Med. J. Cairo Univ., Vol. 90, No. 1, March: 209-218, 2022
www.medicaljournalofcairouniversity.net

Correlation between Progesterone as a Treatment of Preterm Labor and Changes in Fetal Pulmonary Artery Doppler

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Abstract

Background: Progesterone is a crucial drug that is utilized for both preventing and treating preterm birth (PTB). The sonographic echogenicity of the fetal lung changes in an anticipated pattern throughout pregnancy. Fetal pulmonary artery indices have been evidenced to be correlated with proceeding fetal gestational age and assessing maturity of fetal lungs in amniotic fluid.

Aim of Study: To explore the correlation between progesterone as a treatment of preterm labor and changes in fetal pulmonary artery Doppler.

Patients and Methods: This study was a prospective study that was conducted at obstetric and gynecology department of El-Sayed Galal Hospital of Al-Azhar University on 50 pregnant women with singleton pregnancies who presented with preterm labor pain at a gestational age of 28 to 34 weeks and treated with progesterone and 50 normal pregnant women at 37 weeks of gestation during the period from May 2020 to December 2020. Doppler Flow Velocity Waveforms study was done via pulsed-wave Doppler after real time color flow localization of pulmonary trunk. All Doppler indices were measured at 37 weeks of gestation.

Results: Pulmonary artery At/Et ratio was lower in cases who developed preterm labor pain and received progesterone compared with control cases but without significant difference (mean: 0.332±0.066 versus mean: 0.341±0.014) (p=0.069). Moreover, pulsatility index (PI) was nearly similar in both studied groups (p=0.09). The mean resistance index (RI) was lower in the control group than that in patients groups but statistically significant difference (p=0.119). In addition, there was no statistically difference in the mean of PSV & S/D ratio in control group compared to patients group (p=0.562 & 0.467 respectively). There was statistically significant difference between the patients who had adverse neonatal outcome and those who hadn't in both group I and group II regarding all Doppler indices. In the studied subjects the mean Pulmonary artery At/Et had significant positive correlation with age (p=0.004). Also, it had significantly negative correlation with NICU more than 2 weeks, RDS, PI, and RI (p<0.05). ROC curve showed the optimum cutoff for Pulmonary artery At/Et was 0.31 for detecting adverse outcome in patients group with sensitivity 92.9% and specificity 91.7%; an area under the ROC curve (AUROC) 0.975 (95% CI: 0.939-1.000) (p<0.001). Also, in control group ROC curve analysis showed that Pulmonary artery At/Et was significant for predicting outcome of pregnancy (p=0.004) at a cut off value 0.315 with sensitivity of 100% and specificity of 90.1 % and an area under the ROC curve (AUROC) 0.938 (95% CI: 0.868-1.000).

Conclusion: Administration of vaginal progesterone for the prevention of preterm, although having beneficial role in prolongation of pregnancy time, nevertheless it may have adverse events on fetal circulation especially decreasing At/ET ratio, Thus increasing cases at risk for RDS development. Also, we can introduce fetal PA At/Et as noninvasive accurate method for neonatal RDS prediction in at risk- preterm cases who administer progesterone as prophylaxis.

Key Words: *Preterm birth– Progesterone – Pulmonary artery indices.*

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Introduction

PRETERM birth (PTB) hazards are considered the prominent etiology of demise among children less than five years **[1]**.

In spite of upgrades in neonatal care, PTB is the mainstay instigate of handicaps and long-term disabilities in children born with no congenital anomalies. For that reason, prevention of PTBs is the central goal of obstetric care **[2]**.

Respiratory distress syndrome (RDS) is a widespread trouble in the beginig of neonatal life and preterm birth is a crucial trigger **[3]**.

First, the etiology of spontaneous PTB (sPTB) comprises extremely intricate communications between a multitude of factors incorporating but not restricted to genetics, the immune system, hormones, reproductive tissue characteristics, vascular & nervous system, maternal anatomy & microbiome, and the environment **[4]**.

Even with the distinctive features for every single cause of PTB, the end net of them is premature cervical dilatation & effacement, and early initiation of uterine contractions **[5]**.

Progesterone, an essential agent for preserving uterine quiescence, [6] is progressively used for maintenance tocolysis in the high risk women for preterm labor owing to the anti-inflammatory effect, inhibition of gap junction formation in the myometrium, and direct influence on the cervix [7].

Numerous research works were carried out to settle on how was progesterone efficient in protecting from PTB, some of them reported positive results of consuming 17OH- progesterone caproate or vaginal progesterone in diminishing the preterm delivery possibility. Quite the reverse, others notified no proof of preterm delivery prevention via using progesterone [8].

Because of the excess neonatal mortality and morbidity rates allied to RDS, determination of fetal lung maturity has become a point of argue for a long time. The preliminary reports were founded on the evaluation of amniotic fluid. For prediction of fetal lung maturity, lecithin to sphingomyelin ratio, phosphatidylinositol and phosphatidylglycerol in amniotic fluid and fluorescent polarization of amniotic fluid were the proposed modalities. Nevertheless, the prerequisite of amniocentesis makes it invasive procedure with a numerous hazards as rupture of membranes, infection, direct & indirect fetal injury and fetal loss [9].

Ultrasound with Doppler measures, a gold standard for fetus antenatal screening, is considered non-invasive technique to evaluate pulmonary artery pressure in neonates and adults. Therefore, fetal pulmonary artery Doppler velocimetry might be extremely beneficial for predicting fetal lung maturity (FLM) depending on sonographic echogenicity of fetal lung change thus, it had been used in tries to categorize fetuses with pulmonary hypoplasia risks and neonates with RDS [10].

In that context, fetal pulmonary artery acceleration time/ejection time (At/Et) ratio has been shown to be correlated with advancing fetal GA and testing FLM in amniotic fluid [11].

Thus, the aim of this study was to explore the correlation between progesterone as a treatment of preterm labor and changes in fetal pulmonary artery Doppler.

Patients and Methods

This study was a prospective research work that was conducted at El-Sayed Galal Hospital of Al-Azhar University on 50 pregnant women with singleton pregnancies who presented with preterm labor pain at a gestational age of 28 to 34 weeks and treated with progesterone and 50 normal pregnant women at 37 weeks of gestation during the period from May 2020 to December 2020. Whitten consents were obtained from the patients.

Exclusion criteria: Women with medical disorders as: hypertensive disorders associating pregnancy, diabetes (both pre-gestational and gestational), or vascular diseases as systemic lupus erythromtosis (SLE). Also, women with preterm premature rupture of membranes (PPROM), those who had contraindication to progesterone use or those who had any indication for termination of pregnancy. Furthermore, pregnancies with abnormal uterine artery, umbilical artery, and/or middle cerebral artery (MCA) flow velocity waveforms values at initial Doppler scanning or any preterm case who delivered prior to 37 week of gestation were also excluded.

The elected patients were subjected to thorough history taking, complete general, abdominal examination and ultrasonographic examination. Preterm cases received vaginal prontogest 200 daily (Marcyrl Company) and followed-up then using fetal pulmonary artery Doppler at 37 weeks. Doppler Flow Velocity Waveforms (FVW) studies were done with pulsed-wave Doppler after real time color flow localization of pulmonary trunk. All Doppler indices were measured at 37 weeks of gestation. Cases and controls were scanned in the supine and left lateral position and all fetuses were in sinus rhythm and in a quiet state without fetal breathing activities. An axial plane through the fetal thorax to achieve the 4 chamber view of the heart with a systematic examination of the fetal heart was first performed as priory clarified by Li et al., [12] to exclude any major structural defect. The fetal main pulmonary artery (MPA) was then imagined by rotating the transducer from the 4-chamber view to the short-axis view of fetal heart, in that way showing the pulmonary valves and the bifurcation of the right and left branches of the pulmonary artery. The pulsed Doppler sample gate was positioned at the half way of the fetal MPA (between the pulmonary valves and the pulmonary artery bifurcation) and away from the arterial walls. Next, the sample gate was adjusted to 3mm after expanding the image as much as practicable and the angle of insonation (between the sound beam and the direction of blood flow) was maintained at <20°. The Doppler variables included acceleration time (AT; ie, the time interval from the foot to the top of PSV), ejection time (ET; ie, from the beginning to the end of ventricular systole), PSV (the maximum blood flow velocity reached during systole), end-diastolic maximum velocity (EDV),

mean velocity (MV; ie, the time-averaged maximum velocity), pulsatility index (PI = [PSV EDV]/MV), and resistance index (RI = [PSV EDV]/PSV). From these measurements, the AT/ET ratio was calculated [13]. Then, cases were followed up till delivery and the pregnancy outcome were evaluated as regards Apgar score, fetal birth, and admission to the neonatal intensive care unit (NICU).

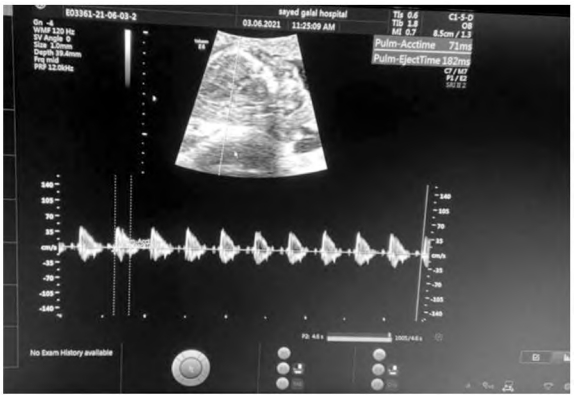

Fig. (1): Doppler ultrasound of fetal pulmonary artery showing AT/ET ratio = 0.39.

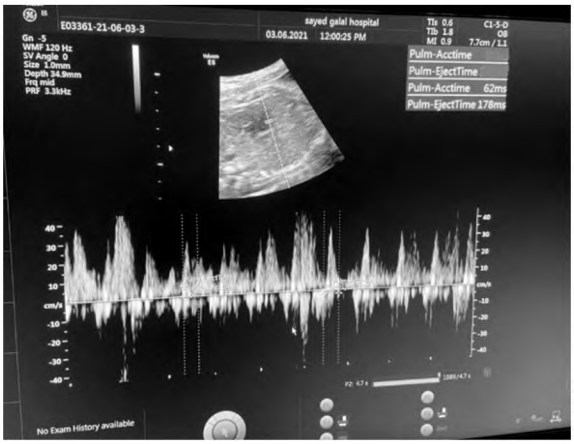

Fig. (2): Doppler ultrasound of fetal pulmonary artery showing AT/ET ratio = 0.348.

Statistical analysis:

Statistical analyses of data were performed via SPSS version 23. Shapiro-Wilks test was used to test normal distribution of variables. Numerical data were expressed as mean ± standard deviation or median and range. Categorical data were summarized as percentages. The significance for the difference between groups was determined by using two-tailed Student's *t*-test. Also Qualitative variables were assessed by chi-squared (χ^2) test. The probability (p) values of 0.05 were considered statistically significant. Mann whitney test was used to compare data that were not normally distributed.

Results

Overall, 100 pregnant women were recruited in this study during the period of research from May 2020 to December 2020 at obstetrics clinic of El-Sayed Galal Hospital of Al-Azhar University. Cases were divided to 50 pregnant women with singleton pregnancies who presented with preterm labor pain at a gestational age of 28 to 34 weeks and treated with progesterone (Group I) and 50 normal pregnant women at 37 weeks of gestation (Group II).

The overall age range was from 18 to 35 years with a mean ± SD was 25.2±3 years. The mean age was 25.04±2.35 years in group (I) and 25.4±3.8 years in group (II), (p=0.567). BMI was higher in cases with preterm labor pain who received progesterone (26.28±4.95kg/m^2) compared to healthy controls (24.96±4.68kg/m^2). Yet, there was no difference between two studied groups regarding BMI (p=0.169) (Table 1).

As regard parity, about 26 (26%) pregnant women in the study had zero parity, 34 (34%) women had only 1 parity, 38 (38%) had 2 to 3 parity and the remaining pregnant women were multipara over 3. Also, the overall mean parity was 1.32±1.08 births and parity range was (0 to 4) birth as shown in Table (1). It was 1.6±1.04 births in women with preterm labor pain who received progesterone and 1.04±1.06 births in control women (p=0.008) (Table 1).

The current study showed that there were 44 (44%) women had previous preterm previously and 28 (28%) had previous history of abortion as illustrated in Table (1). The present study showed that there was statistically significant difference between the two studied groups regarding previous history of preterm labour (p=0.003) whereas there was no statistically significant difference between the two studied groups regarding previous history of abortion (p>0.05).

The majority of the women (56%) (n=56) delivered by caesarean section (CS), while vaginal delivery was conducted in 44 (44%) of women for the current pregnancy. The present study indicated that there was significant difference in the rate of cesarean delivery among cases with preterm labor who received progesterone compared to control cases (68% versus 44%) (p=0.026) (Table 1).

The mean gestational age at delivery was 37.46±0.99 weeks of gestation in all 50 women. It was (37.12±1.01 weeks) in cases with preterm labor who received progesterone compared to

(37.8±0.87 weeks) in control cases. The gestational age at delivery was higher in control group than that in the preterm labor group, with statistically significant difference (p=0.014) (Table 1).

Mean of weight at birth was 2616±278.3g & 2805±406.8g in both patients and control groups respectively as represented. It was detected that there was statistically significant difference between the both studied groups regarding mean birth weight (p=0.008). (Table 1).

As regard neonatal outcome of the current delivery, the overall morbidity was shown in 18 cases (18%) and mortality was 4 (4%). In our study, there was no statistically significant difference in the mortality rate between the two studied groups. The number of neonates admitted to the NICU was higher in the patients group than that in the control group (p=0.009). Significant differences were shown between two groups of neonates regarding percentage of babies presenting with respiratory distress syndrome (p=0.004) (Table 1).

The mean Apgar score was higher in the control group than that in the patients with preterm labor pain who received progesterone (8.84 vs. 7.92). This results showed that the difference in the Apgar score was statistically significant between both studied groups (p<0.001*) (Table 1).

Table (1): Demographic data and neonatal outcomes of the patients and controls.

Variables \ Groups	Group (I) (n=50)	Group (II) (n=50)	p-value
Age (Yrs.)	25.04±2.3	25.4±3.8	0.567
BMI at enrollment (kg/m^2)	26.28±4.95	24.96±4.68	0.169
Parity	1.6±1.04	1.04±1.06	0.008*
Pervious preterm labour:			
None	20 (40%)	36 (72%)	0.003*
1-2	28 (56%)	14 (28%)	
3	2 (4%)	0 (0%)	
Pervious abortion:			
None	38 (76%)	34 (68%)	0.343
1-2	12 (24%)	16 (32%)	
Gestational age at delivery (weeks)	37.12±0.22	37.8±1.07	0.002*
Mode of delivery:			
Vaginal	16 (32%)	28 (56%)	0.026*
Cesarean section	34 (68%)	22 (44%)	
Birth weight [g]	2616±278.3	2805±406.8	0.008**
Neonatal outcomes:			
Neonatal mortality	2 (4%)	2 (4%)	1.000
Neonatal ICU more 2 weeks	14 (08%)	4 (8%)	0.009*
Respiratory distress syndrome (RDS)	4 (16%)	2 (4%)	0.004*
APGAR score	7.92±1.3	8.84±0.688	<0.001*

- Values are expressed as mean ± standard deviation or n (%) unless otherwise specified.
BMI: Body mass index. RDS:Respiratory distress syndrome.

On comparing the Doppler indices between both studied groups, pulmonary artery At/Et ratio was lower in cases who developed preterm labor pain and received progesterone compared with control cases but without significant difference mean: 0.332±0.066 [range: 0.26 to 0.39] versus mean: 0.341±0.014 [range: 0.28- 0.39] (p=0.069). Moreover, pulsatility index (PI) was nearly similar in both studied groups (2.45±0.13 in patients group vs. 2.42±0.12 in control group) (p=0.09). The mean resistance index (RI) was lower in the control group (II) than that in patients groups (I) (0.9± 0.09 vs. 0.86±0.06) but without statistically significant difference (p=0.119). In addition, there was no statistically difference in the mean of PSV in control group compared to patients group (80.04± 15.9 vs. 81.8±14.6) (p=0.562). Paralleled to that, there was no statistically difference in the mean of S/D ratio among both studied groups (p=0.467). (Table 2).

Table (2): Comparison between both studied groups regarding Doppler indices.

Variable	Group (I) (n=50)	Group (II) (n=50)	p-value	Sig.
Pulmonary artery At/Et (Mean ± SD)	0.332±0.066	0.341±0.014	0.069	NS
Pulsatility index (PI) (Mean ± SD)	2.45±0.13	2.42±0.12	0.09	NS
Resistance index (RI) (Mean ± SD)	0.9±0.09	0.87±0.06	0.119	NS
PSV (Mean ± SD)	81.8±14.6	80.04±15.9	0.562	NS
(S/D ratio) (Mean ± SD)	15±5.9	14.1±6.9	0.467	NS

RI: Resistance index. PSV: Peak systolic velocity.
PI: Pulsatility index. S/D : Systolic/diastolic.

This study showed that there was statistically significant difference between the patients who had adverse neonatal outcome and those who hadn't in group I regarding pulmonary artery Doppler indices (p<0.05) (Table 3).

Table (3): Comparison cases who had adverse neonatal outcome and those without regarding Doppler indices in group I.

Variable	Adverse neonatal outcome		p-value	Sig.
	No N=36	Yes N=14		
Pulmonary artery At/Et	0.337±0.016	0.298±0.02	<0.001*	S
Pulsatility index (PI)	2.45±0.107	2.64±0.19	0.03*	S
Resistance index (RI)	0.87±0.05	0.98±0.13	0.015*	S
PSV	83.89±14.09	74.4±14.6	0.003*	S
(S/D ratio)	12.4±5.2	16.43±7.45	0.009*	S

RI. : Resistance index. S/D : Systolic/diastolic.
PI. : Pulsatility index. NS : Non-significant.
PSV : Peak systolic velocity. S : Significant.

In addition, there was statistically significant difference between the patients who had adverse neonatal outcome and those who hadn't in group II regarding Doppler indices (p<0.05) (Table 4).

Table (4): Comparison cases who had adverse neonatal outcome and those without regarding Doppler indices in group II.

Variable	Adverse neonatal outcome		p-value	Sig.
	No N=46	Yes N=4		
Pulmonary artery At/Et	0.352±0.014	0.301±0.00	<0.001 *	S
Pulsatility index (PI)	2.39±0.08	2.74±0.06	<0.001 *	S
Resistance index (RI)	0.86±0.06	1.04±0.42	<0.001 *	S
PSV	81.13±15.04	65.5±6.36	0.001 *	S
(S/D ratio)	9.5±6.01	13.48±0.7	<0.001 *	S

RI. : Resistance index. S/D : Systolic/diastolic.
PI. : Pulsatility index. NS : Non-significant.
PSV : Peak systolic velocity. S : Significant.

Correlation between Pulmonary artery At/Et and other studied parameters:

In the studied subjects the mean Pulmonary artery At/Et had significant positive correlation with age (p=0.004). Also, it had significantly negative correlation with NICU more than 2 weeks, RDS, PI, and RI (p<0.05). However, there was no significant correlation between Pulmonary artery At/Et and other studied parameters (p>0.05) (Table 5).

Table (5): Correlation between Pulmonary artery At/Et and other studied parameters.

Parameters	Pulmonary artery At/Et	
	r	p-value
Age (years)	0.274	0.004*
BMI (Kg/m^2)	–0.098	0.311
Gestational age at delivery	0.003	0.976
Birth weight	0.002	0.982
NICU more than 2 weeks	–0.595	<0.001 **
RDS	–0.501	<0.001 **
1 min APGAR score	0.135	0.159
Pulsatility index (PI)	–0.223	0.019*
Resistance index (RI)	–0.268	0.005*
PSV	0.036	0.723
(S/D ratio)	–0.166	0.1
AT	–0.071	0.462

Diagnostic values of Pulmonary artery At/Et for differentiate babies with adverse outcome from those without:

ROC curve showed the optimum cutoff for Pulmonary artery At/Et was 0.31 for detecting adverse outcome in patients group with sensitivity 92.9% and specificity 91.7%; an area under the ROC curve (AUROC) 0.975 (95% CI: 0.939-1.000) (p<0.001) (Fig. 3).

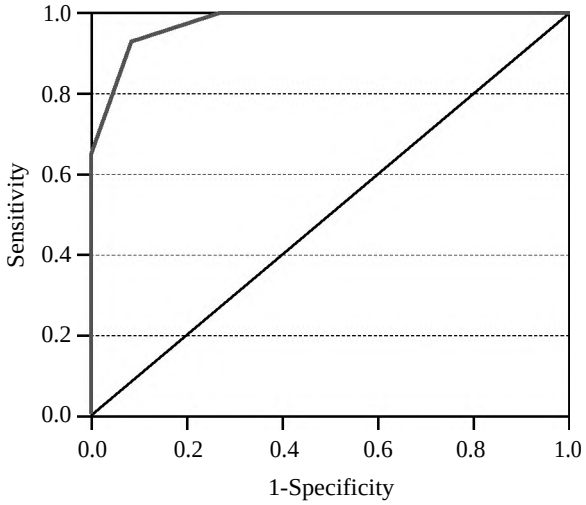

Fig. (3): ROC curve of Pulmonary artery At/Et for predicting adverse outcome in neonates of patients group.

Also, in control group ROC curve analysis showed that Pulmonary artery At/Et was significant for predicting outcome of pregnancy (p=0.004) at a cut off value 0.315 with sensitivity of 100% and specificity of 90.1 % and an area under the ROC curve (AUROC) 0.938 (95% CI: 0.868-1.000) (Fig. 4).

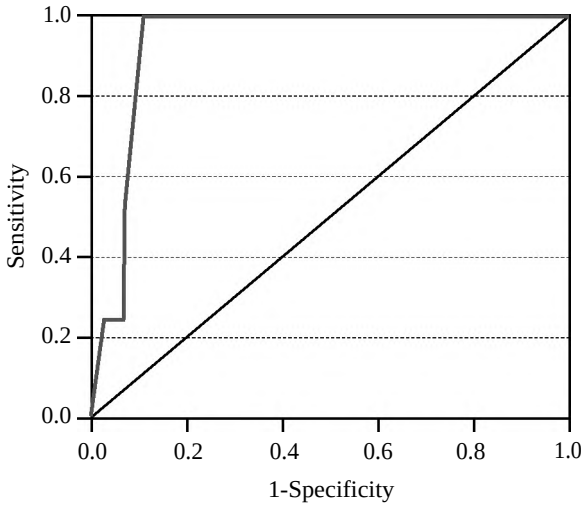

Fig. (4): ROC curve of Pulmonary artery At/Et for predicting adverse outcome in neonates of control group.

Discussion

There are clearly contradictory data concerning the progesterone efficacy for preventing preterm birth **[14,15]**.

Certain meta-analyses, concentrating on solely on women with a short cervix, have indicated that

progesterone is valuable in this situation [16], whereas others focusing on prospectively registered studies found no difference between the groups [17].

The double-blinded randomized controlled OPPTIMUM study conducted by Norman et al., [18] on 1228 women at high risk of preterm birth tested the effect of prophylactic vaginal progesterone (200mg daily) from 22 to 34 gestational weeks at 65 UK National Health Service hospitals and one Swedish hospital during the period from February 2009 to April 2013 and reported a positive effect of progesterone in preventing preterm birth.

Subsequently, the PROGRESS study conducted via Crowther et al., [19] on 787 women at high risk of preterm birth who reported history of a spontaneous prior preterm delivery and randomized them on 100mg daily vaginal progesterone or placebo. They reported that the incidence of RDS was the same in both groups: 10.5% in the progesterone group and 10.6% in the placebo group.

The National Institute of Clinical Excellence (NICE) in the United Kingdom, and the Society for Maternal-Fetal Medicine (SMFM) in the United States all advocated the progestogens use for at high risk women of PTB. The two former organizations support the use of vaginal progesterone for women with a short cervix [20,21].

Saleh Gargari et al., [22] in their study mentioned that vaginal progesterone may increase the demur time of delivery if such efficacy could be authorized by additional investigations, progesterone via vaginal route can abolish hospitalization risk in the first year of life, learning disorders, behavioral problems, and the burden of economic aftereffects owing to preterm delivery.

Moreover, the progesterone administration route may have an impact on the pharmacokinetics and blood concentrations peak time that is 3 to 8 hours for 100mg for vaginal progesterone. There were analogous effects of both intramuscular and vaginal progesterone in a multitude of systematic reviews of randomized controlled trials. Similarly up till now, the ideal dose of vaginal preparations (ranging from 90 to 400mg daily) [22].

The central role of progesterone in continuation of pregnancy is postulated to be through withholding of uterine contractile action via calcium-calmodulin-myosin light chain kinase system inhibition. Besides, progesterone exerts a negative effect on prostaglandin production and interaction at the feto-placental interphase [34].

Tantawy et al., [23] aimed to assess the effectiveness of vaginal progesterone compared to intramuscular route in diminishing the rate of PTB in twin pregnancies and presented that lower percentage of preterm labor, improved compliance less adverse maternal outcomes, and smaller number of admissions to NICU were reported in cases who administered vaginal progesterone exhibited.

In addition, Romero et al., [24] meta-analysis that was conducted for women with a short cervical length using three formulations; 100 and 200mg suppositories and 90mg vaginal gel. They displayed that vaginal progesterone diminished PTB before 33 weeks and neonatal mortality and morbidity. The 3 formerly mentioned formulas were similarly efficacious.

To our knowledge we are the first study to evaluate the effect of vaginal progesterone on preterm labor regarding changes in fetal pulmonary artery Doppler.

On comparing the Doppler indices between both studied groups, pulmonary artery At/Et ratio was lower in cases who developed preterm labor pain and received progesterone compared with control cases but without significant difference mean: 0.332±0.066 [range: 0.26 to 0.39] versus mean: 0.341±0.014 [range: 0.28-0.39] (p=0.069). Moreover, pulsatility index (PI) was nearly similar in both studied groups (2.45±0.13 in patients group vs. 2.42±0.12 in control group) (p=0.09). The mean resistance index (RI) was lower in the control group (II) than that in patients groups (I) (0.9±0.09 vs. 0.86±0.06) but without statistically significant difference (p=0.119). In addition, there was no statistically difference in the mean of PSV in control group compared to patients group (80.04±15.9 vs. 81.8±14.6) (p=0.562). Paralleled to that, there was no statistically difference in the mean of S/D ratio among both studied groups (p=0.467).

These findings may be elucidated by the prolongation of pregnancy by vaginal progesterone effect thus improvement of pulmonary circulation due to lung maturity. So, most Doppler parameters were not different from controls. The difference in pulmonary artery AT/Et ratio may be due to increased number of cases with RDS in patients groups compared to controls due to the effect of progesterone on fetal pulmonary circulation.

This study showed also that there was statistically significant difference between the patients who had adverse neonatal outcome and those who

hadn't in both group I and II regarding all Doppler indices.

In the studied subjects the mean Pulmonary artery At/Et had significant positive correlation with age (p=0.004). Also, it had significantly negative correlation with NICU more than 2 weeks, RDS, PI, and RI (p<0.05). However, there was no significant correlation between Pulmonary artery At/Et and other studied parameters (p>0.05). ROC curve showed the optimum cutoff for Pulmonary artery At/Et was 0.31 for detecting adverse outcome in patients group with sensitivity 92.9% and specificity 91.7%; an area under the ROC curve (AUROC) 0.975 (95% CI: 0.939-1.000) (p<0.001). Also, in control group ROC curve analysis showed that Pulmonary artery At/Et was significant for predicting outcome of pregnancy (p=0.004) at a cut off value 0.315 with sensitivity of 100 % and specificity of 90.1% and an area under the ROC curve (AUROC) 0.938 (95% CI: 0.868-1.000).

In concordance with our results, this study was strengthened by its prospective design and that it examined the association of fetal MPA Doppler indices with the clinical end point of interest, to be precise, RDS. Moety et al., **[11]** work on a group (698) of preterm and term babies, RDS was reported in 55 neonates. They compared fetuses that did not suffer from to those who developed neonatal RDS regarding fetal pulmonary artery Doppler. They stated that RDS had significantly lesser At/Et and PSV and higher PI and RI. Yet, At/Et had the strongest results. This denotes that fetuses who suffer from RDS have higher pulmonary vascular pressure and resistance and dropped pulmonary blood flow than fetuses that do not develop RDS. They also declared that the receiver operating characteristic curve revealed that the cutoff value of 0.305 for At/Et yielded a sensitivity of 76.4% and a specificity of 91.6% for prediction of neonatal RDS with an area under the curve of 0.899. The PI and RI, however, showed lower sensitivity and specificity for predicting RDS like our results.

In recently published study by Elkhalik et al., **[25]**, it was reported that according Pulmonary artery indices, the MPA At/Et was significantly lower in fetuses diagnosed with RDS compared with those without (0.29±0.03 versus 0.4±0.00) and MPA PI and RI were significantly higher mean value (3.28±1.02 and 1.07±0.20cm s-1 versus 2.6 ±0.9 and 0.9±0.2cm s-1) whereas PSV was significantly lower in fetuses with RDS (40.39±6.19 versus 50.3±10.3cm s-1 with no statistically significant difference regarding S/D (p>0.05) between the two groups. They also reported that according to sensitivity, specificity and accuracy of AT/ET in prediction of fetal lung maturity, sensitivity was 98.0, specificity was 92.0% and accuracy was 95.0% at cut off value 0.32.

Azpurua et al., **[8]** explored the relationship between At/Et ratio and fetal pulmonary maturity through amniotic fluid lecithin/sphingomylein (L/S) ratio and the pulmonary artery acceleration to ejection period (PATET) ratio and reported an inverse correlation between acceleration/ejection time and amniotic fluid L/S ratio, proposing that while the At/Et ratio increased, fetal lung immaturity probably exist.

In a novel work conducted by Alsheikh et al., **[26]**, to study the relation between fetal Doppler pulmonary artery indices and neonatal RDS in term neonates found that all of the parameters, comprising pulmonary artery At/Et ratio, RI, PI, and PSV showed good performance as prognosticators of RSD development.

Laban et al., **[27]** in their work, found that 13.8% of delivered neonates had RDS. The authors acknowledged the worth of PA-RI in predicting RDS in term neonates.

In comparison, the study of Kim et al., **[28]** recognized pulmonary artery At/Et ratio but not pulmonary artery RI and PI as a noteworthy predictor of RDS in their study on 42 neonates, including 11 neonates who developed RDS. It is noteworthy to mention that this study included a heterogeneous population of term and preterm babies who gave birth to singleton or twin pregnancies.

Too, the study of Guan et al., **[13]** on 43 preterm neonates stated that only pulmonary artery At and At/Et ratio could forecast neonatal RDS. The predictive capability of pulmonary artery At/Et ratio was also appreciated by the novel research of Büke et al., **[9]** on 105 women and Duncan et al., **[29]** on 95 preterm neonates.

In contrast to our findings and other studies, the study of Güngör et al., **[30]** on 40 preterm babies failed to distinguish any significant variances between neonates who and those who didn't develop RDS regarding the fetal PA Doppler indices even after steroid administration. This may be accredited perhaps to the dissimilar demographic characteristics and clinical presentations of the neonates involved in various studies.

A multitude of studies had focused on the effect of progesterone on vascular Doppler in preterm fetus. The outcomes showed a reduction of umbilical artery PI couple of weeks after the administration of vaginal progesterone in both preterm labor patients and cases with IUGR feti **[31]**. Vasodilator effect of progesterone was illustrated in former studies. Barda et al., **[32]** investigated the effect of solitary-dose progesterone on Doppler flow of umbilical, middle cerebral and uterine arteries during pregnancy with preterm labor and revealed a reduction in middle cerebral artery PI and RI and a reduction in uterine artery RI, which involved the vasodilatory effect of progesterone.

Therefore, we can say that administration of vaginal progesterone for the prevention of preterm, although having beneficial role in prolongation of pregnancy time, nevertheless it may have adverse events on fetal circulation especially decreasing At/ET ratio circulation, Thus increasing cases at risk for RDS development. This needs further research to prove it. Also, we can introduce fetal MPA At/Et as noninvasive accurate method for neonatal RDS prediction in at risk- preterm cases who administer progesterone as prophylaxis.

Conclusion:

Administration of vaginal progesterone for the prevention of preterm, although having beneficial role in prolongation of pregnancy time, nevertheless it may have adverse events on fetal circulation especially decreasing At/ET ratio, Thus increasing cases at risk for RDS development. This needs further research to prove it. Also, we can introduce fetal MPA At/Et as noninvasive accurate method for neonatal RDS prediction in at risk-preterm cases who administer progesterone as prophylaxis.. To our knowledge this was the first work to explore explore the correlation between progesterone as a treatment of preterm labor and changes in fetal pulmonary artery Doppler so, further large scale multi-centric studies will be needed to verify the results and to validate cut off values, and to demonstrate a reliable association between the elevation in pulmonary artery Doppler indices and occurrence of respiratory distress syndrome.

Ethical approval: Approval of ethical committee was obtained from quality education assurance unit, Faculty of Medicine, Al-Azhar University Egypt.

Conflict of interest: The authors declare that they have no conflicts of interest.

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دراسة لتقييم العلاقة بين استخدام هرمون البروجسترون لحالات الولادة المبكرة والتغيرات فى دوبلر الشريان الرئوى للجنين

خلفية البحث: يعد البروجسترون دواء مهم يستخدم للوقاية والعلاج من الولادة المبكرة وتحدث تغيرات فى صدى الموجات فوق الصوتية لرئة الجنين بنمط متوقع طوال فترة الحمل وتم إثبات ارتباط مؤشرات الشريان الرئوى للجنين مع تقدم عمر للجنين وتقييم نضج رئتى الجنين فى السائل الأمنيوسى.

الهدف من البحث: استكشاف الارتباط بين البروجسترون كعلاج للولادة المبكرة والتغيرات فى الشريان الرئوى للجنين دوبلر.

المريضات وطرق البحث: هذه الدراسة عبارة عن دراسة استطلاعية أجريت فى قسم النساء والتوليد فى مستشفى السيد جلال بجامعة الأزهر على ٥٠ امرأة حامل بحمل مفرد عانت من آلام الولادة المبكرة فى عمر الحمل من ٢٨ إلى ٣٤ أسبوعاً وتم علاجهن بالبروجتسرون و ٥٠ امرأة من الحوامل الأصحاء فى الأسبوع ٣٧ من الحمل خلال الفترة من مايو ٢٠٢٠ إلى ديسمبر ٢٠٢٠. وأجريت دراسة أشكال موجة دوبلر لسرعة التدفق عبر دوبلر الموجة النبضية للجذع الرئوى. وتم قياس جميع مؤشرات دوبلر عند ٣٧ أسبوعاً من الحمل.

النتائج: عند مقارنة مؤشرات دوبلر بين كلتا المجموعتين المدروستين، كانت نسبة معدل سرعة الشريان الرئوى أقل فى الحالات التى أصيبت بآلام الولادة المبكرة اللائى تلقين البروجسترون مقارنة بحالات التحكم و لكن دون فرق كبير (المتوسط: ٠.٣٣٢±٠.٠٦٦) (النطاق: ٠.٢٦ إلى ٠.٣٩) مقابل المتوسط: ٠.٣٤١±٠.٠١٤ (النطاق: ٠.٢٨ إلى ٠.٣٩)، p=٠.٠٦٩ (علاوة على ذلك، كان مؤشر النبض (PI) مشابهاً فى كلتا المجموعتين المدروستين (٢.٤٥±٠.١٣ فى مجموعة المرضى مقابل ٢.٤٢±٠.١٢ فى المجموعة الضابطة (p=٠.٠٩) وكان متوسط مؤشر المقاومة (RI) أقل فى المجموعة الضابطة (II) منه فى مجموعات المرضى ٠.٠٩±٠.٠٩) (I) مقابل ٠.٨٦±٠.٠٦ ولكن بدون فرق معنوى. (p=٠.١١٩) بالإضافة إلى ذلك، لم يكن هناك فرق إحصائى فى متوسط PSV فى المجموعة الضابطة مقارنة بمجموعة المرضى. (p=٠.٥٦٢) بالتوازى مع ذلك، لم يكن هناك فرق إحصائى فى متوسط نسبة S/D بين المجموعتين المدروستين. (p=٠.٤٦٧) ومع ذلك وأظهرت هذه الدراسة أيضاً أن هناك فرقاً مهماً من الناحية الإحصائية بين المرضى اللائى كانت لديهن نتائج عكسية عند حديثى الولادة وأولئك بدونها فى كلتا المجموعتين الأولى والثانية فيما يتعلق بمؤشرات دوبلر.

وفى الحالات التى تمت دراستها، كان لمتوسط الشريان الرئوى AT/Et ارتباط إيجابى معنوى مع معدل دخول العناية المركزة لحديثى الولادة لأكثر من أسبوعين، وحدوث متلازمة الضائقة التنفسية، ومعامل سريان الدم والمقاومة (p<٠.٠٠٥). ومع ذلك، لم يكن هناك ارتباط معنوى بين مع العلامات المدروسة الأخرى (p>٠.٠٠٥). أظهر تحليل منحنى روك أن AT/Et للشريان لديه دقة تشخيصية كبيرة للتنبؤ بنتيجة الحمل فى مجموعة المرضى. كما أظهر منحنى روك أن القطع الأمثل Et/AT للشريان الرئوى كان ٠.٣١ لاكتشاف النتائج الضارة فى مجموعة المرضى ذات الحساسية ٩٢.٩٪ وخصوصية ٩١.٧٪ وفى مجموعة التحكم، أظهر منحنى روك أن القطع الأمثل Et/AT للشريان الرئوى كان ٠.٣١٥ لاكتشاف النتائج الضارة مع حساسية ١٠٠٪ وخصوصية ٩٠.١٪.

الإستنتاج: يمكننا القول بأن إعطاء البروجسترون المهبلى للوقاية من الولادة المبكرة على الرغم من أنه مفيد فى إطالة فترة الحمل، إلا أنه قد يكون له آثار سلبية على الدورة الدموية الرئوية للجنين وخاصة نقص نسبة AT/Et للشريان الرئوى، وبالتالى زيادة الحالات المعرضة لخطر الضائقة التنفسية وهذا يحتاج إلى مزيد من البحث لإثبات ذلك. أيضاً، كما يمكننا استخدام نسبة AT/Et للشريان الرئوى للجنين كطريقة دقيقة غير اختراقية للتنبؤ بالخطر الضائقة التنفسية لحدثى الولادة فى الحالات المعرضة لخطر الولادة المبكرة واللائى يستخدمن البروجسترون كوسيلة وقائية.