Original Article

Fetal Hemodynamics and Fetal Growth Indices by Ultrasound in Late Pregnancy and Birth Weight in Gestational Diabetes Mellitus

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Abstract

Background: The offspring of women with gestational diabetes mellitus (GDM) are prone to macrosomia. However, birth weight is difficult to be correctly estimated by ultrasound because of fetal asymmetric growth characteristics. This study aimed to investigate the correlations between fetal hemodynamics, fetal growth indices in late pregnancy, and birth weight in GDM.

Methods: A total of 147 women with GDM and 124 normal controls (NC) were enrolled in this study. Fetal hemodynamic indices, including the systolic/diastolic ratio (S/D), resistance index (RI), pulsatility index (PI) of umbilical artery (UA), middle cerebral artery (MCA), and renal artery (RA), were collected. Fetal growth indices, including biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length, were also measured by ultrasound. Birth weight, newborn gender, and maternal clinical data were collected.

Results: The independent samples *t*-test showed that BPD, HC, and AC were larger in GDM than in NC ($P < 0.05$). Fetal hemodynamic indices of the UA and MCA were lower ($P < 0.05$), but those of the RA were higher ($P < 0.001$) in GDM than in NC. Birth weight was higher in GDM than in NC ($P < 0.001$). Pearson's correlation analysis showed that hemodynamic indices of the UA were negatively correlated with birth weight, BPD, HC, and AC in both groups ($P < 0.05$). MCA (S/D, PI, and RI) was negatively correlated with birth weight, HC, and AC in GDM ($r = -0.164$, -0.206, -0.200, -0.226, -0.189, -0.179, -0.196, -0.177, and -0.172, respectively, $P < 0.05$), but there were no correlations in NC ($P > 0.05$). RA (S/D, PI, and RI) was positively correlated with birth weight in GDM ($r = 0.168$, 0.207, and 0.184, respectively, $P < 0.05$), but there were no correlations in NC ($P > 0.05$).

Conclusion: Fetal hemodynamic indices in late pregnancy might be helpful for estimating newborn birth weight in women with GDM.

Key words: Fetus; Gestational Diabetes Mellitus; Infant; Middle Cerebral Artery; Renal Artery; Ultrasound; Umbilical Artery

Introduction

Gestational diabetes mellitus (GDM) is one of the common complications of pregnancy. In GDM, different degrees of abnormal glucose metabolism occur, and it is initially discovered in the gestational period.[1] In recent years, the morbidity of GDM has gradually increased in developing countries because of continuous economic development, improvement in living standards, and application of new diagnostic criteria.[2] The morbidity of GDM is 13% in China.[3]

GDM-induced newborn and maternal complications include fetal death, fetal malformation, preeclampsia, intrauterine growth retardation, and fetal macrosomia. The incidence of fetal macrosomia ranges between 20% and 40%.[4,5] Diabetic macrosomia may result in neonatal respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, hypocalcemia, and hypomagnesemia. Diabetic macrosomia also increases the cesarean section rate and causes a long

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birth process, neonatal asphyxia, shoulder dystocia, clavicle fracture, and brachial plexus injury. Moreover, diabetic macrosomia raises the risk of subsequent type 2 diabetes.[6,7] Therefore, obstetricians should pay more attention to the prevention of fetal macrosomia in GDM. Currently, the size of the fetus is mainly assessed by measuring fetal growth indices using ultrasound. These indices include biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). Fetal weight is automatically calculated using Hadlock's formula by an ultrasonic instrument.[8] However, birth weight is often inaccurately estimated using ultrasound in GDM in late pregnancy because of fetal asymmetric growth characteristics.[9]

The umbilical artery (UA) is the major vascular pathway connecting the fetus and placenta. The fetus obtains nutrients and oxygen through the umbilical circulation. The systolic/diastolic ratio (S/D), pulsatility index (PI), and resistance index (RI) are the hemodynamic indices of the fetoplacental circulation.[10] The fetal middle cerebral artery (MCA) can directly reflect blood circulation of the fetal brain, and the S/D, PI, and RI are the hemodynamic indices of brain circulation.[11] The fetal renal artery (RA) also tends to directly reflect blood perfusion of the fetal kidney. The RA is one of the organs sensitive to hypoxia and one of the first organs to have endothelial dysfunction.[12]

In this study, we investigated the correlations among fetal hemodynamic indices (S/D, PI, and RI) of the UA, MCA, and RA, fetal growth in late pregnancy, and newborn birth weight in women with GDM and normal controls (NCs, normal pregnant women), with a view to determining whether fetal hemodynamic indices in late pregnancy can assist doctors in estimating newborn birth weight in GDM.

Methods

Clinical data collection

This observational study was conducted in the Department of Ultrasound, Shijitan Hospital Affiliated to the Capital Medical University. The Hospital's Research Ethics Committee approved the study protocol. The need for informed consent was waived because this analysis used currently existing data that were collected during the routine ultrasound examinations. The data were reported in aggregate.

From April 2013 to December 2014, a total of 271 Chinese women who visited the Department of Obstetrics and Gynecology were enrolled in the study. They were divided into the GDM and the NC group during the second trimester of pregnancy based on the GDM diagnostic criteria issued by the American Diabetes Association (ADA) in 2011. The alimentary control (n = 137) or insulin therapy (n = 10) were applied to patients with GDM. Inclusion criteria were (1) aged 25–38 years, (2) gestational weeks ranged from 37 to 40 weeks (within 1 week before delivery), (3) singleton pregnancy, (4) an oral glucose tolerance test (OGTT) was performed in the second trimester of pregnancy, and (5) gestational age was calculated from the first day of the last normal menstrual period and confirmed by the frist trimester ultrasound scans. Exclusion criteria were (1) no other well-known condition affecting fetal blood flow, such as intrauterine growth restriction, anemia, hypoxemia, and pregnancy-induced hypertension; (2) no history of a newborn with congenital anomalies; (3) no history of diabetes mellitus, preeclampsia, renal diseases, blood disorders, or hyperlipidemia; (4) no HIV and syphilis; and (5) no history of smoking and drinking. The following data were extracted from the database of the present study: maternal age, gestational age, body mass index (BMI) before pregnancy, maternal weight, blood pressure, birth weight, and sex of the newborn.

The diagnostic criteria of GDM as defined by the ADA in 2011 were as follows. Plasma glucose concentrations were measured at 0, 60, and 120 min after the woman received a 75 g OGTT in the second trimester of pregnancy. GDM was diagnosed when the patient's plasma glucose levels exceeded or reached one of the following thresholds: fasting glucose level ≥5.1 mmol/L; 1-h glucose level ≥10.0 mmol/L; and 2-h glucose level ≥8.5 mmol/L. The criteria for the diagnosis of gestational-induced hypertension issued by the World Health Organization were systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.

Ultrasound measurements

Color Doppler ultrasonography (Volusion E8; GE Aircraft Engines Group, USA) was performed. A4C-D convex array probe was used for two-dimensional scanning, with a frequency of 2.5–5 MHz, spatial-peak temporal-average intensity <10 mW/cm^2, and mechanical variation of 10%. The mechanical index was kept at <1.9 and the thermal index was kept at <1.5. Ultrasonography was used to detect fetal growth indices. Growth indices included the BPD, HC, AC, and FL. The BPD was measured from the outer edge of the parietal bone near the probe to the inner edge of the other side of the parietal bone in the thalamencephalon. HC was measured in the same location as the BPD using the elliptic function of the ultrasound instrument. AC was measured along the outer layer of the skin in the area including the spine, gastric vacuole, and umbilical vein using the elliptic function. The FL was measured at the center of the two ends of the femur.

The color flow pattern was selected to measure hemodynamic parameters of the UA, MCA, and RA. Measurements were performed at the UA within 5 cm from the placenta, during which the angle between the ultrasound beam and blood flow was adjusted to <20°. For the MCA, in the standard plane for BPD measurement, the probe was moved toward the brain basement membrane until a pair of alisphenoids was visible between the anterior and middle cranial fossa. An additional Doppler spectrum was then applied to reveal the circle of Willis. The sampling volume (2 mm) was placed slightly before the middle part of the MCA, and the angle of the ultrasound beam and blood flow was adjusted to <20° [Figure 1]. For the RA, measurements were

performed at a location close to the renal hilum, and the angle of the ultrasound beam and blood flow was adjusted to <20°. The arterial hemodynamic parameters included the S/D, RI, and PI of the UA, MCA, and RA. For each measurement, at least five cardiac cycles were selected in the Doppler spectrum, and their average value was adopted. All of the measurements were conducted when there was no fetal movement and finished within 15 min by a physician engaged in ultrasonics for 10 years. If the spectrum of arterial hemodynamic parameters was not standard, the measurement was stopped.

Statistical analysis

Data were analyzed using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA). Measurement data are presented as mean ± standard deviation (SD) and count data are expressed as *n* (%). The independent samples *t*-test was used to compare the mean of continuous variables, such as hemodynamic measurements between the two groups. The chi-square test was used as appropriate for comparing characteristics between the two groups. Pearson's correlation coefficient was used to estimate the correlations among the hemodynamic indices (S/D, PI, and RI) of the fetal UA, MCA, and RA in late pregnancy, fetal growth indices (BPD, HC, AC, and FL), and birth weight. A difference of $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Of the 271 pregnant women in this study, 147 had GDM and 124 did not. The children of 48 women with GDM were macrosomia (birth weight ≥4000 g). There were also 4 cases of macrosomia in the NC group.

Maternal clinical data were not significantly different between the two groups ($P > 0.05$). The BPD, HC, and AC of the fetus were higher in the GDM group than in the NC group (all $P < 0.05$). The hemodynamic indices of the fetus were significantly different between the two groups ($P < 0.05$). The hemodynamic indices of the UA and MCA were lower in the GDM group than in the NC group (all $P < 0.05$). However, those of the RA were higher in the GDM group than in the NC group (all $P < 0.05$). Birth weight was significantly higher in the GDM group than in the NC group ($P < 0.05$). Newborn gender was not significantly different between the two groups ($P > 0.05$) [Table 1].

Table 1: Comparison of descriptive data of the mothers, fetuses, and newborns in the GDM and NC groups (mean ± SD)

Variable	NC (n = 124)	GDM (n = 147)	P
Mothers			
Maternal age (years)	29.94 ± 3.60	30.80 ± 3.00	0.924
Gestational age (weeks)	38.0 ± 0.65	38.0 ± 0.68	0.967
BMI before pregnancy (kg/m^2)	22.24 ± 3.20	23.87 ± 3.58	0.106
Maternal weight (kg)	70.35 ± 9.35	73.50 ± 12.06	0.089
Systolic blood pressure (mmHg)	110.32 ± 10.99	112.38 ± 7.22	0.202
Diastolic blood pressure (mmHg)	69.71 ± 7.76	73.58 ± 6.10	0.754
Fetuses			
BPD (mm)	9.18 ± 0.29	9.27 ± 0.31	0.010
HC (mm)	32.56 ± 0.73	33.13 ± 0.90	<0.001
AC (mm)	32.84 ± 1.42	34.25 ± 1.84	<0.001
FL (mm)	7.11 ± 0.22	7.13 ± 0.28	0.065
UA, S/D	2.23 ± 0.26	2.16 ± 0.29	0.037
UA, PI	0.80 ± 0.11	0.76 ± 0.12	0.004
UA, RI	0.55 ± 0.05	0.53 ± 0.06	0.025
MCA, S/D	4.68 ± 0.45	3.44 ± 0.56	<0.001
MCA, PI	1.58 ± 0.11	1.29 ± 0.22	<0.001
MCA, RI	0.78 ± 0.02	0.70 ± 0.06	<0.001
RA, S/D	5.60 ± 0.67	7.29 ± 1.39	<0.001
RA, PI	1.78 ± 0.16	1.95 ± 0.23	<0.001
RA, RI	0.82 ± 0.02	0.86 ± 0.03	<0.001
Newborns			
Birth weight (g)	3345.42 ± 377.54	4010.05 ± 455.16	<0.001
Male/female (%)	54.35 ± 45.43	54.43 ± 44.47	0.200

GDM: Gestational diabetes mellitus; NC: Normal control; SD: Standard deviation; BMI: Body mass index; BPD: Biparietal diameter; HC: Head circumference; AC: Abdominal circumference; FL: Femur length; UA: Umbilical artery; RA: Renal artery; MCA: Middle cerebral artery; S/D: Systolic/diastolic ratio; PI: Pulsatility index; RI: Resistance index.

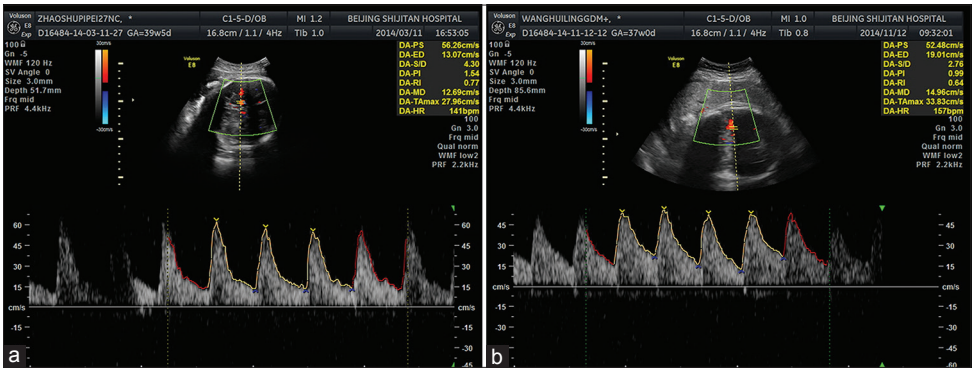

Figure 1: Ultrasound Doppler spectrum of fetal MCA in two groups. (a) Ultrasound Doppler spectrum of MCA in the NC group. (b) Ultrasound Doppler spectrum of MCA in the GDM group. MCA (S/D, PI, and RI) was lower in the GDM group than in the NC group. MCA: Middle cerebral artery; NC: Normal control; GDM: Gestational diabetes mellitus; S/D: Systolic/diastolic ratio; PI: Pulsatility index; RI: Resistance index.

Correlation analyses

In the GDM group, AC, HC, BPD, and FL were positively correlated with birth weight ($r = 0.764$, 0.697, 0.584, and 0.577, respectively, all $P < 0.05$). In the NC group, AC, HC, BPD, and FL were also positively correlated with birth weight ($r = 0.470$, 0.407, 0.465, and 0.236, respectively, all $P < 0.05$) [Table 2].

In the GDM group, hemodynamic indices of the fetal UA (PI and RI) and MCA (S/D, PI, and RI) were negatively correlated with birth weight (all $P < 0.05$). Those of the RA (S/D, PI, and RI) were positively correlated with birth weight (all $P < 0.05$). However, in the NC group, only hemodynamic indices of the UA (S/D, PI, and RI) were negatively correlated with birth weight (all $P < 0.05$) [Table 3].

In the GDM group, hemodynamic indices of the fetal UA (S/D, PI, and RI) were negatively correlated with BPD, HC, and AC (all $P < 0.05$). Hemodynamic indices of the MCA (S/D, PI, and RI) were also negatively correlated with HC and AC (all $P < 0.05$). In the NC group, only UA (S/D, PI) were negatively correlated with BPD, HC, and AC ($P < 0.05$), and also UA (RI) was negatively correlated with BPD and AC ($P < 0.05$) [Table 4].

Discussion

The diagnostic criteria of GDM have been introduced internationally. The problem of GDM has aroused widespread attention, and scientific management has been provided for pregnant women with GDM in China. However, an epidemiological survey showed that even if blood glucose levels are controlled to an ideal level in pregnant women with GDM, macrosomia is still common. Fetuses of women with GDM in late pregnancy are more likely to experience a symmetric growth. At present, the classic theory suggests that high blood glucose levels of mothers with GDM lead to placental glucose transport in late pregnancy. This transport causes hyperglycemia and hyperinsulinemia in the fetuses, increasing the synthesis of fetal protein and fat, and accumulation of liver glycogen.[13] Because of asymmetrical growth of the fetuses, there are some differences in evaluating neonatal weight by measuring growth indices in late pregnancy using ultrasound.[9] Ultrasonography is noninvasive, convenient, repeatable, and easily acceptable. Therefore, this method is still the best way to monitor the intrauterine condition of the fetuses. Our study was designed to further investigate the correlations among fetal hemodynamic indices (S/D, PI, and RI of the UA, MCA, and RA) in late pregnancy, fetal growth indices, and newborn birth weight in GDM and NC group.

We found that birth weight in the GDM group was significantly higher than that in the NC group. The BPD, HC, and AC in the GDM group were also significantly higher than those in the NC group in late pregnancy. Fetal growth indices of the two groups were positively correlated with birth weight. However, AC and HC in the GDM group were strongly correlated with birth weight. These findings reflect the characteristics of asymmetric growth of the fetuses of mothers with GDM in late pregnancy.

The UA, MCA, and RA are important arteries of the circulatory system, playing a pivotal role in fetal growth and development. Many domestic and international studies have focused on studying values of the UA or MCA for predicting preeclampsia, intrauterine growth retardation, fetal distress, and other poor outcomes of pregnancy.[14-16] However, these studies have produced inconsistent results. A study of prediction of birth weight in infants born to mothers with GDM showed that serum hemoglobin levels in pregnant women with GDM were a predictive index of birth weight.[17] However, as a dynamic observation approach, it is invasive and not easily accepted by pregnant women. Our study showed that hemodynamic indices of the UA and MCA in the GDM group were lower than those in the NC group. However, hemodynamic indices of the RA were higher in the GDM group than those in the NC group. We found negative correlations between fetal hemodynamic indices of the UA and birth weight, fetal BPD, HC and AC in the GDM and NC groups. In the GDM group, hemodynamic indices of the MCA were also negatively correlated with fetal HC and AC, as well as birth weight. There were no correlations between hemodynamic indices of the MCA and birth weight, fetal BPD, HC, AC, and FL in the NC group. In the GDM group, but not in the NC group, hemodynamic indices of the RA were positively correlated with birth weight. These findings

Table 2: Correlation of fetal growth indices with birth weight in two groups, respectively

Parameter (mm)	Birth weight in the NC group	Birth weight in the GDM group
BPD	0.465*	0.584*
HC	0.407*	0.697*
AC	0.470*	0.764*
FL	0.236*	0.577*

Pearson's correlation coefficient is given for bivariate correlation. *P<0.05. NC: Normal control; GDM: Gestational diabetes mellitus; BPD: Biparietal diameter; HC: Head circumference; AC: Abdominal circumference; FL: Femur length.

Table 3: Correlation of fetal hemodynamic indices with birth weight in two groups, respectively

Parameter	Birth weight in the NC group	Birth weight in the GDM group
UA, S/D	−0.215*	−0.130
UA, PI	−0.206*	−0.200*
UA, RI	−0.184*	−0.194*
MCA, S/D	−0.108	−0.164*
MCA, PI	−0.114	−0.206*
MCA, RI	−0.120	−0.200*
RA, S/D	0.056	0.168*
RA, PI	0.039	0.207*
RA, RI	0.080	0.184*

Pearson's correlation coefficient is given for bivariate correlation. *P<0.05. NC: Normal control; GDM: Gestational diabetes mellitus; UA: Umbilical artery; S/D: Systolic/diastolic ratio; PI: Pulsatility index; RI: Resistance index; MCA: Middle cerebral artery; RA: Renal artery.

Table 4: Correlation matrix of fetal growth indices with hemodynamic indices in two groups, respectively

Parameters	BPD	HC	AC	FL
NC group				
UA, S/D	−0.233*	−0.287*	−0.366*	−0.127
UA, PI	−0.234*	−0.252*	−0.355*	−0.139
UA, RI	−0.240*	−0.112	−0.340*	−0.117
MCA, S/D	−0.125	−0.057	−0.037	−0.021
MCA, PI	−0.111	−0.080	−0.079	−0.053
MCA, RI	−0.124	−0.110	−0.056	0.038
RA, S/D	−0.123	0.058	0.012	−0.093
RA, PI	−0.105	0.129	0.065	0.137
RA, RI	−0.139	0.038	0.037	−0.117
GDM group				
UA, S/D	−0.217*	−0.233*	−0.213*	−0.153
UA, PI	−0.214*	−0.280*	−0.255*	−0.139
UA, RI	−0.215*	−0.239*	−0.265*	−0.152
MCA, S/D	−0.146	−0.226*	−0.196*	−0.138
MCA, PI	−0.094	−0.189*	−0.177*	−0.105
MCA, RI	−0.127	−0.179*	−0.172*	−0.073
RA, S/D	−0.110	0.041	0.140	0.044
RA, PI	−0.105	0.067	0.132	0.104
RA, RI	−0.076	0.048	0.126	0.033

Pearson's correlation coefficient is given for bivariate correlation. *P<0.05. BPD: Biparietal diameter; HC: Head circumference; AC: Abdominal circumference; FL: Femur length; NC: Normal control; GDM: Gestational diabetes mellitus; UA: Umbilical artery; S/D: Systolic/diastolic ratio; PI: Pulsatility index; RI: Resistance index; MCA: Middle cerebral artery; RA: Renal artery.

showed that hemodynamic indices of the UA, MCA, and RA of the fetus in late pregnancy in GDM might be useful for estimating birth weight in GDM.

Hyperglycemia in pregnant women with GDM tends to increase fetal growth through a series of pathophysiological responses only in late pregnancy.[18] To meet the requirements of fetal growth, placental blood perfusion and blood volume of the UA increase, and vascular resistance decreases. The fetus tends to experience hypoxia and ischemia occurs when demand exceeds supply. A brain-sparing effect is then triggered, leading to dilation of the MCA, which provides 80% of the blood supply to the cerebral hemisphere. Resistance is reduced and brain development is promoted, so reflecting the contribution of the MCA to HC.[19,20] Meanwhile, the RA, which is extremely sensitive to hypoxia and ischemia, tends to contract to redistribute blood flow. Therefore, the S/D, PI, and RI of RA are prone to increasing in order to ensuring the blood supply to major organs of the fetus, such as the brain and liver.

A previous study of 146 women with GDM showed a stronger correlation between uterine artery Doppler and birth weight than did the PI Z-score of the UA.[21] This lack of correlation between the PI Z-score of the UA and birth weight might be due to the small number of newborns with a high birth weight. Recently, a study of 169 women with GDM showed that the PI of the UA of fetuses in pregnant women with GDM was negatively correlated with birth weight (r = −0.25, P = 0.001). This finding suggested that the UA was crucial for fetal growth, which is consistent with our results.[22] A recent study of 226 women with GDM showed that the UA hemodynamic indices (S/D, PI, and RI) in late pregnancy were strongly negatively correlated with birth weight, but they did not correlate with fetal growth indices.[23] In addition, the UA hemodynamic indices in mid-pregnancy were not correlated with birth weight while they were negatively correlated with HC and FL. These findings are not able to explain the effect of the UA on birth weight in late pregnancy. The reason might be associated with insignificant differences in birth weight and fetal growth indices in late pregnancy between the GDM and non-GDM groups.

This study has several limitations. First, maternal age, gestational age, BMI before pregnancy, maternal weight, blood pressure, and gender of the fetus were considered as confounding factors. These factors were not significantly different between the GDM and NC groups. We found that the hemodynamic indices of the fetal RA (S/D, PI, and RI) in late pregnancy were positively correlated with birth weight in the GDM group. However, we failed to show correlations between hemodynamic indices of the RA (S/D, PI, and RI) and fetal growth indices. This might be associated with a small sample size, as well as the potential confounding factors. Second, further studies are required to determine the mechanism of correlation between the MCA and AC. Third, this study was a cross-sectional study. Therefore, a retrospective cohort study and larger sample size are needed to determine whether fetal hemodynamic indices in late pregnancy can be used to estimate the birth weight in GDM.

In conclusion, we propose that fetal Doppler hemodynamic indices (S/D, PI, and RI of the UA, MCA, and RA) in late pregnancy can assist doctors in estimating the birth weight of GDM. It could reduce the delivery of macrosomia as well as related short- and long-term complications.

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Conflicts of interest

There are no conflicts of interest.

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