Fetal Cardiac Functional Abnormalities Assessed by Echocardiography in Mothers Suffering Gestational Diabetes Mellitus: A Systematic Review and Meta-analysis

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Abstract: Abnormal cardiovascular changes especially hypertrophic cardiomyopathy is potentially expected in the fetuses of the diabetic pregnancy women. However, there is still little consensus on quantitative cardiac abnormalities in infants with diabetic mothers. The present study comprehensively analyzed the studies on functional changes in heart in infants of diabetic mothers with a greater focus on occurrence of hypertrophic cardiomyopathy. All comparative studies evaluating and comparing quantitatively the changes in cardiac parameters using echocardiography in fetuses with and without diabetic mothers were eligible for assessment. The included studies were identified through electronically reviewing the manuscripts databases of MEDLINE, EMBASE, Web of knowledge, and Google Scholar from inception to May 2020. The meta-analysis included 11 comparative with overall 849 fetuses for gestational diabetic mothers and 1247 for healthy mothers. Assessing cardiac diameters by fetal echocardiography showed significantly lower mitral E/A ratio, lower tricuspid E/A ratio, higher interventricular septal

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thickness, higher myocardial performance index, higher isovolumic relaxation time, and higher isovolumic contraction time in fetuses of gestational diabetes mellitus group as compared to healthy group adjusting for gestational diabetes mellitus. The presence of gestational diabetes mellitus can potentially affect the fetal cardiac parameters especially as hypertrophic cardiomyopathy leading both cardiac systolic and diastolic dysfunction. (Curr Probl Cardiol 2021;46:100658.)

Introduction

Abnormal cardiovascular changes especially hypertrophic cardiomyopathy is potentially expected in the fetuses of the diabetic pregnancy women.[1,2] This abnormality is characterized by thickening of interventricular septum with extension to ventricular free wall. Such phenomenon can be asymptomatic in most infants without metabolic disturbances and can be resolved within months later, but in some cases and due to its severity, it may be life-threatening.[3,4] Infantile hypertrophic cardiomyopathy can be a consequence of fetal hyperinsulinemia due to mother's diabetic state along with increased affinity of insulin receptors to this hormone leading proliferation followed by hypertrophic changes in cardiac myocytes in infant that can ultimately result in significant changes in ventricular inflow and outflow velocities Any cardiac structural and functional changes in infants of diabetic mothers can be detected by fetal echocardiography and its initial time has been also well understood.[5-7] In this regard, the onset of hypertrophic cardiomyopathy has been recorded before 20 weeks of gestation, of course adjusted for fetal weight.[8] Along with the change as ventricular hypertrophy, some other echocardiogrpahic changes have been also reported in infants of diabetic mothers such as lowering right atrioventricular valve E/A ratio that is an indicator for mother's uncontrolled diabetes status.[9] Using tissue Doppler imaging could obtain more valuable information of fetal gestational diabetes mellitus (GDM)-related cardiac changes.[10] It has been in this regard shown increase in myocardial shortening velocities and long-axis amplitude of motion of left ventricle followed by impaired ventricular diastolic functional state.[11] Overall, although various aspects of cardiac changes have been studied, there is still little consensus on quantitative cardiac dimensions in infants with diabetic mothers. In other words, quantitative assessment of the pathophysiological changes associated with the GDM in such

infants requires systematic evaluation. The present study attempted to comprehensive analyzing the studies on structural and functional changes in heart in infants of diabetic mothers with a greater focus on occurrence of hypertrophic cardiomyopathy.

Materials and Methods

The current systematic review and meta-analysis followed the principles of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" guideline.[12] All retrospective or prospective comparative studies evaluating and comparing quantitatively the changes in cardiac parameters using echocardiography in infants with and without diabetic mothers were eligible for initial assessment. In this regard, those studies which determined the values of cardiac parameters in a single group of diabetic cases or without comparative goal were not included. The included studies were identified through electronically reviewing the manuscripts databases of MEDLINE, EMBASE, Web of knowledge, and Google Scholar from inception to May 2020. No language restriction was considered and thus the non-English manuscript were tried to translate by an expert translator to extract the requested data. Two blinded reviewers independently screened the titles and abstracts of the manuscripts followed by deeply assessment of the full texts for determining the inclusion appropriateness. In this regard, any disagreement across our reviewers was rechecked by the third reviewer as the final arbitrator. The details of eligibility and the reasons for excluding the papers were shown schematically (Fig 1). Thereafter, the details of the data of included papers were extracted and collected at a pre-established form and ultimately finalized. Before finalizing the meta-analysis, the risk of bias was evaluated blindly by the 2 authors using the Cochrane risk of bias tool that the level of bias was qualitatively classified as at high, unclear or low risk of bias.[13] In this regard, the following domains are routinely assessed for determining the level of bias: how selection the participants (selection bias), how performing the measurements by using echocardiography, how managing confounders and missing data, and how measuring the cardiac-related parameters. The fixed effects or random-effects (in case of significant heterogeneity across the data) models were used to obtained pooled dichotomous data using the mean difference (MD) followed by reporting 95% CIs and its-related corresponding p values. The heterogeneity across the studies was assessed by determining I^2 and its related P value as the p value of less than 0.05 indicated significant heterogeneity. A sensitivity analysis was also done, in which observational studies at critical risk of

bias were excluded from the analysis. Publication bias was also assessed by the rank correlation test and also confirmed by the funnel plot analysis. Reported values were 2-tailed, and hypothesis testing results were considered statistically significant at $P = 0.05$. For statistical analysis, the Comprehensive Meta-Analysis Software (CMA, version 3.0) was employed.

Results

The flow diagram of the study selection process is presented in Figure 1. In this context, 52 articles were initially collected by database searching. After removing 2 articles due to evidences of duplication, 50 records were primarily under-screened. Based on the titles and abstracts, 36 records were excluded and the remaining 14 citations were assessed for further eligibility. Of those, 3 were also excluded due to incompleteness of the data and contents. In final, 11 articles were eligible for the final analysis that published between 1995 and 2020. Table 1 describes baseline characteristics of the studies included (Fig 2).

The systematic review and the meta-analysis included 11 comparative with overall 849 infants for gestational diabetic mothers and 1247 infants for healthy mothers. All eligible cases were assessed by echocardiography

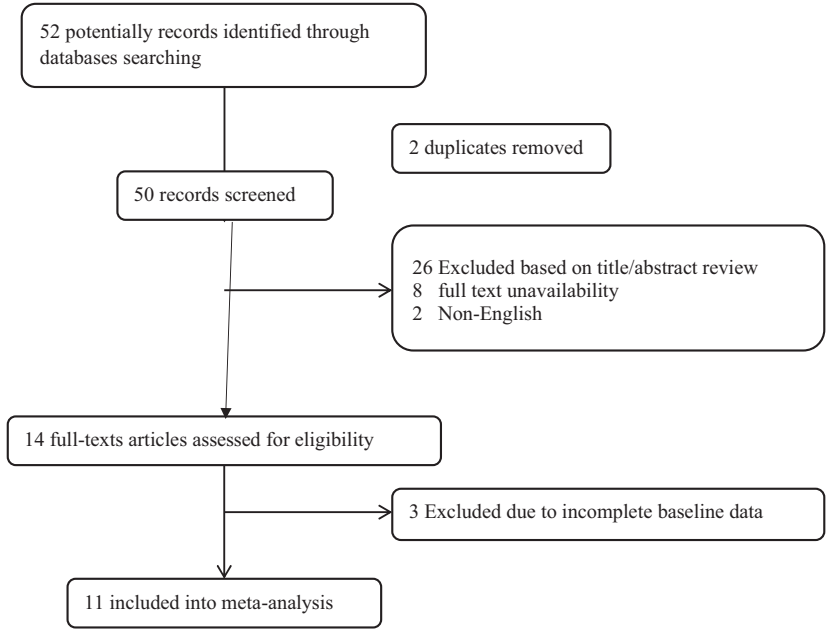

FIG 1. The flowchart of screening the eligible studies.

Table 1. The baseline details of studies included in our meta-analysis

Author, year	No. infants	Age of mother	Birth weight	GA group	Mother HbA1C
Aguilera, 2020[14]	GDM: 161 CTL: 483	34.5 32.4	3500 3300	>34	5.6 —
Atiq, 2017[15]	GDM: 64 CTL: 64	31.2 30.7	— —	<28	— —
Balli, 2013[16]	GDM: 67 CTL: 122	31.5 27.9	3145 3051	<28, 28-34, >34	5.7 5.0
Chu, 2012[17]	GDM: 44 CTL: 70	— —	— —	<28, 28-34, >34	— —
Dervisoglu, 2018[18]	GDM: 36 CTL: 42	29.8 28.8	3541 3436	28-34	5.8 4.7
Gandhi, 1995[19]	GDM: 24 CTL: 23	30.0 25.6	— —	<28, 28-34, >34	6.2 —
Garcia-Flores, 2010[20]	GDM: 24 CTL: 16			28-34	5.5 —
Garg, 2014[21]	GDM: 302 CTL: 294	28.9 27.3	3000 2900	<28	6.3 —
Miranda, 2017[22]	GDM: 76 CTL: 53	33.0 32.0	— —	28-34	— —
Mohsin, 2019[23]	GDM: 25 CTL: 50	31.6 32.1	— —	<28	— —
Russell, 2008[24]	GDM: 26 CTL: 30	— —	— —	<28, 28-34, >34	— —

for assessment of both systolic and diastolic parameters. Because of the confounding effects of gestational age at assessment time on almost all parameters measurable, all analyses were subcategorized according to gestational age as <28 weeks, between 28 and 34 weeks and >34 weeks that was also applied in some included studies. The majority of studies assessed the main cardiac functional parameters including interventricular septal thickness, mitral and tricuspid E/A index, myocardial performance index (MPI), isovolumic relaxation time (IVRT), and isovolumic contraction time (IVCT) that were finally included our pooled meta-analysis, however some other parameters including left ventricular ejection fraction, aortic annulus, tricuspid annulus, or Tricuspid annular plane systolic excursion (TAPSE) were measured in a minority of studies, without the possibility of entering meta-analysis. The overall mean values for cardiac parameters entered to meta-analysis are shown in Table 2 and Figures 3 to 7. We showed that the mean (SD) of the cardiac parameters assessed by echocardiography was significantly different in the fetuses of diabetic and non-diabetic mothers. In this regard, GDM led to significantly lower mitral E/A ratio (weighted MDs of -0.307 [$P< .001$], -0.195 [$P= 0.020$], and -0.785 [$P< 0.001$]), lower tricuspid E/A ratio (weighted MDs of -0.244 [$P=$

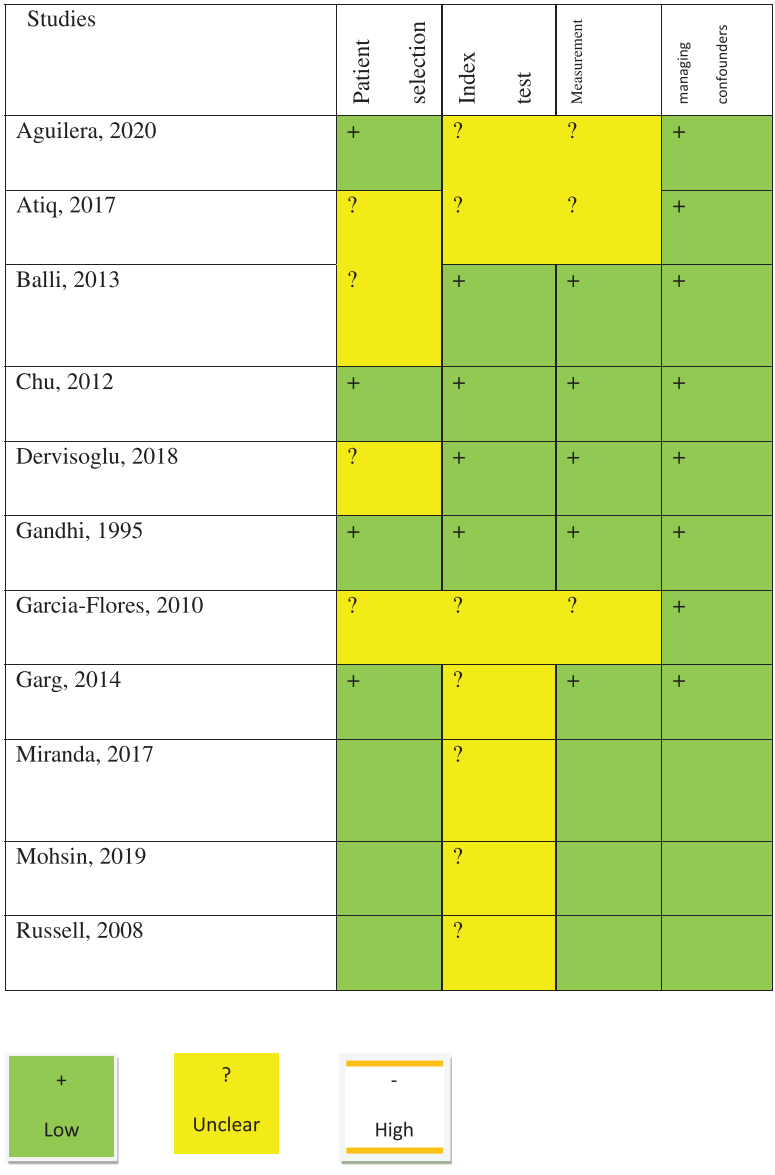

FIG 2. The Assessment of the risk of bias.

0.005], -0.463 [$P< 0.001$], and -1.019 [$P< 0.001$]), higher interventricular septal thickness (weighted MDs of 0.836 [$P< 0.001$), 1.295 [$P < 0.001$], and 0.899 [$P< 0.001$]), higher MPI (weighted MDs of 1.213 [$P< 0.001$], 0.428 [$P< 0.001$], and 0.374 [$P< 0.001$]), and higher IVRT (weighted MDs of 0.579 [$P< 0.001$], 0.600 [$P< 0.001$], and 2.497 [$P<0.001$]) for

Table 2. The cardiac functional parameters

Author, year	Mitral E/A	Tricuspid E/A	MPI	LVEF	IVS	IVRT	IVCT	Aortic annulus	Tricuspid annulus	TAPSE
Aguilera, 2020	GA>34 GDM: 1.30 CTL: 1.38		GA>34 GDM: 0.50 CTL: 0.50	GA>34 GDM: 0.59 CTL: 0.58		GA>34 GDM: 75.0 CTL: 68.0				
Atiq, 2017	GA<28 GDM: 0.59 CTL: 0.63	GA<28 GDM: 0.65 CTL: 0.66	GA<28 GDM: 0.56 CTL: 0.49		GA<28 GDM: 2.2 CTL: 2.1	GA<28 GDM: 45.4 CTL: 41.3	GA<28 GDM: 43.8 CTL: 39.9	GA<28 GDM: 2.9 CTL: 3.8	GA<28 GDM: 7.6 CTL: 7.1	GA<28 GDM: 5.9 CTL: 6.3
Balli, 2013	GA<28 GDM: 0.63 CTL: 0.61 GA 28-34 GDM: 0.76 CTL: 0.77 GA>34 GDM: 0.81 CTL: 0.84	GA<28 GDM: 0.62 CTL: 0.64 GA 28-34 GDM: 0.78 CTL: 0.79 GA>34 GDM: 0.81 CTL: 0.84	GA<28 GDM: 0.43 CTL: 0.41 GA 28-34 GDM: 0.45 CTL: 0.41 GA>34 GDM: 0.46 CTL: 0.41		GA<28 GDM: 2.3 CTL: 2.2 GA 28-34 GDM: 3.8 CTL: 3.1 GA>34 GDM: 4.5 CTL: 3.8	GA<28 GDM: 41.4 CTL: 40.6 GA 28-34 GDM: 45.9 CTL: 42.9 GA>34 GDM: 48.7 CTL: 44.3	GA<28 GDM: 34.8 CTL: 34.4 GA 28-34 GDM: 35.1 CTL: 34.8 GA>34 GDM: 35.6 CTL: 34.2	GA<28 GDM: 4.3 CTL: 4.2 GA 28-34 GDM: 6.1 CTL: 6.1 GA>34 GDM: 6.8 CTL: 6.8		
Chu, 2012	GA<28 GDM: 0.62 CTL: 0.65 GA 28-34 GDM: 0.70 CTL: 0.74 GA>34 GDM: 0.76 CTL: 0.77	GA<28 GDM: 0.64 CTL: 0.69 GA 28-34 GDM: 0.67 CTL: 0.76 GA>34 GDM: 0.69 CTL: 0.78		GA<28 GDM: 0.67 CTL: 0.66 GA 28-34 GDM: 0.63 CTL: 0.66 GA>34 GDM: 0.62 CTL: 0.65	GA<28 GDM: 2.5 CTL: 1.9 GA 28-34 GDM: 3.3 CTL: 2.5 GA>34 GDM: 4.0 CTL: 3.0					
Dervisoglu, 2018	GA 28-34 GDM: 0.72 CTL: 0.73	GA 28-34 GDM: 0.66 CTL: 0.79			GA 28-34 GDM: 3.2 CTL: 3.0					
Gandhi, 1995					GA<28 GDM: 2.7 CTL: 2.2					

(*continued on next page*)

Table 2. (*continued*)

Author, year	Mitral E/A	Tricuspid E/A	MPI	LVEF	IVS	IVRT	IVCT	Aortic annulus	Tricuspid annulus	TAPSE
					GA 28-34 GDM: 3.8 CTL: 3.7 GA>34GDM: 4.5 CTL: 3.8					
Garcia-Flores, 2010	GA 28-34 GDM: 0.73 CTL: 0.69	GA 28-34 GDM: 0.72 CTL: 0.78	GA 28-34 GDM: 0.32 CTL: 0.31					GA 28-34 GDM: 6.3 CTL: 6.0	GA 28-34 GDM: 12.00 CTL: 11.09	
Garg, 2014	GA<28 GDM: 0.68 CTL: 0.71				GA<28 GDM: 3.7 CTL: 2.7					
Miranda, 2017	GA 28-34 GDM: 0.79 CTL: 0.80	GA 28-34 GDM: 0.78 CTL: 0.78	GA 28-34 GDM: 0.55 CTL: 0.56		GA 28-34 GDM: 4.2 CTL: 3.6	GA 28-34 GDM: 54.0 CTL: 54.0				GA 28-34 GDM: 8.9 CTL: 9.2
Mohsin, 2019	GA<28 GDM: 0.59 CTL: 0.63	GA<28 GDM: 0.64 CTL: 0.63	GA<28 GDM: 0.53 CTL: 0.45			GA<28 GDM: 43.7 CTL: 39.7	GA<28 GDM: 43.9 CTL: 38.3			GA<28 GDM: 6.1 CTL: 6.2
Russell, 2008	GA<28 GDM: 0.56 CTL: 0.60 GA 28-34 GDM: 0.62 CTL: 0.58 GA>34 GDM: 0.84 CTL: 0.86	GA<28 GDM: 0.61 CTL: 0.61 GA 28-34 GDM: 0.63 CTL: 0.62 GA>34 GDM: 0.88 CTL: 0.83	GA<28 GDM: 0.56 CTL: 0.49 GA 28-34 GDM: 0.49 CTL: 0.53 GA>34 GDM: 0.57 CTL: 0.58			GA<28 GDM: 46.0 CTL: 41.0 GA 28-34 GDM: 43.0 CTL: 41.0 GA>34 GDM: 59.0 CTL: 52.0	GA<28 GDM: 38.0 CTL: 36.0 GA 28-34 GDM: 35.0 CTL: 34.0 GA>34 GDM: 34.0 CTL: 35.0			

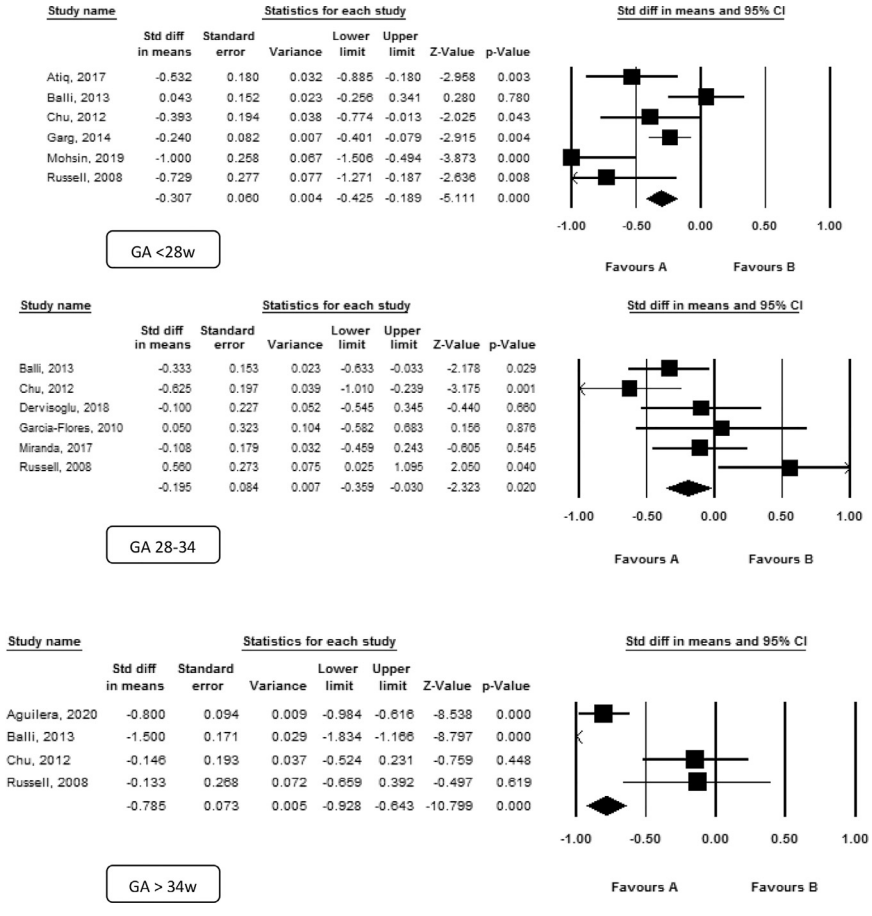

FIG 3. The mean difference in mitral E/A in pooled assessment of the studies.

gestational ages <28 weeks, 28-34 weeks, and > 34 weeks respectively. The heterogeneity across the studies in all measurements was significantly relevant with the I^2 values ranged 76.123 to 98.859. Numerically comparing other cardiac functional parameters between the subgroups with diabetic and non-diabetic mothers also showed higher IVCT as well as lower TAPSE in the former groups. The documents for comparing other parameters including aortic annulus or tricuspid annulus were inadequate for meta-analysis. Assessment of publication and systematic bias showed that almost all studies were considered as low risk or with unclear biases and thus the obtained results could be considered valid and none of the citation was determined to have high risk of bias. However, the Egger test detected a significant publication bias for all assessments.

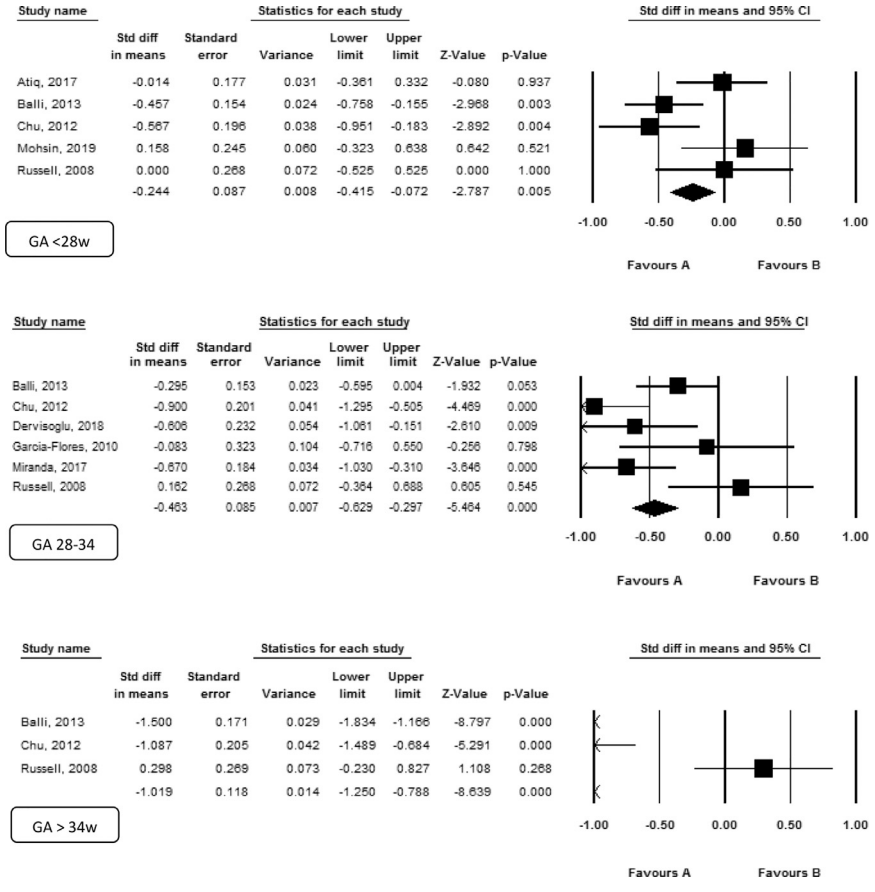

FIG 4. The mean difference in tricuspid E/A in pooled assessment of the studies.

Discussion

GDM is a relatively common condition affecting about 0.5% of all pregnant population.[25] The present evidences show higher likelihood of prenatal mortality and morbidity in GDM background due to both metabolic disturbances as well as cardiovascular abnormalities.[26] The main origin of GDM cardiac abnormality particularly cardiomyopathy has been already uncertain, however various animal and human studies attempted to explain the pathophysiological basis of GDM.[27] Overall, it seems that the presence and severity of infantile hypertrophic cardiomyopathy related to GDM is mainly due to poorly controlled or uncontrolled diabetes in the affected mothers. Some recent studies on still born infants documented some degrees of disorganizing the cardiac myofibrils similar

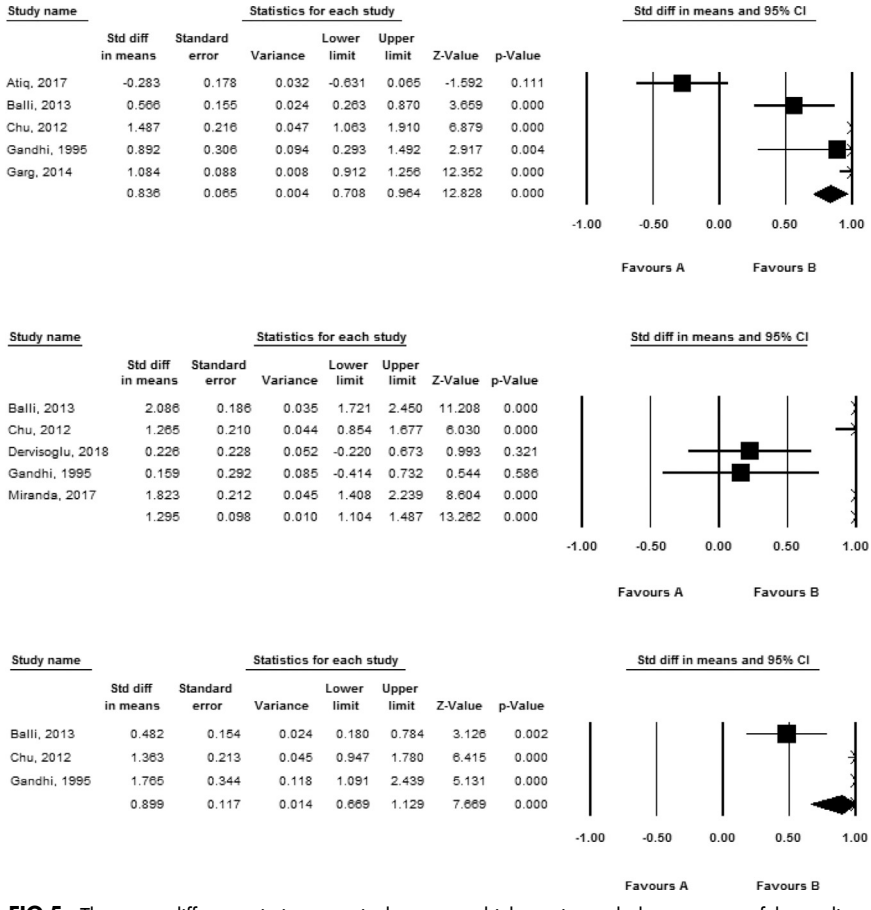

FIG 5. The mean difference in interventricular septum thickness in pooled assessment of the studies.

to that revealed in affected adults.[28] Along with the definitive effects of GDM and its related metabolic effects on cardiac structural and functional conditions, it seems that some baseline fetal and maternal factors can also affect the cardiac dimensions such as gestational age, fetal normal weight gain, and other gestational metabolic abnormalities. As indicated well by different studies, the trend in the change of different cardiac diameters in different trimesters is divergent. Also, some molecular changes have been also demonstrated to be associated with cardiac function in GDM mothers. As shown in animal models, oxidative stress and cell apoptosis are 2 main molecular components involving ventricular hypertrophy following GDM.[29] It has been also revealed that the cardiomyocyte size may increase in diabetic animal models mainly in response to high glucose exposure. In other words, it seems that any

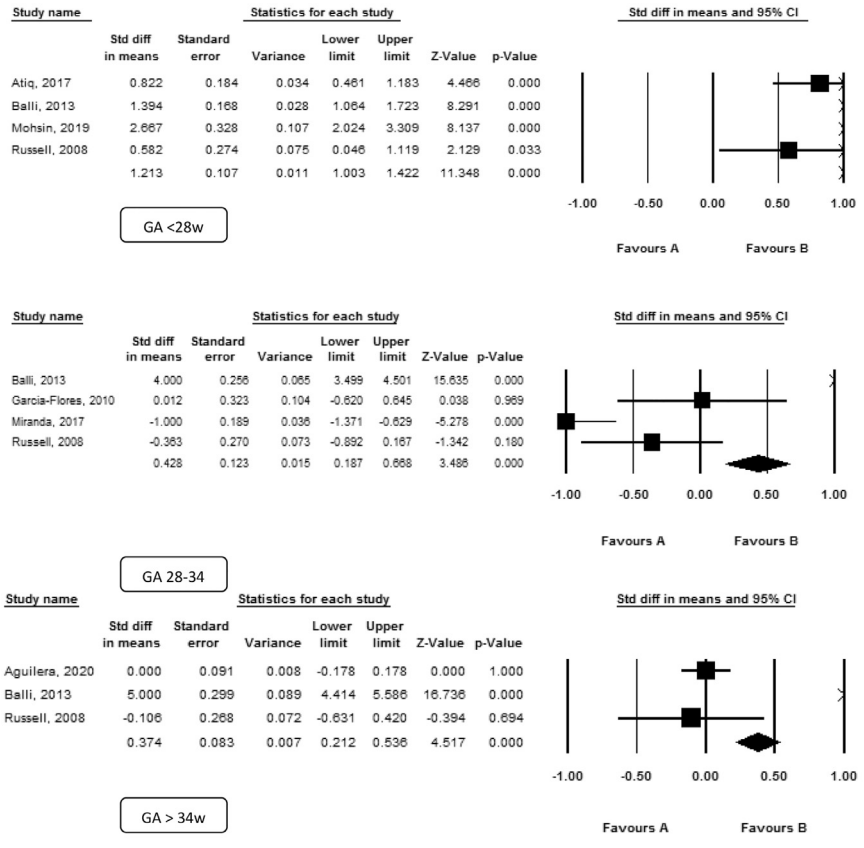

FIG 6. The mean difference in MPI in pooled assessment of the studies.

alteration in cardiomyocyte size rather than cell proliferation or apoptosis is responsible for hyperglycemia-induced fetal cardiac hypertrophy.[30] In line with the present evidences, we could show by our meta-analysis that almost all fetal cardiac functional parameters could be affected by GDM even after adjustment for gestational age. In this context, assessing cardiac diameters by fetal echocardiography showed significantly lowering mitral E/A ratio, lower tricuspid E/A ratio, higher interventricular septal thickness, higher MPI, and higher IVRT and IVCT concluding significant changes in cardiac function in GDM state beginning from the early beginning of the formation of the fetal cardiovascular system.

Despite significant results in our meta-analysis, high heterogeneity and also publication bias across the included studies seems to be the main pitfall in our meta-assessment. For the first issue, it seems that the heterogeneity can be potentially influenced by the experience of operator for

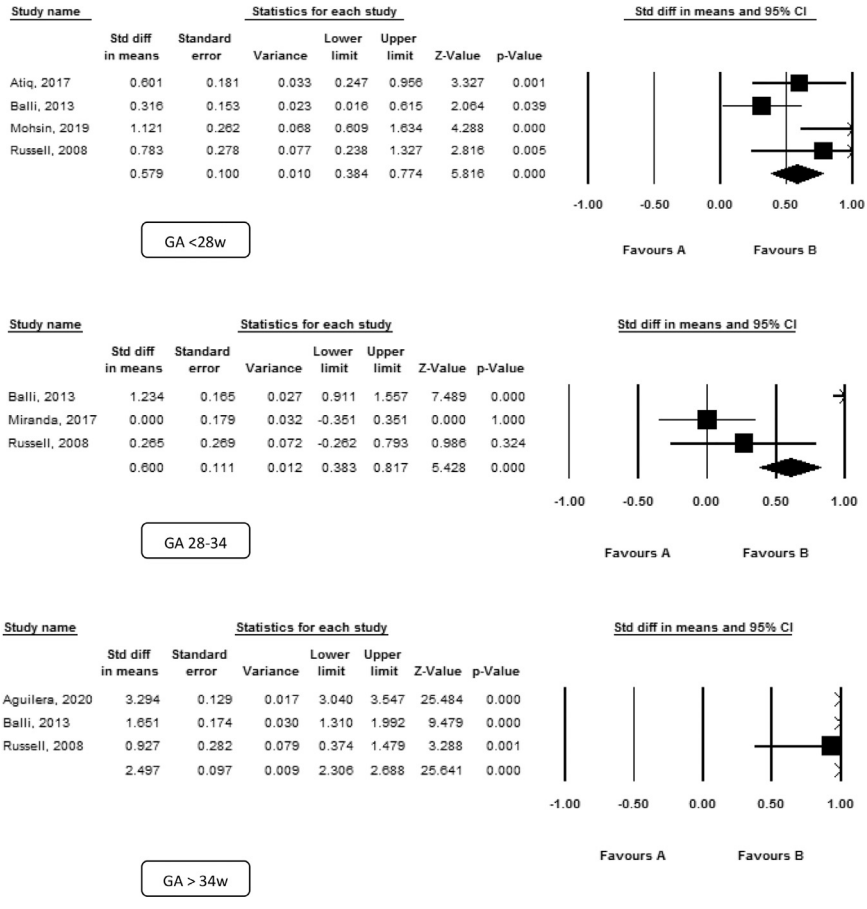

FIG 7. The mean difference in IVRT in pooled assessment of the studies.

performing fetal echocardiography or the type of tools employed for fetal cardiac assessment, while fetal echocardiography needs to several years training and experiences. We tried to remove the confounding effect of gestational age as a main confounder by its subcategorizing to 3 time sections of less than 28 weeks, 28-34 week and more than 34 weeks, however adjusting other probable confounders such as baseline medical status of mothers, parity, mothers' age, or the trend of weight gaining the fetus could not be possible. However, in spite of all probable confounding effects, the impairment in cardiac parameters wad shown to be definitive.

As the final conclusion, the presence of GDM can potentially affect the fetal cardiac parameters may leading hypertrophic cardiomyopathy and ultimately to neonatal death. This importance should be considered in all

cases of the GDM, and a regular evaluation and screening program should be considered for each case involved.

Conclusion

The presence of GDM can potentially affect the fetal cardiac parameters especially as hypertrophic cardiomyopathy leading both cardiac systolic and diastolic dysfunction.

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