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RESEARCH

Reference ranges for peak systolic velocity ratio of ophthalmic artery Doppler from first to third trimester based on serial Doppler measurements

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Abstract

Background Maternal ophthalmic artery Doppler assessment has been proposed as one of the predictors for preeclampsia at any given time. Changes in ophthalmic artery Doppler preceding the onset of PE have been reported in several studies. Some parameters of ophthalmic artery Doppler studies have been proposed, but peak systolic velocity ratio is the most reliable indicator in the prediction of preeclampsia. However, limited previous studies have investigated the reference value across pregnancy.

Study design This was a prospective longitudinal cohort study of low-risk singleton pregnancies without evidence of fetal anomaly, visiting antenatal care between February 2024 and December 2024 at Maternal and Children Harapan Kita hospital in Jakarta and Dr. Sardjito hospital in Yogyakarta, Indonesia. Women were recruited from 11 weeks until 40 weeks' gestation. They underwent serial ultrasound monitoring. Association of ophthalmic artery Doppler PSV was modeled with fractional polynomial regression. Equations for mean ± SD of the estimated curves were calculated, as well as GA-specific reference charts of centiles for ophthalmic artery PSV ratio from 11 + 0 weeks to 40 + 0 weeks.

Result We included 998 low-risk pregnancies and a total of 2439 ultrasound scans (median 3, range 2–4 per patient) were available for analysis. Goodness-of-fit assessment revealed that second-degree smoothing was the most accurate fractional polynomial for describing the course of ophthalmic artery PSV ratio curves. We observed a decrease in PSV ratio until 26 weeks and a substantial increase afterwards. The 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97th centiles according to GA for ophthalmic artery PSV ratio are provided, as well as equations to allow calculation of any value as a centile.

Conclusion Ophthalmic artery PSV ratio showed non-linear behavior in which it decreased from 11 weeks until the end of trimester 2, and it started to increase until the end of pregnancy.

Keywords Ophthalmic artery Doppler · Reference value · Pregnancy

What does this study add to the clinical work

This study established trimester-specific reference ranges for PSV ratio of the ophthalmic artery using serial Doppler measurements throughout pregnancy. These normative data provide a valuable tool for a reference framework for future research into hypertensive disorders and other pregnancy complications.

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Introduction

Preeclampsia is a complex condition caused by various pathways. Preeclampsia is thought to result from the interplay of reduced blood flow and oxygen to the uterus and placenta, heightened inflammatory reactions, immune imbalances, altered genetic changes, imbalanced blood vessel growth factors, and disrupted gut bacteria [1]. Doppler ultrasonography has emerged as a valuable non-invasive tool for evaluating hemodynamic changes during pregnancy. The ophthalmic artery, which is the first branch of the internal carotid artery, has a Doppler velocity waveform with two systolic peaks. The first systolic wave is created by cardiac systole: ejection of blood into the aorta and from there to the internal carotid artery. The second wave is formed by the systolic pulse wave reaching smaller, higher resistance arterioles and being reflected back towards the heart [2]. An increase in the ratio of the second to the first PSV could be due to an increase in peripheral vascular resistance and/or a reduction in cardiac output.

Maternal ophthalmic artery Doppler assessment has been proposed as one of the predictors for preeclampsia at any given time. Changes in ophthalmic artery Doppler preceding the onset of PE have been reported in several studies.

Establishing the reference value of ophthalmic artery PSV ratio in the general population is crucial for validating the clinical value and its utilization as a marker to predict preeclampsia. Limited previous studies have investigated the reference value. The study aimed to develop a reference chart with gestational age (GA)-specific centiles for ophthalmic artery—PSV ratio in low-risk pregnancy, based on longitudinal data.

Methods

This was a longitudinal prospective cohort study of women attending serial antenatal scans from 11 to 40 weeks conducted from February 2024 to September 2024 at the Fetal Medicine Department of Harapan Kita Maternal Children Hospital in Jakarta and Dr. Sardjito Hospital in Yogyakarta, Indonesia. The study was conducted in agreement with the Declaration of Helsinki and approved by the institutional review board of the Medical and Health Research Ethics Committee, Universitas Gadjah Mada. All participants were provided with written informed consent to record their information for scientific purposes. The study was conducted and reported following the reporting of observational studies in epidemiology (STROBE) guidelines.

The ophthalmic artery PSV ratio was assessed according to follow protocol: patient was in the supine position, with the head inclined approximately at 30 degrees, and a small amount of clear gel was applied to the closed eyelid.

Population

Low-risk women with singleton pregnancy, uncomplicated pregnancy, and neonatal outcome attending for routine antenatal care were assessed by serial US scans during the first, second, and third trimesters of pregnancy. Women who commenced antenatal care at 11 weeks' gestation and who had two US scans throughout pregnancy were included. Inclusion criteria were as follows: maternal age ≥ 18 years; singleton pregnancy; natural conception; unremarkable medical history; no use of tobacco. Exclusion criteria included risk profile for adverse pregnancy/perinatal outcome due to maternal pregestational or gestational diseases (Type-I or Type-II diabetes, cardiovascular disease, malignancy, gynecological disease, endocrine disease, antiphospholipid syndrome, chronic hypertension and history of PE or preterm birth in any previous pregnancy) and chromosomal or major structural fetal abnormalities.

Standard ultrasound assessment

Women were enrolled as determined by US measurement of crown-rump length [3]. At each US assessment, right ophthalmic artery PSV was measured in all participants by two standardized operators.

Statistical analysis

Sample size considerations were performed before analyzing the prospectively collected data. Considering the sample size calculation for a generic regression line and using the SD of both dependent and independent variables plus the value of the slope, we found that 300 observations are needed to achieve a 90% power at a type-I error of 5%.

Several distributions and smoothing techniques were explored for the construction of the best-fitting curve on the basis of our data. Starting with the simplest model assuming a normal distribution, different degrees of fractional

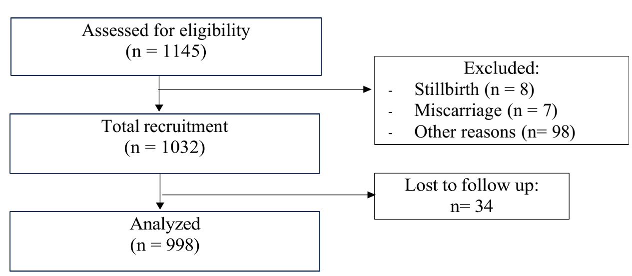

Fig. 1 Flowchart showing patient selection

Table 1 Maternal demographic characteristics and pregnancy outcome

Characteristics	Value
Maternal age (years)	30.8 ± 5.0
Nulliparous	383 (38.4%)
Multiparous	615 (61.6%)
Body mass index	26.7 ± 5.2
Birth weight (g)	3056 ± 554
Small for gestational age	11 (1.1%)
Hypertensive	9 (0.9%)
Preterm birth (< 37 weeks)	48 (4.8%)
Neonatal mortality	0
Caesarean delivery	272 (27.3%)

Data are given as mean ± SD, *n*(%) or median (interquartile range). *Birth weight < 10th centile

polynomials we compared using standard goodness of fit analyses. This was implemented using the xriml module (2021) in STATA (StataCorp. LLC, College Station, TX, USA) [4].

Results

Among the 998 women who attended Maternal and Children Harapan Kita Hospital and Dr. Sardjito Hospital for US assessment, they had serial scans starting from 11 weeks until 40 weeks. Therefore, data for analysis were obtained from women. A total of 2439 scans with a median of three per patient (range, 2–4) were performed. The patient selection process is shown in Fig. 1.

Maternal demographic characteristics, pregnancy and neonatal outcomes are reported in Table 1. The mean maternal age was 30.8 ± 5.0 years. The GA-specific 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97th fitted centile curves for mean ophthalmic artery PSV ratio are shown in Fig. 2. Equations for ophthalmic artery PSV ratio according to gestational age is reported in table 2. The calculated GA-specific standard values for the 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97th centiles of ophthalmic artery PSV ratio from 11 + 2 to 40 + 0 weeks' gestation are reported in Table 3.

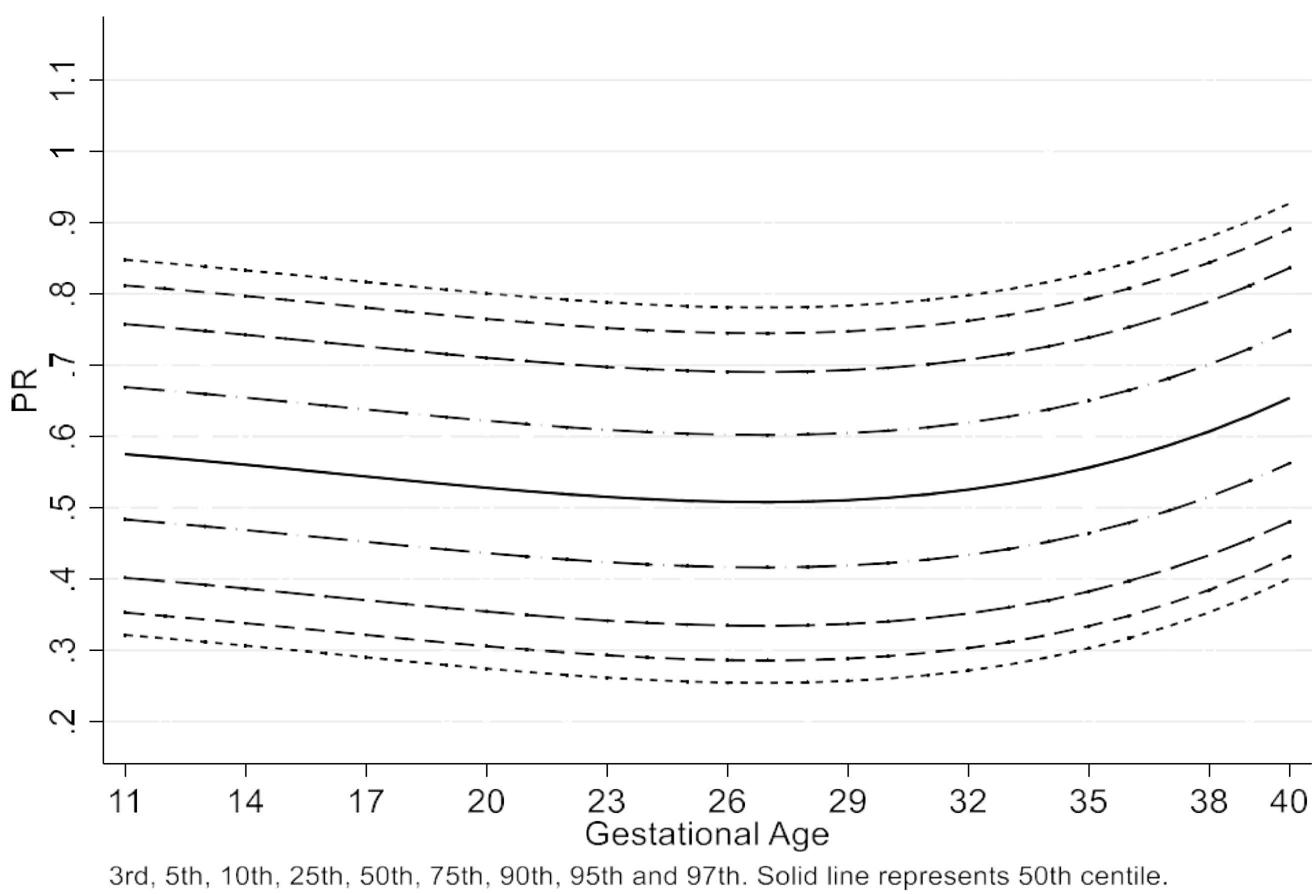

Fig. 2 Smoothed centile curves for ophthalmic artery PSV ratio according to gestational age from 11 to 40 weeks in low-risk population

Table 2 Equations for ophthalmic artery PSV ratio according to gestational age from 11 + 0 weeks to 40 weeks in healthy low risk singleton pregnancies

Parameter	Equation
Skewness	0.14
Mean	0.5155377–0.0139039x (GA^3-19.58286314) + 0.0107842 x (GA^3*ln(GA)-19.41741963)
Coefficient of variation	(GA/10)^3*ln(GA/10)-19.41741963

Table 3 Ophthalmic artery PSV ratio according to gestational age (GA) from 11 to 40 weeks in low risk pregnancies

GA (weeks)	Centile								
	3rd	5th	10th	25th	50th	75th	90th	95th	97th
11	0.322	0.353	0.402	0.483	0.575	0.669	0.757	0.812	0.847
12	0.317	0.348	0.397	0.479	0.570	0.664	0.752	0.807	0.843
13	0.312	0.343	0.392	0.474	0.565	0.659	0.748	0.802	0.838
14	0.307	0.338	0.387	0.469	0.560	0.654	0.742	0.797	0.833
15	0.301	0.333	0.381	0.463	0.555	0.649	0.737	0.791	0.827
16	0.296	0.327	0.376	0.458	0.549	0.643	0.731	0.786	0.822
17	0.290	0.322	0.370	0.452	0.544	0.638	0.726	0.780	0.816
18	0.285	0.316	0.365	0.447	0.538	0.632	0.720	0.775	0.811
19	0.280	0.311	0.360	0.441	0.533	0.627	0.715	0.770	0.805
20	0.275	0.306	0.355	0.436	0.528	0.622	0.710	0.764	0.800
21	0.270	0.301	0.350	0.432	0.523	0.617	0.705	0.760	0.796
22	0.266	0.297	0.346	0.427	0.519	0.613	0.701	0.755	0.791
23	0.262	0.293	0.342	0.424	0.515	0.609	0.697	0.752	0.788
24	0.259	0.290	0.339	0.421	0.512	0.606	0.694	0.749	0.785
25	0.256	0.288	0.336	0.418	0.510	0.604	0.692	0.746	0.782
26	0.255	0.286	0.335	0.417	0.508	0.602	0.690	0.745	0.781
27	0.255	0.286	0.335	0.416	0.508	0.602	0.690	0.744	0.780
28	0.255	0.287	0.335	0.417	0.509	0.603	0.691	0.745	0.781
29	0.257	0.289	0.337	0.419	0.511	0.605	0.693	0.747	0.783
30	0.261	0.292	0.341	0.422	0.514	0.608	0.696	0.750	0.786
31	0.265	0.297	0.345	0.427	0.519	0.613	0.701	0.755	0.791
32	0.272	0.303	0.352	0.434	0.525	0.619	0.707	0.762	0.798
33	0.280	0.312	0.360	0.442	0.534	0.628	0.716	0.770	0.806
34	0.290	0.322	0.370	0.452	0.544	0.638	0.726	0.780	0.816
35	0.303	0.334	0.383	0.465	0.556	0.650	0.738	0.793	0.829
36	0.317	0.349	0.397	0.479	0.571	0.665	0.753	0.807	0.843
37	0.334	0.366	0.414	0.496	0.588	0.681	0.770	0.824	0.860
38	0.354	0.385	0.434	0.515	0.607	0.701	0.789	0.843	0.879
39	0.376	0.407	0.456	0.537	0.629	0.723	0.811	0.865	0.901
40	0.401	0.432	0.480	0.562	0.654	0.748	0.836	0.890	0.926

Discussion main findings

This study provides robust reference ranges for gestational age-specific ophthalmic artery in a population of low-risk pregnancies. Ophthalmic artery PSV ratio showed non-linear characteristics, in which it decreased from 11 weeks until the end of trimester 2, and it started to increase until the end of pregnancy.

Interpretation

The need to develop ophthalmic artery PSV ratio charts derived from the lack in the literature of recent longitudinal studies based on a standardized method [5, 6]. Classic polynomial regression is used widely for the description of continuous biometric data. Fractional polynomials are an alternative to regular polynomials, providing flexible parameterization for continuous variables encompassing a wide range of shapes, including and overcoming all those generated by classical polynomials. Fractional polynomials differ from regular polynomials in allowing use of logarithms as well as non-integer and repeated powers.

Strengths and limitations

Longitudinal approach with minimal two observations per patient contributed to reducing heterogenicity. Finally, fractional polynomial analysis implemented in a complex statistical approach due to its inherent flexibility enabled a better depiction of the real pattern of ophthalmic artery PSV ratio throughout pregnancy. However, the inclusion of only Indonesian population represents a limitation of this study as it may affect generalizability of the findings. Further study with other populations is warranted.

Author contributions RAK, ITR, DSN initiated the conception and design of the study; RAK, ITR, AW, AN performed data acquisition; AS analyzed the data. RAK, ITR, DSN, AW, AN validated and interpreted the data and results. All authors contributed to data interpretation; RAK drafted the initial draft of the manuscript; all authors revised the manuscript for intellectual content; all authors have approved the final draft of the manuscript.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare that there are no competing interests.

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