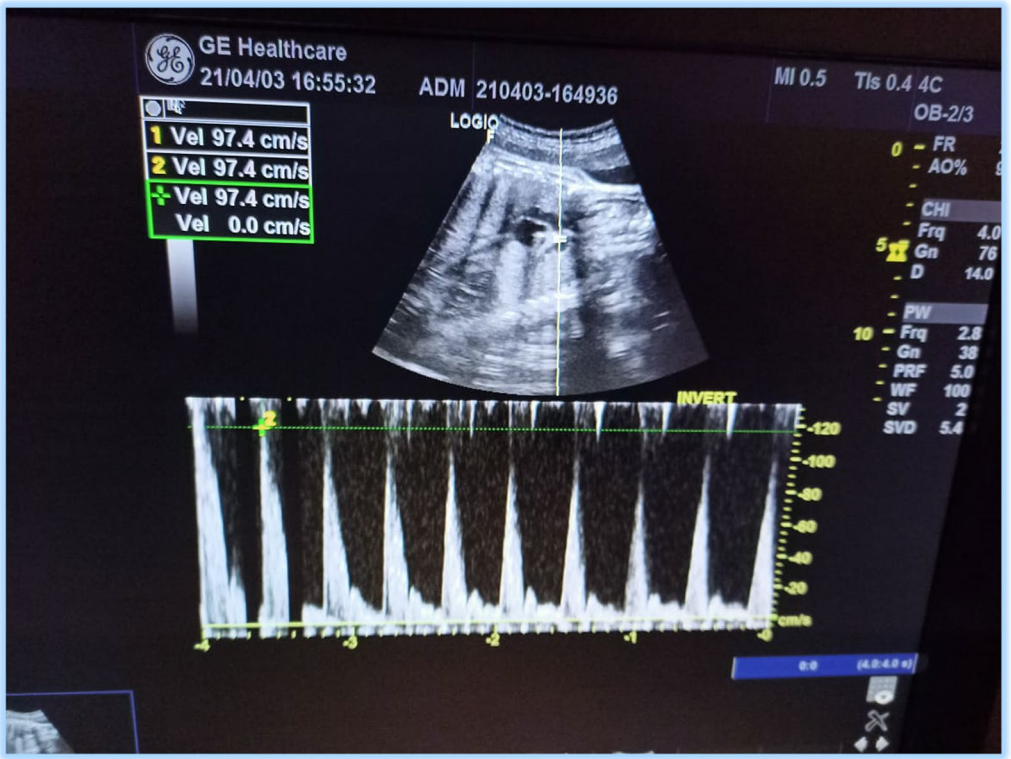

Fig. 1 Female patient 32 years, GA: 37W + 4d, G 3 P 2 + 0, previous 2 CS, LMP: 11/7/2021, EDD: 18/4/2022 with history of preeclampsia. 3D sagittal ultrasound images showing: singleton fetus, cephalic presentation and placenta fundal anterior. Fetal biometry: BPD 93.8, HC 33.8, AC 34.2, FL 73.4, EFWT 3.235, PSV 97, RI 0.92, PI 2.73. Baby did not need NICU admission

delivery; 78 (86.7%) of the newborns delivered without RDS, and 12 (113.3%) of the newborns exhibited neonatal RDS, 7 (14%) of the control and 5 (12.5) of PIH.

The mean age of cases is larger than in control, and mean gestational age of pregnancy termination is lesser in pregnancy-induced hypertension, and there are no significant changes in PSV of DA between control and cases, but RI of DA shows significant difference.

P value showed no significant difference in control and PIH group, as our study was performed at late gestational age and most of patients in the study were more than 35 weeks, and lung maturity is observed to be higher in hypertensive cases compared to normal cases with the same gestational age.

GA, PSV, RI, PI of DA have significant difference (*P* value < 0.001) between normal neonates and others that needed NICU; thus, we can predict the lung maturity, but other parameters as biometry and GA show no significant difference.

Table 1 shows the cutoff value for GA, PSV, RI, PI, *P* value is significant with cutoff value (35.7, 89.9, 0.80, 2.14), with sensitivity (71.4, 100, 85.7, 85.7%) and specificity (93, 97.7, 97.7, 93%), respectively; newborns with a GA ≤ 35.7, DA PSV ≤ 89.9, PI ≤ 2.14 cm/s, and or RI ≤ 0.80 cm/s are significantly more likely to have RDS in the control.

Table 2 shows *P* value is significant with cutoff value (35.7, 91.1, 0.80, 2.14), with sensitivity (71.4, 100, 85.7, 100%) and specificity (71.7, 100, 85.7, 100%), respectively. Newborns with a GA ≤ 35.7, DA PSV ≤ 91.1, PI ≤ 2.14 cm/s, and or RI ≤ 0.80 cm/s are significantly more likely to have RDS in the PIH group.

Tables 3 and 4 show Combining the PSV and GA shows higher sensitivity, specificity, PPV, NPV than when each used alone in both control and PIH groups.

The Doppler parameters (DA PI, RI and PSV) showed higher sensitivity and specificity (100% and 100%); therefore, there were higher NPV and accuracy than when each used alone in control group.

Table 5 shows the predictive values of combining Doppler parameters were assessed. Combining (DA PI, RI and PSV) showed higher sensitivity and specificity; therefore, there were higher PPV, NPV and accuracy than when each used alone in PIH group.

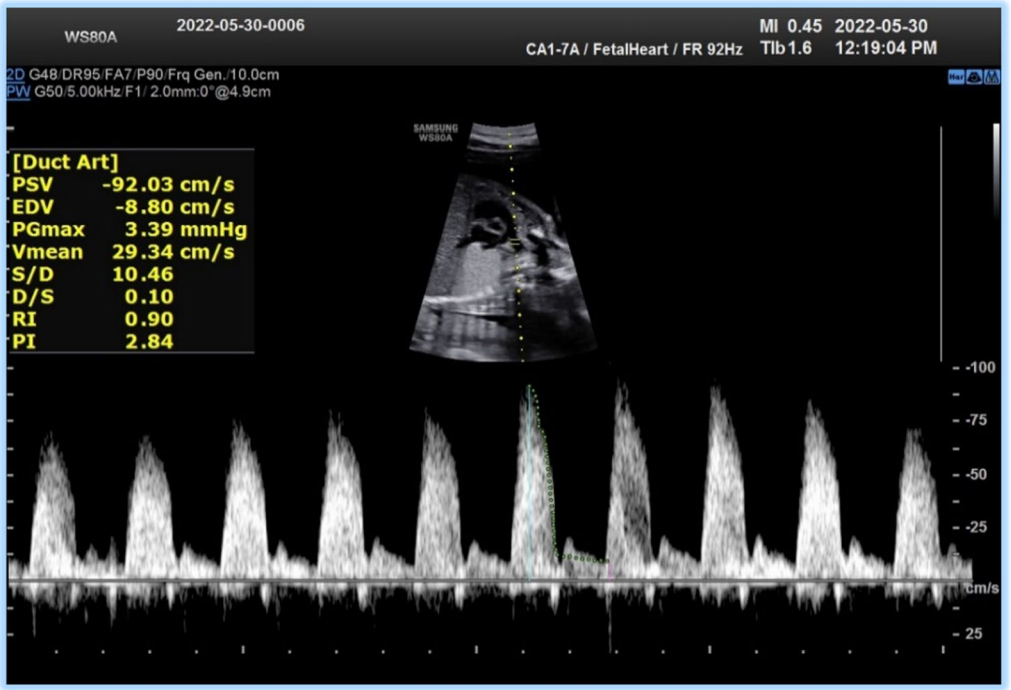

Fig. 2 Female patient 24 years, GA: 38W + 6d, G 3 P 1 + 0, previous 1 CS, LMP: 3/9/2021, EDD: 10/6/2022 without history of preeclampsia. 3D sagittal ultrasound images showing: singleton fetus, cephalic presentation and placenta fundal anterior. Fetal biometry: BPD 90.2, HC 35.4, AC 36.2, FL 73.4, EFWT 3.727, PSV 92, RI 0.90, PI 2.84. Baby did not need NICU admission

Discussion

In Egypt, it was found that (4.2%) had pregnancy-induced hypertension, (3.8%) had preeclampsia and (0.3%) had eclampsia. Preeclampsia is a multisystem disorder of pregnancy defined by the combination of new-onset hypertension and proteinuria that contribute substantially to perinatal morbidity and mortality worldwide. Preeclampsia complicates 2–8% of all pregnancies in the world [6].

Several studies were carried out to test many parameters for prediction of FLM, such as evaluation of amniotic fluid L/S ratio, lamellar body count (LBC). However, these were limited by being with low accuracy and poor sensitivities and specificities in addition to the main disadvantage of the need of amniocentesis. Also a number of noninvasive sonographic tests such as placental maturation, fetal biometry, long bones ossification centers and thalamic echogenicity are used nowadays for fetal lung maturity (FLM) assessment. However, none had proved to be sufficiently accurate. Because of the high neonatal mortality and morbidity rates related to RDS, determination of FLM has become a point of interest [3].

In our study, the mean age of mothers that had pregnancy-induced hypertension was higher than control cases and that agreed with Sheen et al. (2018), who found that advanced maternal age shows high association with preeclampsia and PIH.

Also, we found that there is no significant difference in birth weight between normotensive and hypertensive groups. In a study done by Xiong et al. [8], he found the women delivering before 37 weeks, birth weights were significantly lower among women with gestational hypertension than those with normal blood pressure. However, for women delivering at ≥ 37 weeks, the birth weights were generally higher among women with gestational hypertension than those with normal blood pressure. After adjustment for confounding factors, for women delivering before 37 weeks, birth weights remained significantly lower among babies born to women with gestational hypertension than those with normal blood pressure ($P < 0.01$). For women delivering at ≥ 37 weeks, there was no statistically significant difference in mean birth weights between women with gestational hypertension and those with normal blood pressure.

When assessing the fetal weight, we observed that there is no significant difference in fetal weight between PIH cases and control and no significant difference in birth weight between cases that needed NICU and others who didn't need. That agrees with the study performed by Xiong et al. [8] in which there were no differences in mean birth weight between women with gestational

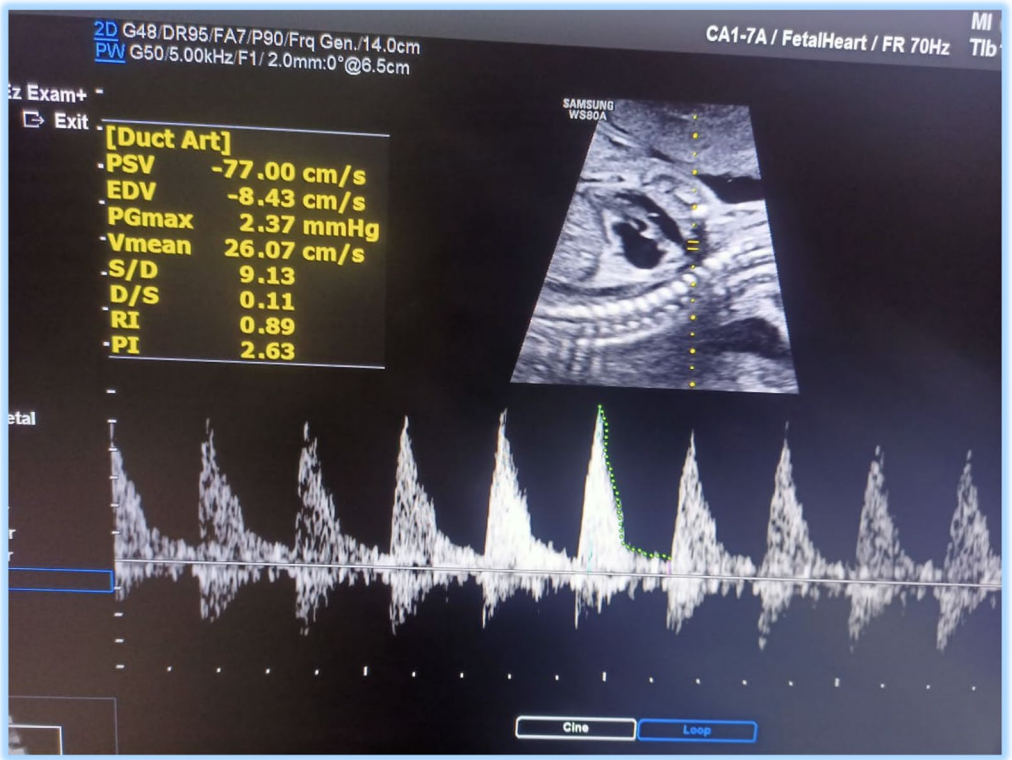

Fig. 3 Female patient 36 years, GA: 34W + 4d, G4 P2 + 1, previous 2 CS, LMP: 16/6/2021, EDD: 23/3/2022 with history of gestational hypertension. 3D sagittal ultrasound images showing: singleton fetus, cephalic presentation and placenta fundal anterior. Fetal biometry: BPD 89.8, HC 32.8, AC 31.2, FL 69.4, EFWT 2.482,PSV 77, RI 0.89, PI 2.63. Baby had RDS and needed NICU admission

hypertension and women with normal blood pressure. He also found that the majority of the babies born to mothers with different types of pregnancy-induced hypertension were appropriate for gestational age or even large for gestational age and most babies born to mothers with severe pre-eclampsia or pre-eclampsia and gestational hypertension had similar fetal growth to those born to normotensive mothers.

The present study had shown that ductus arteriosus (DA), Doppler indices (PSV, PI, RI) and GA were positively correlated with lung maturity in normal pregnancies. It identified ductus arteriosus (DA) PSV (cutoff ≥ 89.9), (DA) PI (cutoff ≥ 2.14), (DA) RI (cutoff ≥ 0.80), GA (cut off ≥ 37 0.7) with a specificity of (97.7, 93,97.7,93), respectively, as reliable predictors of neonatal RDS in normal pregnancies and ductus arteriosus (DA) PSV (cutoff ≥ 91.1), PI (cutoff ≥ 2.14), RI (cutoff ≥ 0.80), GA (cut off ≥ 35 0.7) with a specificity of (97.1,100, 97.7,93), respectively, as reliable predictors of neonatal RDS in patients with pregnancy-induced hypertension. Furthermore, combination of these measures (PSV, RI, PI) of DA had greater sensitivity & specificity and accuracy than when either measure was carried out alone. Therefore, these measurements might be alternatives to other invasive procedures requiring amniocentesis for assessment of fetal lung maturity before delivery; these agree with Ramirez et al., who said that the amniocentesis during the third trimester of the pregnancy has decreased because of the ability to assess the fetal lung maturity with ultrasound or other diagnostic techniques [4].

We found the ductus arteriosus (DA) (PSV, PI, RI) was positively correlated with GA in control and PIH cases, and the neonates that need for NICU in both groups showed decreased PSV. These results are totally consistent with those of Sosa et al., who found that there is a progressive increase in the velocity of the ductus arteriosus as gestational age increases, due to a decrease in the impedance of the pulmonary circulation and an increase in the impedance of circulation through the ductus arteriosus [7].

We observed that there is significant difference between GA and ductus arteriosus (DA) (PSV, RI, PI) in the control group between neonates that needed NICU and normal babies with mean GA (35.6, 37.4), mean PSV of ductus arteriosus (DA) (80.9, 104.4), RI (0.79, 0.85), PI (2.04, 2.3) in cases who needed NICU and normal babies, respectively; this is comparable to the results of Saso

Fig. 4 Female patient 34 years, GA: 34W + 4d, G3P2 + 0, previous 2 CS, LMP: 26/6/2021, EDD: 2/4/2022, medically free. 3D sagittal ultrasound images showing: singleton fetus, cephalic presentation and placenta fundal anterior. Fetal biometry: BPD 85.2, HC 31.5, AC 30.5, FL 70.1, EFWT 2.455, PSV 85, RI 0.78, PI 1.963. Baby had RDS and needed NICU admission

Table 1 The cutoff value for GA, PSV, RI and PI in control

Control	Area under the curve	*P* value	95% Confidence interval		Cut off	Sensitivity %	Specificity %
			Lower bound	Upper bound			
GA	0.844	< 0.001	0.681	1.007	35.7857	71.4	93
DA PSV	0.997	< 0.001	0.986	1.007	89.9	100	97.7
RI	0.939	< 0.001	0.825	1.052	0.80	85.7	97.7
PI	0.919	< 0.001	0.795	1.042	2.14	85.7	93

Table 2 Cutoff value for GA, PSV, RI and PI in PIH cases

PIH cases	Area under the curve	*P* value	95% confidence interval		Cut off	Sensitivity %	Specificity %
			Lower bound	Upper bound			
GA	0.923	< 0.001	0.835	1.010	35.7857	71.4	93
DA PSV	0.994	< 0.001	0.976	1.012	91.10	100	97.1
RI	0.994	< 0.001	0.977	1.012	0.8	85.7	97.7
PI	1.000	< 0.001	1.000	1.000	2.14	100	100

et al. (2019) who found a cutoff point of 98 cm/s for the PSV of ductus arteriosus (DA), with sensitivity of 91.5% and a specificity of 100%, with a PPV of 0.71 and a NPV of 1.0 for lung maturity.

In addition to that we found that there is significant difference between GA and ductus arteriosus (DA) (PSV, RI, PI) in the PIH group between neonates who needed NICU and others who didn't need, mean GA (34.2,

Table 3 Accuracy of combined GA and PSV in PIH group

		Lung maturity			
		Need NICU		No	
		Count	%	Count	%
Combined GA and PSV	Need NICU	4	80.0	0	0.0
	No	1	20.0	35	100.0

Table 4 Accuracy of combined RI, PI and PSV in control

		Lung maturity			
		Need NICU		No	
		Count	%	Count	%
Combined RI, PI and PSV	Need NICU	7	100.0	0	0.0
	No	0	0.0	43	100.0

Table 5 Predictive values of combining PSV and GA in PIH group

Statistic	Value (%)	95% CI
Sensitivity	80.00	28.36–99.49%
Specificity	100.00	90.00–100.00%
Positive predictive value	100.00	
Negative predictive value	97.22	85.84–99.51%
Accuracy	97.50	86.84–99.94%

36.4), mean PSV of ductus arteriosus (DA) (82.5, 100.5), RI (0.79, 0.86), PI (2.04, 2.3) in NICU cases and normal babies, respectively.

We also found that there is no significant difference in PSV, PI of ductus arteriosus (DA) between normal cases and in patients of PIH; as to our knowledge, no any similar studies are available to compare the results.

In our study, 14% (7 cases) of control candidates needed NICU and 12.5% (5 cases) of cases who needed NICU, (*P* value showed no significant difference in control and PIH group), as our study was carried out in late gestational age and most of patients in the study were more than 35 weeks, and lung maturity is observed to be higher in hypertensive cases compared to normal cases with the same gestational age that agreed with Shah et al. who found a lower incidence of RDS in preterm (< 34 gestational weeks) infants born to preeclamptic mother than in a control group.

The predictive values of combining these parameters were assessed. Combining the Doppler parameters (ductus arteriosus (DA) PI, RI and PSV) showed higher sensitivity and specificity (100% and 100%); therefore, there are higher NPV, PPV and accuracy than when each used alone in control, so it is better to combine GA, PSV, RI, PI of ductus arteriosus (DA) to detect lung maturity in control and PIH groups to get more accurate results.

This study had many strength points:

- It is the first one that discusses the cutoff level of ductus arteriosus (DA) PSV, RI, PI in the prediction of neonatal RDS in cases PIH. PIH is a dynamic process, so we can terminate the pregnancy once fetal lung maturity is detected and before deterioration of the maternal condition.
- We can use this parameter in the prediction of neonatal RDS in other high-risk pregnancies.
- We can measure ductus arteriosus (PSV, RI, PI) with 2D ultrasound with Doppler with no need for a high-end ultrasound machine or 4D ultrasound.
- We can predict fetal lung maturity with a non-invasive technique instead of other invasive techniques with its drawbacks.

There are some limitations of the study:

- Fetal echo performance is difficult at advanced gestational age between 32- and 40-week gestation because of high echogenicity of fetal ribs, so anterior position of the fetal chest is preferred to get an optimum view and oligohydramnios associated in some PIH cases which adds more difficulty in the performance of fetal echo and the detection of fetal ductus arteriosus Doppler indices.
- More number of cases are needed to confirm our research.

Conclusions

In neonates of 32–40 weeks of gestation of patients undergoing delivery, the detection of fetal lung maturity by noninvasive predictor would be best carried out by doing ductus arteriosus (DA) PSV, PI, RI as they proved to be of valuable significance in assessment of fetal lung maturity. Furthermore, combination of these measures (PSV, RI, PI) of DA had greater sensitivity & specificity and accuracy than when either measure was performed alone. Therefore, these measurements might be alternatives to other invasive procedures requiring amniocentesis for assessment of fetal lung maturity before delivery.

There is no significant difference in measurements of ductus arteriosus (DA) (PSV PI and RI) in comparing between normal pregnancies and PIH women, but significant differences in these indices were found in comparing between normal cases and the others who need NICU.

Abbreviations

DA	Ductus arteriosus
GA	Gestational age
HELLP	Hemolysis, elevated liver enzymes and low platelet count
LBC	Lamellar body count
NBW	Neonatal birth weight
NICU	Neonatal intensive care unit
NPV	Negative predictive value
PI	Pulsatility index
PIH	Pregnancy-induced hypertension
PPV	Positive predictive value
PSV	Peak systolic velocity
RI	Resistance index
RDS	Respiratory distress syndrome

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Author contributions
SB, ST and KH analyzed and interpreted the patient data regarding the ultrasonographic findings of the hypertensive pregnant group. HM and MR analyzed and interpreted the patient data regarding the ultrasonographic findings of the control group. AA revised all the data interpreted by other authors. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The current study had been approved by Cairo University Kasr Alainy Faculty of Medicine Research and Ethical committee. The committee's reference number is not applicable. Informed consent had been obtained from the patients.

Consent for publication
Not applicable because of the retrospective type of study.

Competing interests
The authors declare that they have no competing interests.

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