Prediction of Perinatal Outcomes in Patient with Pre-eclampsia: Maternal Hyperoxygenation Test on Fetal Doppler Flow

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Objective: *Investigate if the maternal hyperoxygenation test in pregnancy with pre-eclampsia could be used for prediction of perinatal outcomes.*
Material and Method: *Fifty-four singleton pre-eclampsia pregnant women were enrolled in the present study. Positive hyperoxygenation test was defined as an increase of the middle cerebral artery (MCA) or the ductus venosus (DV) pulsatility index (PI), or a decrease of the uterine artery or the umbilical artery (UA) PI by at least 20%. Results of hyperoxygenation test were analyzed for the correlation with perinatal outcomes.*
Results: *Fetuses with positive hyperoxygenation test of the MCA had a birth weight less than the negative group significantly. Furthermore, there was a significantly higher rate of small for gestational age (SGA) neonates and admission to the neonatal intensive care unit (NICU) in cases with positive test of the MCA.*
Conclusion: *The present study shows the correlation of positive hyperoxygenation test of the MCA and low birth weight, SGA, and NICU admission.*

Keywords: *Echocardiography, Doppler, Hyperoxia, Oxygen, Pre-eclampsia, Pregnancy outcome, Ultrasonography, Prenatal*

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Pre-eclampsia is a medical condition where hypertension arises in pregnancy (pregnancy-induced hypertension) in association with significant amounts of protein in the urine. It appears likely that there is a substance or substances from the placenta that may cause endothelial dysfunction in the maternal blood vessels of susceptible women[1]. Pre-eclampsia occurs in as many as 5-8% of pregnancies, usually in the second or third trimester, and after the 32nd week. It is much more common in women who are pregnant for the first time[2]. This condition relates with adverse maternal and neonatal morbidity[2,3]. Maternal complications include eclampsia, and placental abruption, etc. Neonatal morbidities consist of fetal hypoxia, intraventricular hemorrhage, preterm birth, etc[4].

Several authors have reported changes of the uterine artery and fetal Doppler flow in pregnancy with pre-eclampsia[1,5-7]. In this condition, fetuses may have abnormal Doppler ultrasonography and biophysical profile. Thus, several Doppler studies have been performed to investigate the correlation of abnormal Doppler flow and/or biophysical profile and perinatal outcomes[1,5-8]. However, the sensitivity of abnormal Doppler flow and/or biophysical profile for prediction of adverse perinatal outcomes is still less than 50%[1,5,7-8].

Recently, experimental studies have investigated fetal Doppler flow on maternal hyperoxygenation[9-12]. Maternal hyperoxygenation test has studied in some conditions for prediction of neonatal outcomes[13,14].

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In fetuses with hemodynamic compromise, maternal oxygen administration can induce relevant hemodynamic changes, mainly characterized by the recovery of normal cerebral vascular resistance[15]. Furthermore, the lack of these modifications seems to be highly predictive of imminent fetal distress[16,17].

Because there is no excellent indicator for prediction of neonatal outcomes in pre-eclampsia, the aim of the present study was to investigate whether the maternal hyperoxygenation test in pregnancy with pre-eclampsia could be used for prediction of perinatal outcomes.

Material and Method

The present study was conducted as a prospective study. After obtaining approval from the Ethical Committee of Faculty of Medicine, Thammasat University, fifty-eight singleton pregnant women admitted to Thammasat University Hospital for pre-eclampsia between January 2, 2007 and January 31, 2008 were recruited for the present study. Mild and severe pre-eclampsia was diagnosed according to the classification and definition of the American College of Obstetricians and Gynecologists. All fetuses had normal structural scanning. Two fetuses with abnormal karyotypes and two cases who received tocolytic drugs were excluded. Written informed consent was obtained from the participants.

After a routine fetal scan with biometry, Doppler ultrasounds were obtained from the uterine artery, umbilical artery, middle cerebral artery, and ductus venosus. Thereafter, the women were administered oxygen by face-mask for 10 minutes before Doppler measurements from the uterine artery, umbilical artery, middle cerebral artery, and ductus venosus were repeated during the oxygen administration. These recordings were obtained within 10-15 minutes. All measurements were performed by one sonologist (first author).

Oxygen at 100% was given at a flow rate of 8 l/min through a close-fitting face-mask with a reservoir and a non-rebreathing valve.

Fetal ultrasound studies were performed on all fetuses with a coaxial pulsed Doppler color flow imaging system (Aloka ProSound SSD - α5sv Tokyo, Japan) employing 3.5-7.5 MHz transducer in range-gated Doppler mode. Care was taken to use the lowest possible high-pass filter and the smallest possible sample volume. Doppler recording from the uterine artery, from the free loop of the umbilical artery, the proximal part of the middle cerebral artery and the proximal segment of the ductus venosus were obtained with an angle less than 15°.

Only stable recordings without signs of fetal breathing or grossly movements were accepted for analysis. The pulsatility indices were averaged from three consecutive waveforms.

The demographic data, characteristics of pre-eclampsia and neonatal outcomes were recorded. Neonatal outcomes included birth weight, Apgar score, admission to the neonatal intensive care unit (NICU) and neonatal complication. Adverse neonatal outcomes included cesarean section due to fetal distress, Apgar score at 5 min less than 7, stillbirth, hypoxic-ischemic encephalopathy, major (grade 3 or 4) intra- or periventricular hemorrhage, periventricular leukomalacia and necrotizing enterocolitis.

Small for gestational age defined as neonatal birth weight is less than 10th percentile for gestational age.

Even though the criteria of positive hyperoxygenation test is controversial, the authors used the criteria as the study of Broth RE et al[14]. Therefore, a positive hyperoxygenation test was defined as decrease of the uterine artery pulsatility index (PI), decrease of the umbilical artery PI, increase of the middle cerebral artery PI, and increase of the ductus venosus PI of at least 20 percent. Negative results were defined as change of less than 20 percent.

Statistical Package for the Social Sciences 11.5 (SPSS) software was used to analysis these data. Independent student t-test was used for continuous data and Chi-square test was used to compare groups for significant differences.

Results

Of the fifty-four pregnant women with pre-eclampsia, 34 cases were primigravida and 43 cases were nulliparae. The mean of maternal age was 28 years. The average gestational age was 34 weeks. Sixteen cases were severe pre-eclampsia with the mean of systolic blood pressure was 180 mmHg and the mean of diastolic blood pressure was 114 mmHg. The average duration between hyperoxygentation test and delivery was 10 hours (range 1-30 hours).

Hyperoxygenation test of the uterine artery, umbilical artery, middle cerebral artery, and ductus venosus is presented in Table 1.

Fetuses with positive hyperoxygenation test of the middle cerebral artery had birth weight significantly less than the negative group ($p < 0.0001$). Furthermore, there was a significantly higher rate of

Table 1. Hyperoxygenation test of the uterine artery, umbilical artery, middle cerebral artery and ductus venosus

Vessels	Hyperoxygenation test			
	Mild pre-eclamsia (n)		Severe pre-eclampsia (n)	
	Negative	Positive	Negative	Positive
Uterine artery	32	6	14	2
Umbilical artery	37	1	14	2
Middle cerebral artery	38	0	8	8
Ductus venosus	27	11	9	7

small for gestational age (SGA) neonates and admission to the neonatal intensive care unit (NICU) in cases with positive test of the middle cerebral artery ($p < 0.0001$). The other vessels did not show any significant differences between positive and negative groups (Table 2-5).

In 16 cases of severe pre-eclampsia, fetuses with positive hyperoxygenation test of the middle cerebral artery had a birth weight significantly less than the negative group as shown in Table 6.

Discussion

There were no adverse neonatal outcomes in the present study. It was different from the previous study[18] that showed the adverse perinatal outcome was as high as 14.7%. This dissimilarity might be from the difference of the study design as the present study was a prospective study.

The results of the present study showed only the positive group of the middle cerebral artery had a low birth weight, SGA, and NICU admission more than the negative group significantly. In the other vessels, there was no significant difference between the two groups.

In eight cases with positive hyperoxygenation test of the middle cerebral artery, all were fetuses with intra-uterine growth restriction (IUGR) and mothers had severe pre-eclampsia pregnancy. All fetuses in this positive hyperoxygenation group also had abnormal

Table 2. Correlation of hyperoxygenation test of the uterine artery and perinatal outcomes

Perinatal outcomes	Hyperoxygenation test		p-value
	Negative	Positive	
n (percent)	46 (85.2)	8 (14.8)	
Gestational age (weeks) (mean ± SD)	35.30 ± 2.46	34.98 ± 3.11	0.746
Birth weight (grams) (mean ± SD)	2415 ± 688	2169 ± 625	0.350
SGA (n (percent))	11 (23.9)	2 (50.0)	0.947
Preterm birth (n (percent))	29 (63.0)	5 (62.5)	0.977
NICU admission (n (percent))	10 (21.7)	3 (37.5)	0.336

SD, standard deviation; SGA, small for gestational age; NICU, neonatal intensive care unit

Table 3. Correlation of hyperoxygenation test of the umbilical artery and perinatal outcomes

Perinatal outcomes	Hyperoxygenation test		p-value
	Negative	Positive	
n (percent)	51 (94.4)	3 (5.6)	
Gestational age (weeks) (mean ± SD)	35.2 ± 2.6	36.5 ± 0.6	0.396
Birth weight (grams) (mean ± SD)	2376 ± 684	2420 ± 748	0.914
SGA (n (percent))	40 (78.4)	1 (33.3)	0.076
Preterm birth (n (percent))	31 (60.78)	3 (100)	0.172
NICU admission (n (percent))	13 (25.5)	0 (0)	0.316

SD, standard deviation; SGA, small for gestational age; NICU, neonatal intensive care unit

Table 4. Correlation of hyperoxygenation test of the middle cerebral artery and perinatal outcomes

Perinatal outcomes	Hyperoxygenation test		p-value
	Negative	Positive	
n (percent)	46 (85.2)	8 (14.8)	
Gestational age (weeks) (mean ± SD)	35.4 ± 2.5	34.3 ± 2.9	0.246
Birth weight (grams) (mean ± SD)	2515 ± 626	1591 ± 389	<0.0001
SGA (n (percent))	5 (10.9)	8 (100)	<0.0001
Preterm birth (n (percent))	28 (60.9)	6 (75.0)	0.445
NICU admission (n (percent))	7 (15.2)	6 (75.0)	<0.0001

SD, standard deviation; SGA, small for gestational age; NICU, neonatal intensive care unit

Table 5. Correlation of hyperoxygenation test of the ductus venosus and perinatal outcomes

Perinatal outcomes	Hyperoxygenation test		p-value
	Negative	Positive	
n (percent)	36 (66.7)	18 (33.3)	
Gestational age (weeks) (mean ± SD)	35.2 ± 2.7	35.3 ± 2.1	0.923
Birth weight (grams) (mean ± SD)	2349 ± 706	2435 ± 640	0.667
SGA (n (percent))	9 (25.0)	4 (22.2)	0.822
Preterm birth (n (percent))	22 (61.1)	12 (66.7)	0.653
NICU admission (n (percent))	9 (25.0)	4 (22.2)	0.822

SD, standard deviation; SGA, small for gestational age; NICU, neonatal intensive care unit

Table 6. Correlation of hyperoxygenation test of the middle cerebral artery and perinatal outcomes in severe pre-eclampsia

Perinatal outcomes	Hyperoxygenation test		p-value
	Negative	Positive	
n (percent)	8 (50.0)	8 (50.0)	
Gestational age (weeks) (mean ± SD)	35.4 ± 3.1	34.3 ± 2.9	0.463
Birth weight (grams) (mean ± SD)	2291 ± 717	1591 ± 389	0.029
SGA (n (percent))	2 (25.0)	8 (100.0)	0.002
Preterm birth (n (percent))	5 (62.5)	6 (75.0)	0.590
NICU admission (n (percent))	2 (25.0)	6 (75.0)	0.046

SD, standard deviation; SGA, small for gestational age; NICU, neonatal intensive care unit

PI of the middle cerebral artery as support by previous studies[1,8].

In 16 cases of severe pre-eclampsia, the positive hyperoxygenation of the middle cerebral artery still demonstrated significant low birth weight in ($p = 0.029$). Additionally, there still was a significantly higher rate of admission to the neonatal intensive care unit (NICU) in cases with positive test of the middle cerebral artery ($p = 0.046$). While, rate of preterm did not differ significantly ($p = 0.590$).

The risk of adverse effects on the maternal administration of 100% oxygen has previously been discussed[10]. Maternal hyperoxia usually lasted for 20-25 minutes and during this period, the authors

could not demonstrate any hemodynamic changes that suggested adverse effects related to oxygen administration.

The limitation of the present study was the small number of cases of severe pre-eclampsia. The higher rate of low birth weight, SGA, and NICU admission in the positive group of the middle cerebral artery happened in only severe pre-eclampsia cases and might occur by chance. The conclusion of the correlation between maternal hyperoxygenation test and neonatal outcomes could be only addressed by bigger sample size studies.

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การทำนายผลของทารกแรกเกิดในหญิงตั้งครรภ์ที่มีความดันโลหิตสูงขณะตั้งครรภ์โดยการทดสอบด้วยการให้ออกซิเจนแก่หญิงตั้งครรภ์เพื่อดูการเปลี่ยนแปลงการไหลเวียนเลือดของทารกในครรภ์

อธิตา จันทเสนานนท์, จรินทร์ทิพย์ สมประสิทธิ์, เด่นศักดิ์ พงศ์โรจน์เผ่า

วัตถุประสงค์*: เพื่อศึกษาว่าการเปลี่ยนแปลงการไหลเวียนเลือด ของทารกในครรภ์จากการให้ออกซิเจน แก่หญิงตั้งครรภ์ (Hyperoxygenation test) ที่มีภาวะความดันโลหิตสูงขณะตั้งครรภ์นั้น จะสามารถใช้ทำนายผลของทารกแรกเกิดได้หรือไม่*

วัสดุและวิธีการ*: ทำการศึกษาในหญิงตั้งครรภ์ที่มีภาวะความดันโลหิตสูงขณะตั้งครรภ์ (pre-eclampsia) จำนวน 54 ราย hyperoxygenation test จะแปลผลเป็น บวก เมื่อมีการเปลี่ยนแปลงของ pulsatility index ของ middle cerebral artery หรือ ductus venosus เพิ่มขึ้น หรือ มีการลดลงของ pulsatility index ของ uterine artery หรือ umbilical artery ตั้งแต่ร้อยละ 20 จากนั้นผลของ hyperoxygenation test จะถูกนำมาหาความสัมพันธ์กับผลของการตั้งครรภ์*

ผลการศึกษา*: Hyperoxygenation test ของ หลอดเลือด middle cerebral artery นั้นพบว่า ในกลุ่มที่ได้ผลเป็นบวก ทารกมีน้ำหนักแรกเกิดน้อยกว่ากลุ่มที่มีผลการทดสอบเป็นลบอย่างมีนัยสำคัญทางสถิติ และกลุ่มที่มีผลการทดสอบเป็นบวกมีภาวะ small for gestational age (SGA) และ การรักษาตัวในหอผู้ป่วยทารกแรกเกิดวิกฤติ (NICU) มากกว่ากลุ่มที่มีผลการทดสอบเป็นลบ อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$)*

สรุป*: จากการศึกษานี้พบว่า มีความสัมพันธ์ระหว่างผลบวกของ hyperoxygenation test ของหลอดเลือด middle cerebral artery กับน้ำหนักแรกเกิดที่น้อย ภาวะ SGA และ การรักษาตัวในหอผู้ป่วยทารกแรกเกิดวิกฤติ*