

Original Article

Doppler Waveform Indices of Fetal Middle Cerebral Artery in Normal 20 to 40 Weeks Pregnancies

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Background: One of the main methods for evaluation of fetal well-being is analysis of Doppler flow velocity waveform of fetal vessels. Evaluation of Doppler wave of the middle cerebral artery can predict most of the at-risk fetuses in high-risk pregnancies. In this study, we tried to determine the normal ranges and their trends during pregnancy of Doppler flow velocity indices (resistive index, pulsatility index, systolic-to-diastolic ratio, and peak systolic velocity) of middle cerebral artery in 20 – 40 weeks normal pregnancies in Iranians.

Methods: In this cross-sectional study, 1037 women with normal pregnancy and gestational age of 20 to 40 weeks were investigated for fetal middle cerebral artery Doppler examination.

Results: Resistive index, pulsatility index, and systolic-to-diastolic ratio values of middle cerebral artery decreased in a parabolic pattern while the peak systolic velocity value increased linearly with progression of the gestational age. These changes were statistically significant ($P < 0.001$ for all four variables) and were more characteristic during late weeks of pregnancy. The mean fetal heart rate was also significantly ($P < 0.001$) reduced in correlation with the gestational age.

Conclusion: Doppler waveform indices of fetal middle cerebral artery are useful means for determining fetal well-being. Herewith, the normal ranges of Doppler waveform indices for an Iranian population are presented.

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Keywords: Doppler ultrasonography • fetus • middle cerebral artery • pregnancy

Introduction

Currently, Doppler ultrasonography (DU) velocimetry of uteroplacental, umbilical, and fetal vessels has become the established method for antenatal monitoring.¹⁻³ Circulatory changes, reflected in certain fetal Doppler waveforms, predict adverse perinatal outcome.^{4,5}

Although umbilical arteries are the common vessels assessed by DU, recent studies have shown

the efficacy of the middle cerebral artery (MCA) Doppler assessment.^{6,7} Today, with the advancement of pulsed and color-coded DU combined with better reproducibility, the MCA has emerged as the vessel of choice in the Doppler assessment of fetal intracranial as well as other organs perfusion.^{8,9}

Applicability of Doppler indices in the diagnosis of abnormalities is possible only when there are reference normal values for each index. Although various investigators have described and established gestational age-related reference curves,¹⁰⁻¹² this is the first study performed in Iran.

The objective of this study was to determine new DU gestational age-dependent reference curves for the MCA indices including resistive index (RI), pulsatility index (PI), systolic to diastolic (S/D) ratio, peak systolic velocity (PSV), and fetal heart rate (FHR) in a normal Iranian obstetric population of 20 to 40 weeks' gestation.

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Patients and Methods

In a cross-sectional study conducted between February 2004 and May 2007, we analyzed the Doppler measurements of 1037 low-risk pregnant women with gestational age between 20 and 40 weeks. Those women were referred to our department for routine prenatal care. The research protocol was approved by the local Ethics Committee and an informed written consent was obtained from every subject involved in the study prior to the examination.

Prior to Doppler assessment, routine obstetric ultrasonography was done for each subject.

The examinations were performed by a single investigator in Al-Zahra Obstetrics and Gynecology Hospital using a Hitachi unit EUB-525 (Hitachi Medical Corporation, Tokyo, Japan) with a 3.5 MHz convex transducer. Doppler parameters were optimized in each examination. Every woman underwent only one examination to measure the fetal MCA. After color localization of the MCA, the Doppler flow velocity was measured from the proximal portion of MCA. Securing the best image quality for flow velocity waveforms, at least three waveforms were measured by ultrasonologist and averaged.

Women who met the following criteria were included in the study: I) low-risk pregnancy, II) normal neonatal anatomy, III) accurate gestational age based on the last normal menstruation date adapted with ultrasound parameters, IV) gestational age between 20 and 40 weeks, V) normal fetal growth (between 10th and 90th percentiles of the growth chart), VI) normal Doppler pattern of uterine and umbilical arteries, VII) nonsmoking and nonalcoholic women, and VIII) no history of hypertension, diabetes mellitus, autoimmune conditions, preeclampsia, abnormal vaginal discharge and bleeding, induced pregnancy, hydrops fetalis, and consumption of hormonal contraceptive agents. Finally, only those who delivered a full-term, healthy baby with birth weight between the 10th and 90th percentiles for gestational age and gender were included for further analysis.

Exclusion criteria were: I) congenital abnormalities, II) oligohydramnios (amniotic fluid index [AFI]<5) according to Phelan's criteria,¹³ III) biophysical profile <6, or estimated fetal weight outside the 90% of the normal range,¹⁴ and IV) abnormal fetal biometry with an estimated fetal weight below the 10th percentile or higher than the 90th percentile in comparison with the first

trimester or early second trimester ultrasound findings (cases of intrauterine growth retardation [IUGR], small for gestational age [SGA], and large for gestational age [LGA]).

Statistical analysis was performed using SPSS version 13.0. Variables were presented as mean±SD. A *P* value of <0.05 was considered statistically significant. Pearson's correlation coefficient and regression were used for evaluation of correlation between indices and gestational age. Reference ranges (90% range between the 5th and 95th percentiles) and the 95% confidence interval were calculated for each parameter and presented as graphs. Linear, quadratic, and cubic regression models were fitted to estimate the relationship between fetal Doppler variables and gestational age (in weeks). The best fitting model for each variable was then selected.

Results

A total of 1037 women were evaluated for this study of whom only 978 (94.31%) were enrolled in the final analysis and 59 were excluded from the study for the previously-mentioned criteria.

The number of patients according to gestational age in weeks, patients' characteristics, mean±SD for the MCA RI, PI, S/D ratio, and PSV are shown in Table 1. Values and nomograms of RI, PI at 5, 50, and 95th percentiles for each gestational age are shown in Figures 1 and 2, respectively. The reference curve of the RI follows a parabolic pattern, increasing from 0.76 at 20th week of gestation to 0.85 at 28th week and decreasing to 0.67 at 40th week of gestation (Figure 1). A similar pattern was also observed for the PI (from 1.72 to a maximum of 2.05 at 28th week to 1.23; Figure 2) and S/D ratio (from 5.34 to a maximum of 7.13 at 30th week to 3.16). Regarding PSV, an increase of 20 to 54.42 cm/s with a peak PSV of 60.85 at 39th week was noted for the observation interval. However, the reference curve of FHR demonstrated a decreasing trend from 151.69 to 136.5 beats per minute from 20th to 40th weeks of gestation.

There was a strong positive linear correlation between RI and PI ($P<0.001$, $r=0.886$), RI and S/D ratio ($P<0.001$, $r=0.860$), and PI and S/D ratio ($P<0.001$, $r=0.863$) and a negative linear correlation between PSV and PI ($P<0.001$, $r=-0.170$) and PSV and S/D ratio ($P=0.012$, $r=-0.125$). None of the RI, PI, PSV, or S/D ratio was correlated to the FHR.

Table 1. Mean±SD of demographic and Doppler ultrasonographic findings in the study group.

Gestational age (wk)	No. of patients	Age of patients	Heart rate of fetus	Patients gravidity	RI	PI	PSV	S/D ratio
20	41	23.25±3.41	151.69±5.88	1.31±0.6	0.76±0.04	1.72±0.29	20±12.23	5.34±1.55
21	48	27.38±6.34	149.63±5.72	1.79±0.88	0.77±0.06	1.79±0.26	23.15±12.69	5.81±1.9
22	43	26.38±6.37	149.77±7.39	1.69±0.85	0.76±0.05	1.82±0.28	23.77±11.69	5.91±1.79
23	54	26.74±6.7	144.48±8.04	1.81±1.03	0.78±0.04	1.94±0.28	22.72±11.02	6.31±1.97
24	45	27.36±5.95	146.43±6.92	2±1.35	0.81±0.05	1.94±0.43	27.92±11.38	6.21±1.61
25	52	25.23±5.21	148.54±7	1.81±0.98	0.81±0.05	1.9±0.36	27.14±9.2	6.38±1.59
26	44	27.79±4.51	142±7.4	1.74±0.8	0.82±0.05	1.95±0.39	30.56±10.14	6.36±1.47
27	42	27.1±5.31	144.24±7.75	2.1±1.04	0.83±0.04	2.03±0.38	36.13±9.37	6.69±1.37
28	41	26.5±3.62	143.7±7.57	1.6±0.69	0.85±0.07	2.05±0.49	37.24±6.6	6.95±1.64
29	55	25.97±5.56	141.43±8.59	1.6±0.85	0.84±0.05	2.02±0.4	36.54±9.7	6.87±1.46
30	46	26.5±4.47	140.6±11.06	1.7±0.82	0.83±0.04	1.98±0.34	46.42±11.16	7.13±1.35
31	50	27.53±7.7	138.77±10.67	1.57±0.77	0.82±0.04	1.97±0.35	41.24±10.14	6.6±1.66
32	46	27.29±5.97	140.76±8.28	2.06±0.82	0.82±0.07	1.92±0.33	49.28±9.77	7.09±2.21
33	47	27.3±4.78	138.39±8.78	1.52±0.73	0.79±0.06	1.76±0.3	47.3±10.73	5.84±2.00
34	42	27.05±6.02	138.67±9.91	1.81±0.98	0.79±0.04	1.79±0.28	57.1±9.29	5.1±1.18
35	49	29.21±4.65	136.37±10.13	2.26±1.36	0.8±0.05	1.75±0.33	52.06±9.61	5.33±1.84
36	48	27.92±5.62	139.88±9.52	2.33±1.09	0.75±0.05	1.54±0.26	56.65±12.2	4.31±1.15
37	43	27.94±5.05	137±9.66	1.63±0.88	0.73±0.07	1.43±0.31	53.93±16.34	4.12±1.31
38	51	25.29±5.65	134.71±7.76	1.53±0.8	0.68±0.06	1.25±0.21	56.97±15.91	3.22±0.67
39	45	28.33±5.66	136.33±9.3	2.27±1.43	0.68±0.05	1.23±0.15	60.85±18.96	3.22±0.46
40	46	26.50±2.33	136.50±10.19	1.63±0.51	0.67±0.04	1.23±0.16	54.42±23.48	3.16±0.44

RI= resistive index; PI=pulsatility index; S/D ratio=systolic-to-diastolic ratio; PSV=peak systolic velocity; FHR=fetal heart rate.

Discussion

In fetal intracranial circulation, diastolic blood flow appears earlier than the fetal aorta and umbilical artery representing redistribution of the flow to the most vital fetal organ.¹⁵ Also, comparing changes in the fetal cerebral circulation with changes in the systemic circulation or the umbilical arteries have shown that fetal cerebral circulation changes to be more promising as a predictor of the

condition of the fetus.^{6,16} So, the MCA has been the vessel of choice to assess fetal cerebral circulation.

Comparing the RI as found in our reference curves with that published by Kurmanavicius et al.¹⁷ it is clear that reference limits during 24th to 40th weeks of gestation are lower (about 0.6 – 1.1) for our curves. A reason for these conflicting results may be the different mathematical methods used for derivation of the indices. With similar

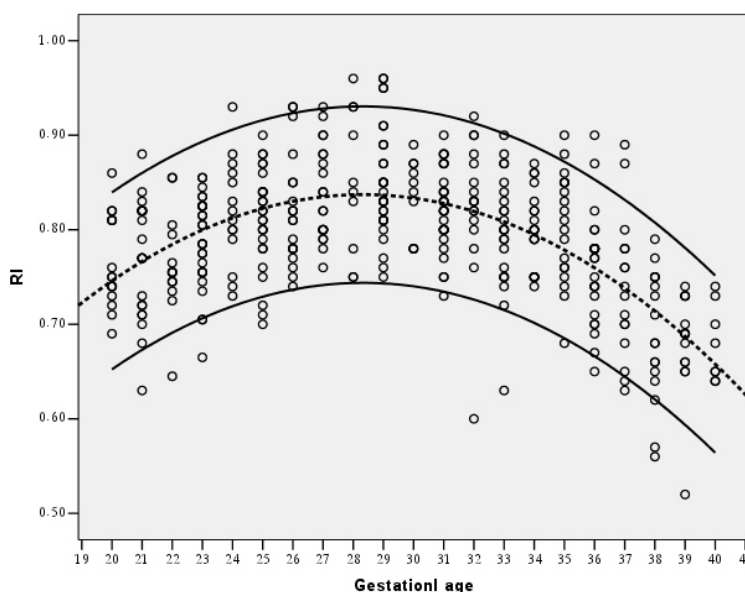


Figure 1. Individual measurements and calculated reference ranges for the resistive index (RI) in the MCA. The standard boundaries include 90% of the normal patient population ($r^2=0.386$, $P<0.001$).

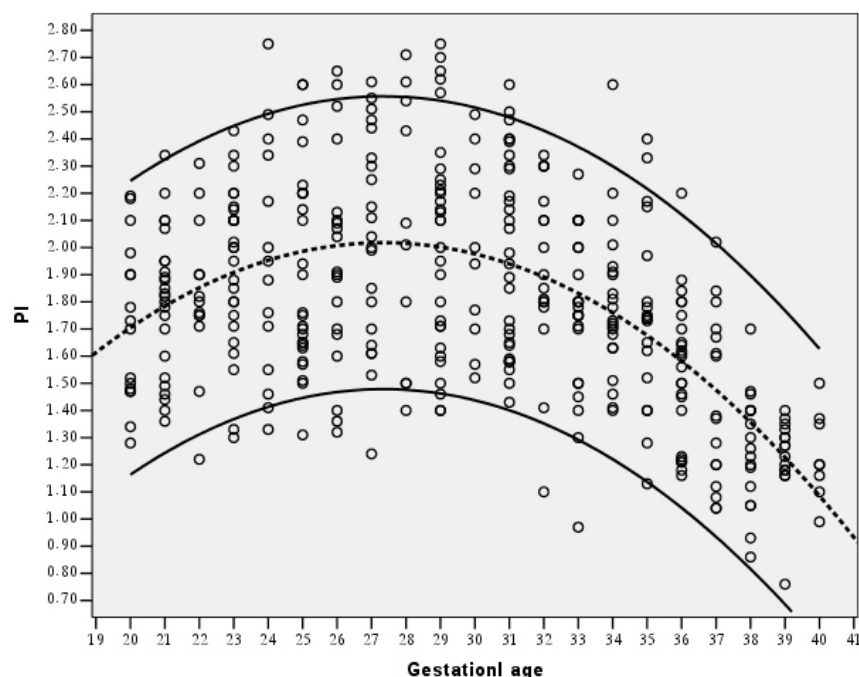


Figure 2. Individual measurements and calculated reference ranges for the pulsatility index (PI) in the MCA. The standard boundaries include 90% of the normal patient population ($r^2=0.340$, $P<0.001$).

parabolic pattern, our ranges were closer to the Bahlmann et al.'s report.⁷

Despite the parabolic shape of our PI curve and the presence of a peak at 28th week of gestation, generally, there was a fall in the fetal MCA PI with advancing gestational age (Figure 2) which is comparable with other studies.^{18,19} This decrease probably reflects a decreasing vascular resistance with advancement of gestational age or an association with deoxyribonucleic acid production in fetal brain.^{18,19}

A comparison of the reference ranges established in this study with those obtained in the USA²⁰ and Germany³ shows almost identical parabolic pattern and reference values for the PI over the entire observation period. Conversely, the results reported by Vyas et al.,²¹ Mari and Deter,²² Komwilaisak et al.,²³ and Bahlmann et al.,⁷ show higher PI values, despite the similarity of their curves with our chart. This discrepancy may be due to the eight- to 11-fold smaller number of patients included in Vyas et al.'s and Mari and Deter's studies and the different statistical methods used for analyses.

There are no available studies on S/D ratio range and pattern, except that of Ertan et al.²⁴ who have reported a chart with decreasing slope toward the end of gestation. In our study, S/D ratio chart had a parabolic pattern similar to those obtained

for RI and PI (20th week: 5.34, 40th week: 3.16, and peak in 30th week: 7.13). Because the same factors were used to calculate the RI, PI, and S/D ratio, these indices showed a similar pattern.

Our study demonstrated that the MCA PSV was increased during the second half of pregnancy. Although patterns were similar, values were different and showed an average of 6 cm/s higher than that reported by Bahlmann et al.⁷ Comparison of the PSV ranges in the MCA measured in this study with those reported by Kurmanavicius et al.²⁵ and Mari and Deter²⁶ demonstrates good agreement, although there are minor differences in values. Marked disparity, especially for the upper reference limits, become apparent in the period prior to 28 weeks of gestation. Explanations for this phenomenon were the use of different statistical methods, and different sample sizes. An inverse correlation between PSV and the fetal hemoglobin concentration or hematocrit may also interfere with the results of studies.²⁶

Although studies in early periods of gestation (first trimester) showed that FHR increases as pregnancy progresses,^{27,28} but we demonstrated that after 20th week of gestation (during late second and third trimesters), the rate decreases as gestational age increases. Similar results were reported by Snijders et al. and Park et al.^{29,30}

This is of clinical importance to determine

whether given MCA Doppler indices are normal or not; so, normal MCA Doppler indices must be defined for each week of gestational age. Since these parameters may be varied among different populations, population-specific charts may be needed. The DU reference curves for the MCA described in this paper (especially, the lower reference limits of the PI and RI) can be used in assessment of fetal hypoxic, anemic disorders, and IUGR,^{22,31} because these processes are identified by demonstration of low-impedance Doppler waveforms of the MCA.²¹

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References

- Dubiel M, Breborowicz GH, Marsal K, Gudmundsson S. Fetal adrenal and middle cerebral artery Doppler velocimetry in high-risk pregnancy. *Ultrasound Obstet Gynecol.* 2000; **16**: 414 – 418.
- Kurjak A, Kupesic S, Zudenigo D. Doppler ultrasound in all three trimesters of pregnancy. *Curr Opin Obstet Gynecol.* 1994; **6**: 472 – 478.
- Baschat A, Gembruch U. The cerebroplacental Doppler ratio revisited. *Ultrasound Obstet Gynecol.* 2003; **21**: 124 – 127.
- Trudinger BJ, Cook CM, Giles WB, Ng S, Fong E, Connelly A, et al. Foetal umbilical artery velocity waveforms and subsequent neonatal outcome. *Br J Obstet Gynaecol.* 1991; **98**: 378 – 384.
- Arduini D, Rizzo G. Doppler studies of deteriorating growth-retarded fetuses. *Curr Opin Obstet Gynecol.* 1993; **5**: 195 – 203.
- Gramellini D, Folli MC, Raboni S, Vadora E, Merialdi A. Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome. *Obstet Gynecol.* 1992; **79**: 416 – 420.
- Bahlmann F, Reinhard I, Krummenauer F, Neubert S, MacChiella D, Wellek S. Blood flow velocity waveforms of the fetal middle cerebral artery in a normal population: reference values from 18 weeks to 42 weeks of gestation. *J Perinat Med.* 2002; **30**: 490 – 501.
- Mari G, Moise KJ Jr, Deter RL, Kirshon B, Carpenter RJ Jr, Huhta JC. Doppler assessment of the pulsatility index in the cerebral circulation of the human fetus. *Am J Obstet Gynecol.* 1989; **160**: 698 – 703.
- Noordam MJ, Hoekstra FM, Hop WC, Wladimiroff JW. Doppler color flow imaging of fetal intracerebral arteries relative to fetal behavioral states in normal pregnancy. *Early Hum Dev.* 1994; **39**: 49 – 56.
- Royston P, Wright EM. How to construct 'normal ranges' for fetal variables. *Ultrasound Obstet Gynecol.* 1998; **11**: 30 – 38.
- Wellek S, Merz E. Age-related reference ranges for growth parameters. *Methods Inf Med.* 1995; **34**: 523 – 528.
- Manning FA, Platt LD, Sipos L. Antepartum fetal evaluation: development of a fetal biophysical profile. *Am J Obstet Gynecol.* 1980; **136**: 787 – 795.
- Phelan JP. Amniotic fluid index. In: Chervenak FA, Campbell S, Isaacson GC, eds. *Ultrasound in Obstetrics and Gynecology.* 2nd ed. Boston: Little, Brown; 1993: 565 – 568.
- Manning FA, Morrison I, Harman CR, Lange IR, Menticoglou S. Fetal assessment based on fetal biophysical profile scoring: experience in 19,221 referred high-risk pregnancies. II. An analysis of false-negative fetal deaths. *Am J Obstet Gynecol.* 1987; **157(4 Pt 1)**: 880 – 884.
- Kurjak A, Kupesic S. *Color Doppler in Obstetrics, Gynecology, and Infertility.* Zagreb-Seoul: Art Studio Azinovic-Medison; 1999.
- Arduini D, Rizzo G. Prediction of fetal outcome in small for gestational age fetuses: comparison of Doppler measurements obtained from different fetal vessels. *J Perinat Med.* 1992; **20**: 29 – 38.
- Kurmanavicius J, Florio I, Wisser J, Hebisch G, Zimmermann R, Müller R, et al. Reference resistance indices of the umbilical, fetal middle cerebral, and uterine arteries at 24 – 42 weeks of gestation. *Ultrasound Obstet Gynecol.* 1997; **10**: 112 – 120.
- Chandran R, Serra-Serra V, Sellers SM, Redman CW. Foetal cerebral Doppler in the recognition of foetal compromise. *Br J Obstet Gynaecol.* 1993; **100**: 139 – 144.
- Alcázar JL, Rovira J, Ruiz-Pérez ML, López-García G. Transvaginal color Doppler assessment of fetal circulation in normal early pregnancy. *Fetal Diagn Ther.* 1997; **12**: 178 – 184.
- Arduini D, Rizzo G. Normal values of Pulsatility Index from fetal vessels: a cross-sectional study on 1556 healthy fetuses. *J Perinat Med.* 1990; **18**: 165 – 172.
- Vyas S, Nicolaides KH, Bower S, Campbell S. Middle cerebral artery flow velocity waveforms in foetal hypoxaemia. *Br J Obstet Gynaecol.* 1990; **97**: 797 – 803.
- Mari G, Deter RL. Middle cerebral artery flow velocity waveforms in normal and small-for-gestational-age fetuses. *Am J Obstet Gynecol.* 1992; **166**: 1262 – 1270.
- Komwilaisak R, Saksiriwuttho P, Ratanasiri T, Kleeboon P, Seejorn K. Pulsatility index of the middle cerebral artery in normal fetuses. *J Med Assoc Thai.* 2004; **87**: S34 – S37.
- Ertan AK, Hendrik HJ, Tanriverdi HA, Bechtold M, Schmidt W. Fetomaternal Doppler sonography nomograms. *Clin Exp Obstet Gynecol.* 2003; **30**: 211 – 216.
- Kurmanavicius J, Streicher A, Wright EM, Wisser J, Müller R, Royston P, et al. Reference values of fetal peak systolic blood flow velocity in the middle cerebral artery at 19 – 40 weeks of gestation. *Ultrasound Obstet Gynecol.* 2000; **17**: 50 – 53.
- Mari G, Adrignolo A, Abuhamad AZ, Pirhonen J, Jones DC, Ludomirsky A, et al. Diagnosis of fetal anemia with Doppler ultrasound in the pregnancy complicated by maternal blood group immunization. *Ultrasound Obstet Gynecol.* 1995; **5**: 400 – 405.
- Mäkikallio K, Jouppila P, Räsänen J. Human fetal cardiac function during the first trimester of pregnancy. *Heart.*

- 2005; **91**: 334 – 338.
- 28** Włoch A, Rozmus-Warcholinska W, Czuba B, Borowski D, Włoch S, Cnota W, et al. Doppler study of the embryonic heart in normal pregnant women. *J Matern Fetal Neonatal Med.* 2007; **20**: 533 – 539.
- 29** Snijders RJ, McLaren R, Nicolaides KH. Computer-assisted analysis of fetal heart rate patterns at 20 – 41 weeks' gestation. *Fetal Diagn Ther.* 1990; **5**: 79 – 83.
- 30** Park MI, Hwang JH, Cha KJ, Park YS, Koh SK. Computerized analysis of foetal heart rate parameters by gestational age. *Int J Gynaecol Obstet.* 2001; **74**: 157 – 164.
- 31** Wladimiroff JW, vd Wijngaard JA, Degani S, Noordam MJ, van Eyck J, Tonge HM. Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth-retarded pregnancies. *Obstet Gynecol.* 1987; **69**: 705 – 709.