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# Assessment of fetal cardiac diastolic function of gestational diabetes mellitus using dual-gate Doppler

Qingsha Hou, MD[a,b], Fang Yan, MD[b], Xudong Dong, PhD[b], Huanling Liu, BMed[b], Jie Wu, MD[b], Jiao Li, MD[b], Yunchuan Ding, BMed[a,*]

**Abstract**

Gestational Diabetes Mellitus (GDM), as a common complication of pregnancy, has an increasing trend globally. GDM leads to maternal complications and fetal complications. Fetal cardiac diastolic dysfunction is strongly associated with GDM. This study aims to assess the ventricular diastolic function of fetuses exposed to GDM by looking into the diagnostic parameters using both conventional method and Dual-gate Doppler method (DD). And to investigate the potential of DD method in early detection of fetal cardiac diastolic dysfunction.

56 women diagnosed with GDM and 55 non-GDM pregnant women were enrolled in their 24 to 30 weeks of gestation. Conventional method and DD method were applied to measure mitral and tricuspid inflow velocities E-waves, A-waves on pulsed-wave Doppler, and mitral and tricuspid annular velocities e′-waves, a'-waves on Tissue Doppler imaging. E/A, e'/a' and E/e′ ratio was calculated. The difference between GDM and control groups was statistically tested and analysed using one-sample Kolmogorov-Smirnov test, Student *t* test, Mann-Whitney *U* test and Kruskal-Wallis test and Bland–Altman plot analysis.

Intraobserver intraclass correlation coefficients of E/A, e'/a', and E/e' value of both mitral and tricuspid valve are all greater than 0.80, while interobserver intraclass correlation coefficients are between 0.71 and 0.88. Right (6.35 vs 6.79; $P = .001$) ventricular function showed significantly lower E/e' ratios in the GDM group compared with control fetuses by conventional method. Both left (6.16 vs 6.59; $P = .036$) and right (6.28 vs 6.75; $P = .01$) ventricular function showed significantly lower E/e' ratios in the GDM group compared with control fetuses by DD method.

Exposure to high level of maternal blood glucose leads to impaired diastolic function in the fetuses. Fetal right ventricular function is a potential key point to study to enable an early detection for fetal diastolic dysfunction since the alteration and damage are more likely to happen in right ventricular. Measurement of E/e' ratio using DD method is considered as a promising method in fetal cardiac diastolic function assessment. Well or poorly control of the GDM does not have significant influence on the fetal diastolic function thus an early detection of GDM and GDM induced fetal cardiac dysfunction is necessary.

**Abbreviations:** DD method = dual-gate Doppler method, GA = gestational age, GDM = gestational diabetes mellitus, ICC = intraclass correlation coefficients, LV = left ventricular, PW Doppler = Pulsed-wave Doppler, RV = right ventricular, TDI = tissue Doppler imaging.

**Keywords:** diastolic, dual-gate Doppler, dysfunction, fetal, gestational diabetes mellitus

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*The authors promise that this study was performed according to the international, national, and institutional rules considering animal experiments, clinical studies and biodiversity rights. The study protocol was approved by ethics committee of the first people's hospital of Yunnan province (YYLH006)*

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*[a] Department of Ultrasound, Yan'an Hospital Affiliated to Kunming Medical University, 245, East of Renmin Road, Kunming, Yunnan, P.R. China, [b] Department of Obstetrical, The First People's Hospital of Yunnan Province, No. 157 Jinbi Rd, Xishan District, Kunming, Yunnan, P.R. China.*

*[*] Correspondence: Yunchuan Ding, Department of Ultrasound, Yan'an Hospital Affiliated to Kunming Medical University, 245, East of Renmin Road, Kunming, Yunnan 650051, P.R. China (e-mail: dd82109@163.com).*



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## 1. Introduction

As the most common endocrine complication of pregnancy,[1] the prevalence of Gestational Diabetes Mellitus (GDM) has an increasing prevalence globally in recent decades[2–6] along with advancing maternal age and increasing of obesity.[7–11] Compared with the estimated prevalence of GDM worldwide, Asian population has higher prevalence of 20.9%,[3] in which the prevalence in mainland China is as relatively high as 14.8%.[5] The prevalence of GDM is also positively associated with gestational age (GA) and it ranges from 25.7% at 23 weeks of gestation[12] to 33.3% in third trimester of pregnancy.[13] By 2017, approximately 18.4 million of live births were affected by GDM.[14]

GDM leads to not only maternal complications and diabetes in later life of the mother[15,16] but also immediate and later fetal complications.[17–21] The risk of stillbirth,[22,23] congenital malformations,[24,25] macrosomia and macrosomia related obstetric complications[26] increases of mothers with GDM. GDM is also responsible for serious consequences for fetal development and health risks in later life of the offspring.[27,28]

Intrauterine exposure to high level of maternal blood glucose significantly increases the insulin secreting in fetal pancreas, leading to fetal hyperinsulinemia. An exceeding storage of glucose and fat will occur along with the increased insulin, making the fetus larger than the normal, thus increases the demand of oxygen, which will cause hypoxemia.[26,29,30] Fetal heart is one of the major organs affected by hyperinsulinemia and hypoxemia.[31] Myocardial hypertrophy has been extensively reported in fetuses of GMD mothers,[32,33] especially cardiac width and interventricular septum thickness measured during diastole.[13] Besides morphological changes, ultrasound scanning of the fetal heart suggestive of maternal diabetes can result in changes on functional impairment.[34] These functional changes include increased heart rates, ventricular filling disorder, outflow tract obstruction and decrease of compliance particularly in the right ventricular (RV)[35] leading to diastolic and systolic dysfunction.[36] which may persist and potentially has short- and long-term consequences to the offspring health.[37–41]

Fetal echocardiography has widely applied to evaluate fetal cardiac anomalies in utero.[42] In recent years, attention has shifted to assessment fetal intrauterine cardiac dysfunction, it would be extremely helpful to detect ventricular dysfunction at an early stage. Diastolic dysfunction, which may be developed before systolic dysfunction, showing the earliest change of fetal hypertrophic cardiomyopathy with GDM.[43] However, it remains a challenge to assess fetal diastolic function.[42] Pulsed-wave Doppler (PW Doppler) measure diastolic flow across the atrioventricular (AV) valve, E wave represents the early passive filling velocity caused by ventricular relaxation, while A wave represents the active filling velocity caused by atrial contraction in late diastole.[44] The E/A ratio was defined as for ventricular diastolic function analysis,[45] which may be influenced by loading conditions. Recent studies have reported the utility of Tissue Doppler Imaging (TDI), which allows directly measurement the velocity of the longitudinal motion of the mitral annulus and the tricuspid annulus.[46] TDI does not depend on the loading conditions.[33,47,48] And e'-wave reflects ventricular relaxation (elongation). a'-wave reflects atrial contraction and late ventricular filling. The E/e' ratio is one of the echocardiographic parameters applied recently to assess the ventricle diastolic function of adults and children. However, there are not many studies in fetal E/e′ measurement.[42,49]

Dual-gate Doppler method (DD) is a technology enables assessment of two Doppler waveforms simultaneously at any two separate locations, even in combination with pulsed and tissue Doppler. DD method allows to determine E/e′ at the same heartbeat, showing the blood flow and TDI wave form in real time.[42] It is a prospective method to assess fetal cardiac diastolic function.

The aim of this study was to assess fetal ventricular diastolic function in fetuses of GDM mothers compared to fetuses of non-GDM mothers, using both conventional method and DD method to explore the potential of this novel technique in fetal cardiac diastolic function assessment.

## 2. Methods

### 2.1. Population

This prospective cross-sectional study recruited women attending for a routine antenatal care and having the routine OGTT screen screening between 24 to 28 weeks of gestation in the obstetrics department in The First People's Hospital of Yunnan Province, China, during May 2019 to February 2020. Women with uncomplicated, singleton pregnancies and between 24 and 30 weeks of gestation were included. While women with multiple pregnancy, fetal structural or chromosomal abnormality, fetal arrhythmias, fetal growth restriction, or maternal chronic disease, were excluded. Among the whole population underwent a 75-g OGTT at 24 to 28 weeks of gestation, 56 of them with one or more plasma venous glucose values greater than or equal to 5.1 mmol/l at 0 hour; 10.0 mmol/l at 1 hour; or 8.5 mmol/l at 2 hour were diagnosed as GDM according to the IADPSG recommendations.[50] At the time of fetal scanning, the blood glucose levels of all the women in our study were properly registered in accordance with guidelines from the National Institute for Health and Care Excellence.[51]The control group were formed by 55 non-GDM women matching the gestational weeks who were randomly selected from all the non-GDM women for the routine antenatal care. Therefore, a total of 111 subjects were enrolled. All subject signed informed consents before they attend the ultrasound scan, and this study was approved by ethics committee of the first people's hospital of Yunnan province (YYLH006).

In the GDM group, all 56 women's blood glucose level were measured every day. 41 of them were treated with diet alone (n = 41), while 15 of them had insulin therapy (n = 15). Depending on the blood glucose level after treatment, the GDM group were further subdivided into two sub-groups, the well-controlled group and the poorly-controlled group. 38 GDM women with fasting and 2 hours after meal blood glucose no greater than 5.3mmol/L and 6.7mmol/L respectively[52] were in the well-controlled group. While the other 18 GDM women with sustained high blood glucose were put in the poorly-controlled group.

Fetal examinations were performed from 24 to 30 gestational weeks. Maternal information was noted during the ultrasound examination, including age, height, weight, body mass index, gravidity, parity, GA, and diabetes treatment. GA was re-estimated according to the crown-rump length measurement in the first trimester. Fetal biometry including biparietal diameter, head circumference, abdominal circumference, femur length, and estimated fetal weight were measured and noted. Standard obstetric Doppler evaluation including determination of the

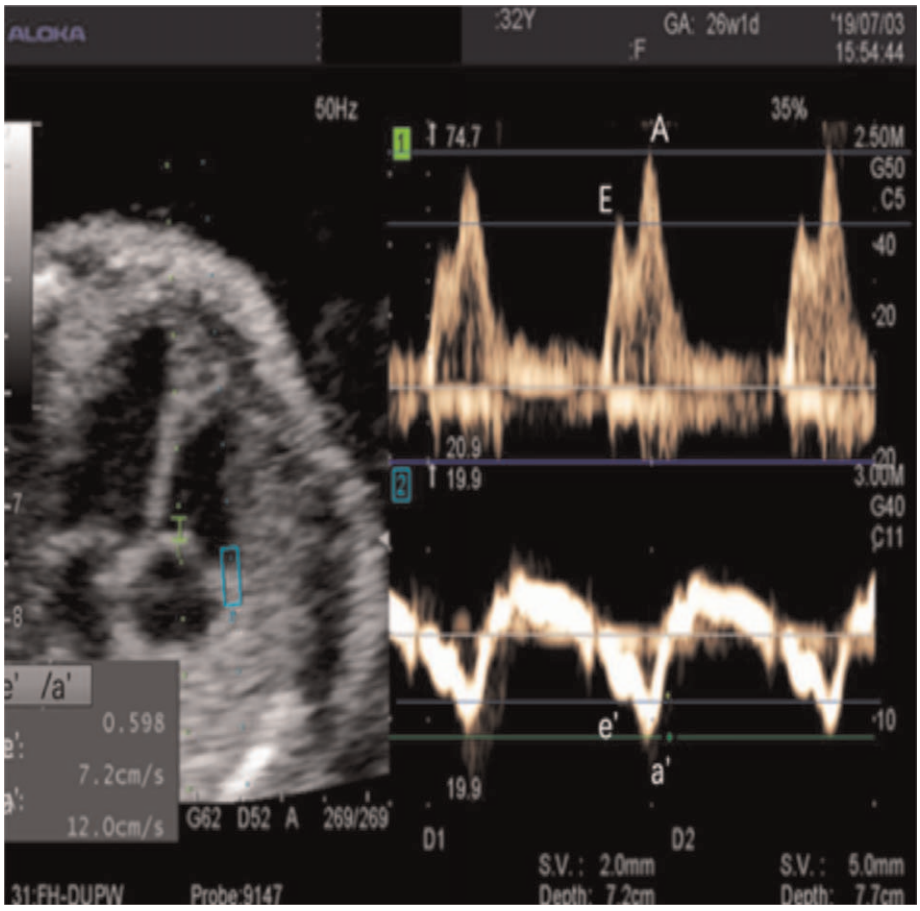


**Figure 1.** A represented graphic showing an apical/basal four-chamber view of measurement of fetal tricuspid inflow Peak wave velocities (peak E and peak A) and tricuspid annular peak wave velocities (e'and a') using dual-gate Doppler. In the left panel, PW Doppler spectrum (shown in bright green) was placed just below the tricuspid valve leaflets, while TDI Doppler spectrum (shown in cyan blue) was placed in the tricuspid valve annular. In the right panel, Upper waveform obtained using pulsed-wave Doppler imaging and lower waveform using tissue Doppler imaging.

pulsation index for the ductus venosus, umbilical artery, and middle cerebral artery,[53] were carried out. The cerebroplacental ratio was calculated.

### 2.2. Fetal echocardiography

All echocardiographic examinations were performed using an ALOKA F75 ultrasound system with the 4C probe. Each fetal was performed with both conventional method and DD method in one single observing time slot during the study period to assess the cardiac function.

The conventional method was performed as follows. After obtaining a clear apical/basal four-chamber view, the inflow across the atrioventricular were measured by PW Doppler, and the myocardial motion of heart was derived by TDI assessment separately with an incidence angle of less than 25°. The PW Doppler sample was opened to 3 mm and placed just below the atrioventricular (AV) valve leaflets. The inflow signal was obtained, and the E wave velocity and A wave velocity were recorded. TDI spectrum was performed in the basal part of the ventricular free wall. Atrioventricular valve annulus myocardial wall motion velocity e'-wave and a'-wave were recorded.

The Dual-gate Doppler (DD) method was performed as follows. In the apical/basal four-chamber view, with an incidence angle of less than 25°, As can be seen from the left panel of Figure 1, PW Doppler spectrum (shown in bright green) was placed just below the atrioventricular valve leaflets, while TDI spectrum (shown in cyan blue) was placed in the basal part of the ventricular free wall.[42] As depicted in the right panel of Figure 1, flow velocity and myocardial velocities parameters E-wave, A-wave, e'-wave, a'-wave were recorded in the same cardiac cycle due to the character of DD method.

### 2.3. Statistical analysis

Statistical analysis was performed using SPSS software version 22.0 (IBM Corp, Armonk, NY). The normality of distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean (standard deviation [SD]); non-normal variables were reported as median (interquartile range [IQR]). Means of two continuous normally distributed variables were compared by independent samples Student $t$ test. While means of two non-normally distributed variables were respectively compared by Mann-Whitney $U$ test and Kruskal-Wallis. $P < .05$ was considered statistically significant and all statistical tests were 2-sided.

To evaluate the reproducibility of E/A, e'/a', E/e' measured by DD method, intra- and interobserver agreement was calculated

**Table 1**

**Baseline maternal and fetal characteristics.**

| | Control group (n = 55) | GDM group (n = 56) | *P* |
|---|---|---|---|
| Maternal characteristics | | | |
| Age (yr, mean ± SD) | 29.75 ± 0.50 | 32.77 ± 0.54 | .000 |
| Height (cm, mean ± SD) | 159.87 ± 0.65 | 159.41 ± 0.66 | .619 |
| Weight (kg, median [IQR]) | 54 (49–58) | 57 (53–64.75) | .004 |
| BMI (median [IQR]) | 21.23 (19.31–22.59) | 22.35 (20.94–25.03) | .001 |
| Gravidity (median [IQR]) | 2 (1–3) | 2 (2–3.5) | .084 |
| Parity (median [IQR]) | 0 (0–1) | 0 (0–1) | .673 |
| Gestational age at delivery (weeks, mean ± SD) | 39.3 ± 1.4 | 38.8 ± 1.5 | .23 |
| Fetoplacental ultrasound evaluation | | | |
| Gestational age at ultrasound examination (mean ± SD) | 26.31 ± 0.19 | 26.88 ± 0.22 | .051 |
| Weight (g, mean ± SD) | 921.10 ± 25.62 | 1038.77 ± 32.58 | .005 |
| UAPI (mean ± SD) | 1.06 ± 0.02 | 1.03 ± 0.02 | .400 |
| MCAPI (mean ± SD) | 1.64 ± 0.03 | 1.60 ± 0.03 | .327 |
| VDPI (median [IQR]) | 0.53 (0.42–0.64) | 0.52 (0.40–0.63) | .288 |
| Cerebroplacental ratio (median [IQR]) | 1.63 (1.36–1.80) | 1.55 (1.30–1.87) | .868 |

BMI = body mass index, GDM = gestational diabetes mellitus, MCAPI = fetal middle cerebral artery doppler pulsatility index, UAPI = fetal umbilical artery doppler pulsatility index, VDPI = fetal ductus venosus doppler pulsatility index.

using intraclass correlation coefficients (ICC) with a 95% confidence interval, among 20 randomly selected non-GDM subjects. Intraobserver ICC was calculated by one-way classification, and all measurements were performed twice by the same observer (Hou). While interobserver ICC was calculated by two-way random model, and the fetal echocardiographic measurements were performed by a second observer (Yan), who was blinded to the results of the first observer. Intra- and interobserver agreement was calculated using the intraclass correlation coefficient. ICC $>$ 0.80 were considered as excellent and 0.70 to 0.80 as good. To evaluate the feasibility of DD method, E/e' ratio in left ventricular (LV) and RV separately resulting from both conventional and DD method were compared using Bland–Altman plot analysis with 95% limits of agreement for each comparison (average difference ± 1.96 standard deviation of the difference).

## 3. Results

One hundred and eleven singleton pregnancies were recruited to study the fetal cardiac diastolic function using fetal color Doppler. Clinical information of the study population including 55 women in the control group and 56 women in the GDM group was noted. As shown in Table 1, the mean maternal height, median gravidity, median parity, mean GA at ultrasound examination and GA at delivery of control group are consistent with GDM groups. Also, there were no difference in fetoplacental Doppler parameters between the two groups. However, the mean maternal age, maternal weight, body mass index, and estimated fetal weight of the GDM group were higher than those of the control group.

To prove the repeatability and feasibility of DD method, E/A, e'/a', and E/e' value of 20 randomly selected subjects in control group were measured by two observers respectively. As shown in Table 2, intraobserver ICC of E/A, e'/a', and E/e' value of mitral valve is 0.80, 0.88, and 0.86 respectively, while for tricuspid valve the E/A, e'/a', and E/e' value are 0.86, 0.91 and 0.87. On the other hand, interobserver ICC of E/A, e'/a', and E/e' value of mitral valve are 0.71, 0.85, and 0.82 respectively, while for tricuspid valve, the E/A, e'/a', and E/e' value are 0.79, 0.83, and 0.88. Intraobserver ICC are all greater than 0.80, which are considered as excellent. Interobserver ICC are between 0.71 and 0.88, which are considered as excellent or good.

Figure 2 shows the Bland-Altman plot, where the panel A shows the difference of early diastolic filling to early diastolic annular velocity (E/e') ratio in LV between conventional method and DD method and the panel B shows the difference of E/e' in RV. For both panels, the differences of E/e' ratio between two methods tend to agree, which indicates there is no systematic bias between the two methods.

To develop that the conventional method and DD method may be used interchangeably to assess fetal cardiac diastolic function, Table 3 presents the E/A, e'/a' and E/e' ratio of mitral and tricuspid valve resulting from both conventional method and DD method to compare the fetal diastolic cardiac function between the control and GDM group. No significant difference can be seen in mitral or tricuspid valve E/A and e'/a' ratio resulting from both methods between the two groups ($P > .05$). However, E/e' ratio of mitral valve was significantly decreased ($P < .05$) in the GDM group compared with control group when using DD method while no significant change can be seen when using conventional method. Notably, E/e' ratio of tricuspid was significantly decreased ($P < .05$) in the GDM group compared

**Table 2**

**Intraobserver and interobserver ICCs for fetal cardiac function by DD the methods.**

| | Intraobserver | Interobserver |
|---|---|---|
| Mitral valve | | |
| E/A ratio | 0.80 | 0.71 |
| e'/a' ratio | 0.88 | 0.85 |
| E/e' ratio | 0.86 | 0.82 |
| Tricuspid valve | | |
| E/A ratio | 0.86 | 0.79 |
| e'/a' ratio | 0.91 | 0.83 |
| E/e' ratio | 0.87 | 0.88 |

E/A, Transvalvular early diastolic velocity to later diastolic velocity; e'/a', early diastolic myocardial velocity to late atrial contraction myocardial velocity ratio; E/e', transvalvular early diastolic velocity to myocardial early diastolic velocity ratio.

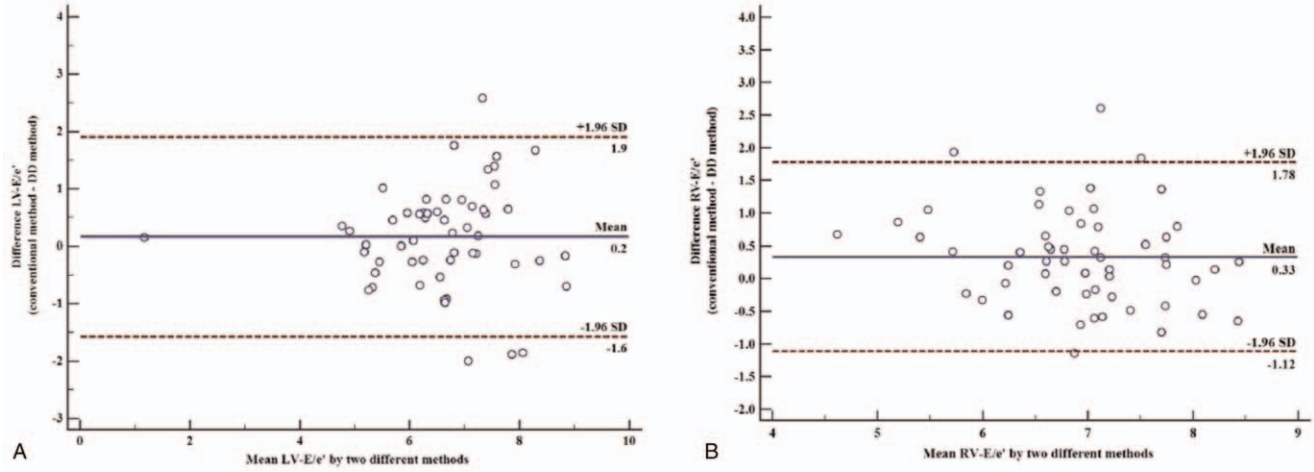


**Figure 2.** The graphic of Bland–Altman plots analysis. The panel A shows the difference of early diastolic filling to early diastolic annular velocity (E/e') ratio in left ventricular (LV) between conventional method and DD method; The panel B shows the difference of E/e' in right ventricular (RV) between conventional method and DD method. Mean difference and 95% limits of agreement are marked.

with control group according to both methods. As we can see in Figure 3, in both panel A and B, representing LV and RV separately, GDM group shows a trend of decreasing for E/A and E/e' ratio and a trend of increasing of e'/a' with both conventional and DD method.

To see how the high glucose level of GDM mother affects the fetus, fetal cardiac diastolic function in both left and RV was assessed by comparing the E/A, e'/a', and E/e' ratio of GDM and control group using DD method. Variables of GMD and control group in fetal left and right ventricle resulting from DD method are shown in Table 4. No significant difference can be seen in most the dimensional variables between the two groups. Analysis of functional variables showed that mitral E/e' ratio, tricuspid E/e' ratio and tricuspid E-wave velocity were significant lower in GDM group as compared to the control ($P < .05$). While tricuspid e'-wave velocity was significant higher in GDM group as compared to the control ($P < .05$). Comparing the doppler parameters in RV and LV, RV demonstrates more evidence of diastolic dysfunction, as they have statistically lower E velocity, E/e' ratio values and statistically higher e' velocity, while LV has statistically lower E/e' ratio.

Table 5 shows the comparison of variables of well or poorly controlled group measured by DD method. No significant difference in the dimensional variables between the two groups was detected ($P > .05$).

## 4. Discussion and conclusions

Intrauterine exposure to hyperglycemia environment leads to fetal cardio myocyte hyperplasia and disordered of the myofibrils, thereby induces fetal cardiac enlargement and myocardial remodeling.[54] The oxidative metabolism of fetus increases additionally, which might lead to a more hypoxemia environment, and increase the vulnerability of the fetus to hypoxemia.[55] These

**Table 3**

**Comparison measurement of normal and GDM fetuses cardiac diastolic cardiac function using both conventional and dual-Doppler method.**

| Doppler parameter | Normal fetuses (mean ± SD) n = 55 | Fetuses of mothers with GDM (mean ± SD) n = 56 | *P* (unpaired *t* test) |
|---|---|---|---|
| Mitral valve | | | |
| E/A ratio (Conventional method) | 0.652 ± 0.062 | 0.637 ± 0.045 | .151 |
| E/A ratio (DD method) | 0.642 ± 0.071 | 0.631 ± 0.056 | .336 |
| e'/a' ratio (Conventional method) | 0.617 ± 0.098 | 0.630 ± 0.111 | .517 |
| e'/a' ratio (DD method) | 0.628 ± 0.097 | 0.643 ± 0.092 | .401 |
| E/e' ratio (Conventional method) | 6.677 ± 1.314 | 6.683 ± 1.417 | .984 |
| E/e' ratio (DD method) | 6.586 ± 1.282 | 6.164 ± 0.740 | .036 |
| Tricuspid valve | | | |
| E/A ratio (Conventional method) | 0.715 ± 0.067 | 0.702 ± 0.067 | .293 |
| E/A ratio (DD method) | 0.692 ± 0.058 | 0.679 ± 0.056 | .232 |
| e'/a' ratio (Conventional method) | 0.588 ± 0.065 | 0.600 ± 0.091 | .428 |
| e'/a' ratio (DD method) | 0.593 ± 0.075 | 0.610 ± 0.083 | .256 |
| E/e' ratio (Conventional method) | 6.792 ± 0.681 | 6.354 ± 0.615 | .001 |
| E/e' ratio (DD method) | 6.748 ± 0.954 | 6.282 ± 0.911 | .010 |

E/A, transvalvular early diastolic velocity to later diastolic velocity; e'/a', early diastolic myocardial velocity to late atrial contraction myocardial velocity ratio; E/e', transvalvular early diastolic velocity to myocardial early diastolic velocity ratio; Data are expressed as mean ± SD, median (interquartile range), or number (percentage).

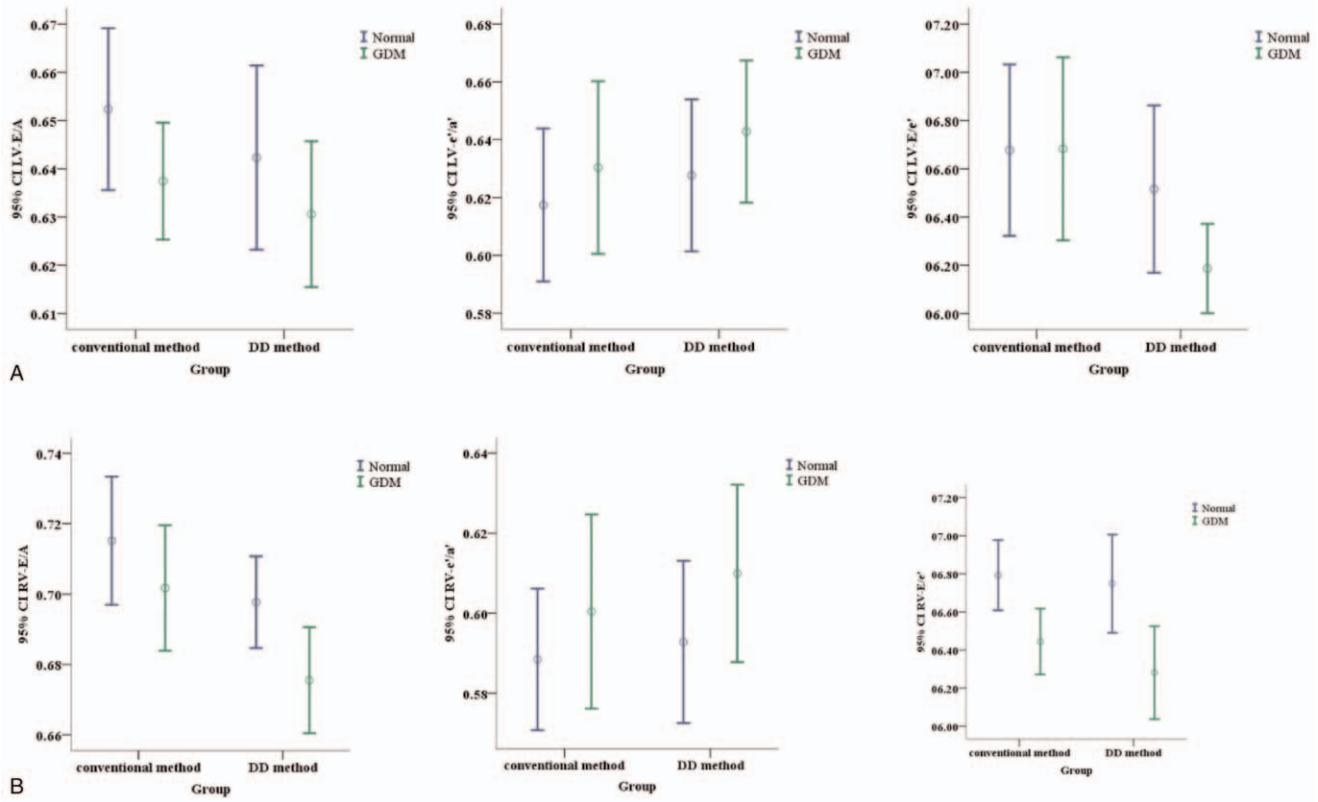


**Figure 3.** Error bar chart showing comparison of E/A, E/e' and e'/a' measured by conventional method and Dual-Doppler method in left (shows in panel A) and right (shows in panel B) ventricular of normal and GDM fetuses. E/A represent the ratio of transvalvular early diastolic velocity E to later diastolic velocity A; e'/a' represent the ratio of early diastolic myocardial velocity e' to late atrial contraction myocardial velocity a'; E/e' represent the ratio of transvalvular early diastolic velocity E to myocardial early diastolic velocity e'. blue line = control group, green line = GDM group, LV = left ventricular, RV = right ventricular.

events may lead to fetal cardiovascular dysfunction, such as diastolic dysfunction impairment even heart failure.[56] The results of this study indicate the presence of impairment in fetal diastolic function is because of the reduced ventricular compliance and increase in myocardial velocities in the gestational diabetes group. Furthermore, our data shows that diastolic function of the right ventricle is more likely to be damaged than that of the left ventricle because that the high blood glucose causes placental vascular

**Table 4**

**DD method comparison of fetal diastolic cardiac function in the control and GDM groups.**

| Doppler parameter | Normal fetuses (mean ± SD) n = 55 | Fetuses of mothers with GDM (mean ± SD) n = 56 | *P* (unpaired *t* test) |
|---|---|---|---|
| Mitral valve LV | | | |
| Peak E (cm/sec) | 33.313 ± 6.429 | 32.375 ± 4.272 | .367 |
| Peak A (cm/sec) | 50.373 ± 8.827 | 50.066 ± 5.562 | .827 |
| E/A ratio | 0.642 ± 0.071 | 0.631 ± 0.056 | .336 |
| e'(cm/sec) | 5.153 ± 0.599 | 5.036 ± 0.549 | .285 |
| a' (cm/sec) | 8.322 ± 1.187 | 7.946 ± 1.141 | .092 |
| e'/a' ratio | 0.628 ± 0.097 | 0.643 ± 0.092 | .401 |
| E/e' ratio | 6.586 ± 1.282 | 6.164 ± 0.740 | .036 |
| Tricuspid valve RV | | | |
| Peak E (cm/sec) | 39.895 ± 4.557 | 37.704 ± 4.396 | .011 |
| Peak A (cm/sec) | 55.767 ± 6.693 | 53.982 ± 5.984 | .141 |
| E/A ratio | 0.692 ± 0.058 | 0.679 ± 0.056 | .232 |
| e'(cm/sec) | 5.812 ± 0.703 | 6.102 ± 0.748 | .037 |
| a'(cm/sec) | 9.955 ± 1.070 | 10.062 ± 1.267 | .629 |
| e'/a' ratio | 0.593 ± 0.075 | 0.610 ± 0.083 | .256 |
| E/e' ratio | 6.748 ± 0.954 | 6.282 ± 0.911 | .010 |

E/A, transvalvular early diastolic velocity to later diastolic velocity; e'/a', early diastolic myocardial velocity to late atrial contraction myocardial velocity ratio; E/e', transvalvular early diastolic velocity to myocardial early diastolic velocity ratio; Data are expressed as mean ± SD, median (interquartile range), or number (percentage).

**Table 5**

**DD methods comparison of fetal diastolic cardiac function in the well and poorly-controlled groups.**

| Doppler parameter | Well-controlled (mean ± SD) n = 38 | Poorly-controlled (mean ± SD) n = 18 | *P* (unpaired t test) |
|---|---|---|---|
| Mitral valve LV | | | |
| Peak E (cm/sec) | 32.74 ± 4.216 | 31.59 ± 4.404 | .351 |
| Peak A (cm/sec) | 50.46 ± 5.390 | 49.23 ± 5.980 | .443 |
| E/A ratio | 0.65 ± 0.054 | 0.64 ± 0.068 | .725 |
| e'(cm/sec) | 4.99 ± 0.548 | 5.14 ± 0.551 | .337 |
| a' (cm/sec) | 8.08 ± 1.159 | 7.66 ± 1.077 | .192 |
| e'/a' ratio | 0.63 ± 0.088 | 0.66 ± 0.091 | .048 |
| E/e' ratio | 6.63 ± 1.049 | 6.20 ± 1.020 | .159 |
| Tricuspid valve RV | | | |
| Peak E (cm/sec) | 37.85 ± 4.088 | 37.64 ± 5.111 | .867 |
| Peak A (cm/sec) | 54.88 ± 6.271 | 52.09 ± 4.967 | .104 |
| E/A ratio | 0.69 ± 0.071 | 0.72 ± 0.080 | .166 |
| e'(cm/sec) | 6.06 ± 0.698 | 6.13 ± 0.864 | .756 |
| a'(cm/sec) | 10.20 ± 1.201 | 9.78 ± 1.388 | .251 |
| e'/a' ratio | 0.60 ± 0.060 | 0.64 ± 0.116 | .102 |
| E/e' ratio | 6.30 ± 0.823 | 6.24 ± 1.098 | .804 |

E/A, transvalvular early diastolic velocity to later diastolic velocity; e'/a', early diastolic myocardial velocity to late atrial contraction myocardial velocity ratio; E/e', transvalvular early diastolic velocity to myocardial early diastolic velocity ratio; Data are expressed as mean ± SD, median (interquartile range), or number (percentage).

resistance, inducing RV diastolic dysfunction. The RV provides about 60% of the combined fetal cardiac output and is more sensitive to afterload changes.[43,57]

Evolving of assessment methods of fetal cardiac function has never stopped over the past 20 years. This study focuses on seeking an efficient, reliable, and robust diagnostic tool to detect fetal diastolic dysfunction of mothers with GDM. Fetal tricuspid inflow peak velocities (peak E and peak A), tricuspid annular peak velocities (e'and a'), E/A ratio, e'/a' ratio, and E/e' ratio were put into the analysis, aiming to assess the fetal ventricular dysfunction in an early stage.

E/A ratio is a widely use parameter of assessing fetal diastolic function.[33,58] With the development of gestation, an increase of E/A ratio in fetus which may reflect myocardial maturational[58] due to increased activity and passive ventricular filling of fetus can be seen.[33] However, fetuses of diabetic mothers were found having impaired LV function with a significant decrease mitral valve E/A.[47,58,59] On the contrary, in some other research,[57,60] both LV and RV diastolic function in fetal of gestational diabetes were studied, and significantly decreased E/A ratio can be seen. However, LV diastolic parameters did not show significant change.

In our study, tricuspid E velocity was remarkably lower in GDM group than the control group. The decreased tricuspid E velocity indicates the right ventricle is sensitive to stressful intrauterine conditions, and more likely to be impaired in fetuses of diabetes mothers in consequence of its compliance and relaxation. E/A ratio, however, showed no significant change between GDM group and control group. In some other similar research using conventional method, it is believed that the heart rate and loading conditions have interference in atrioventricular inflow[43] It is difficult to get a precise measure of the intrinsic myocardial property with unavoidable interference factors. However, TDI, as a new technology, enables a direct measurement of the velocity of the longitudinal motion of the atrioventricular annulus,[46] not depending on the loading conditions.[33,47,48] TDI is more specific than PW Doppler for evaluate of fetal diastolic dysfunction.[35] In this study, E/A ratio showed no advantage comparing with over parameter to assess the cardiac function.

Whether e'/a' is an appropriate parameter to assess fetal cardiac diastolic function is controversial. Our data does show a significantly increase tricuspid e' velocity and a trend of increase e'/a' ratio, which nevertheless shows no statistical significance in GDM group. For fetuses of maternal diabetes, it is believed that a higher myocardial velocity in the atrioventricular annuluses would occur to physiological counter the limited ventricular compliance in early diastole, and this acceleration happens particularly in the RV.[35] S. Balli[33] found an increased tricuspid e' velocity and e'/a' ratio in GDM group compared with the control group. They considered the result as a consequence of an adaptation process to the present situation rather than a pathological process. However, Pinar[57] showed that the tricuspid e' velocity and e'/a' ratio were lower in the GDM group than the control group, indicating that fetal functional change was a result of diabetes.

The E/e' ratio has been frequently applied in recent echocardiographic studies to assess fetal ventricle diastolic function, because it correlates well with ventricular filling pressure.[61] With an advancing fetal age, e'-wave increases progressively faster than E-wave, thus E/e′ decreases with an increasing GA and levels out in the early third trimester.[61] Balli[33] found fetal E/e' ratio decreases drastically in diabetic mothers. However, there was no difference in LV and RV E/e' ratio between the control group and GDM group. Hatém[35] found significantly decreased E/e' ratio in both LV and RV in fetuses of diabetic mother, resulting from higher myocardial velocities rather than changes in early atrioventricular filling flows. Noting the conventional method were used in the above-mentioned studies, therefore, interference may occur from different cardiac cycle to affect the result of E/e' ratio.

In our study, E/e' ratio was measured using both conventional method and DD method, Bland-Altman plot shows no systematic bias between the conventional method and the DD method. The results suggest that the DD method is a feasible approach. E/e' ratio of RV measured by conventional method was found significant lower in the GDM group compared with the control group (6.35 vs 6.79, $P = .001$). While both left and RV function assessed by the DD method showed significant decreased E/e' ratio in the GDM group (6.16 vs 6.59, $P = .036$; 6.28 vs 6.75, $P = 0.01$).

There is no technical complication to apply DD method and it gives good reproducibility. DD method enables assessment of 2 Doppler waveforms simultaneously at any two separate locations, even in combination with pulsed and tissue Doppler. Obtaining E and e' value in same cardiac cycle minimises the error. Our data found that mitral E/e' ratio was significantly decreased in the GDM group compared with control group when using DD method, but not presented alterations assessed by conventional method. Does the DD method have an advantage over conventional method to detect fetal RV dysfunction? Further research is needed to proof that DD method is more specific and with a better sensitivity comparing with the conventional method.

Variables of well and poorly controlled groups showed no significant difference, which means fetal exposure to hyperglycemia environment have diastolic dysfunction, even well controlled. Ventricular dysfunction happened to fetuses of well-controlled GDM mothers, therefore, an early detection of GDM is vital. Using DD methods to evaluate cardiac function in fetuses of GDM is prospective and helpful to provide information to obstetricians in the early stage.

The deficiency of this study is that no calculation was performed for neither study power nor sample size, though the study power was sufficient to detect alterations in cardiac parameters between study groups. Furthermore, this study does not have a complete postnatal follow-up of these fetuses. It is necessary to have a further study including a greater number of GDM pregnancies, and a complete postnatal follow-up.

To conclude, high blood glucose of women with GDM will cause impaired diastolic function in the fetuses. To assess fetal diastolic function, RV is arguably the key to look at for early impairment detection, since the alteration and damage are more likely to happen in RV. Measurement of E/e' ratio using DD method is considered as a feasible and robust method to detect fetal diastolic function in fetal cardiac diastolic function assessment. Well or poorly control of the GDM does not have significant influence on the fetal diastolic function. An early detection of GDM and GDM induced fetal cardiac dysfunction is necessary.

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## Author contributions

**Conceptualization:** Xudong Dong.
**Data curation:** Jie Wu.
**Formal analysis:** Fang Yan.
**Funding acquisition:** Huanling Liu.
**Investigation:** Jiao Li.
**Project administration:** Qingsha Hou.
**Supervision:** Yunchuan Ding.

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