Research Article

Carditrophin-1 (CT-1) level and Echocardiographic changes in macrosomic neonate infants

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Abstract

Background: Fetal macrosomia, or otherwise large-for-gestational - age (LGA) fetus/infant, applies to a birth weight (BW) between 4000 and 4500g, and BW > 90th percentile for gestational age. Cardiotrophin-1(CT-1), cardiomyocytes-produce chemokine, member of the interleukin- 6 cytokine family, which acts upon the glycoprotein (GP) 130 trans- membrane receptor, plays fundamental role in fetal heart development this is up-regulated by hypoxia and inflammation and exerts potent hypertrophic action on cardiac cells. It mediates the hyperglycemia/hyperinsulinemia-induced myocardial hypertrophy and systemic atherosclerosis, and is actively involved in cardiovascular pathology. **Aim of the study**: To evaluate the Cardiotrophin-1level and echocardiographic findings in macrosomic neonate's in maternity and children hospital. **Methods:** It is a case control study. A total 80 neonates enrolled. They were divided into 2 groups; 40 neonates' macrosomic, 40 neonates control were healthy. Cord blood was collected and analyzed for plasma level of cardiotrophin-1 and echo study for cases and control. **The two groups** were subjected to careful detailed history perinatal history, complete clinical examination, echo study and laboratory investigations including: plasma level of cardiotrophin-1, random blood sugar. **Results**: There were significant difference in weight, length, body area surface of macrosomic neonates at p <0.001. CT-1 is significantly high in Macrosomic neonates p<0.001. ASD was comment defect in our study present in eighteen (56.3%) Macrosomic neonates, while the increase in **IVSD** was highly significant in macrosomic neonates compared to control. A subgroup analysis (in the Macrosomic group) showed increased cord blood CT-1 concentrations in Macrosomic neonates with CHD, as compared to Macrosomic neonates without CHD (p1 =0.029). Subgroup analysis (in the Macrosomic group) showed increased cord blood CT-1 concentrations in IDM median 280(pg. /mL) as compared to controls median 59(pg. /mL) p2 <0.001, CT-1 concentrations was significantly elevated in Macrosomic of IDM Median 280(pg. /mL) as compared to Macrosomic of Non-diabetic mothers p1<0.001, but still significantly high in Macrosomic neonates of Non-diabetic mothers Median was 280 (pg. /mL) versus (59) in control p3<0.001. CT-1 concentrations were similar in Macrosomic with CHD and Macrosomic without CHD neonates, and positively correlated with Infant RBS (r =*0.949*, r = *0.948* respectively p<*0.001)*. CT-1 concentrations were positively correlated with body surface area and birth weight in Macrosomic with CHD (r =0.888, r =0.800 respectively) and Macrosomic without CHD neonates (r =0.917, r =0.920 respectively). **Conclusion:** plasma cardiotrophin-1 level is significant high in macrosomic neonates, cardiac hypertrophy and anomalies are common on macrosomic neonates.

Keywords; cardiotrophin-1, macrosomia, echocardiography.

Introduction

Fetal macrosomia, or otherwise large-for-gestational-age (LGA) fetus/infant, applies to birth weight (BW) between 4000 and 4500g, and BW > 90th percentile for gestational age.[1] (Briana et al., 20), Causes of fetal macrosomia including maternal diabetes, pre-pregnancy overweight/obesity and excessive weight gain during pregnancy and constitutional.[2] (Mitanchez et al., 2015), increasing prevalence of GDM is reported worldwide[3] (Carolan et al.,

2012), Hyperglycemia and hyperinsulinism in utero may lead to fetal hypertrophic cardiomyopathy, affecting the interventricular septum and possibly the myocardium, occasionally severely impacting morbidity and mortality. Furthermore, cardiovascular complications, as high systolic blood pressure, cardiac remodeling and insulin resistance may appear later in life.[4] (Chen et al., 2012)

Cardiotrophin-1(CT-1), cardiomyocytes-produce chemokine, member of the interleukin- 6 cytokine family, which acts upon the glycoprotein (GP) 130 transmembrane receptor, plays fundamental role in fetal heart development this is up-regulated by hypoxia and inflammation and exerts potent hypertrophic action on cardiac cells. It mediates the hyperglycemia/ hyperinsulinemia-induced myocardial hypertrophy and systemic atherosclerosis,[5] (Gamella-Pozuelo et al., 2015)

Patients and methods

This is a case-control study that included 80 neonates those neonates have been delivered in maternity and children hospital

According to our inclusion criteria, 40 neonates were macrosomic, which divided to two sub groups according to presence or absence of congenital heart diseases and infant of diabetic or not IDM. The remaining 40 neonates were healthy with appropriate weight for age, served as control group.

Then included neonates were subjected to the following:

1. Thorough history taking including detailed perinatal history; maternal diseases and drug intake, high risk pregnancy, gestational age in weeks, mode of delivery, presence of meconium, antenatal ultrasound and risk factors of infection.

2. Thorough clinical examination including; anthropometric measures performed on percentile charts, general, cardiac, chest, abdominal and neurological examination, and random blood sugar at time of birth, admitted to NICU or not.

3. Laboratory investigation; plasma cardiotrophin-1 level, random blood sugar for neonate and his mother.

4. Echocardiographic study; it includes M mode, and two-dimensional, pulsed and continuous wave Doppler and color flow mapping.

Results

Table (1) Demographic data of the studied groups:

		Macrosomic neonates N=40	Controls N=40	P value
Age (in days)	*Median IQR*	4 (3-7.8)	4 (3-5)	0.091
Sex	*Male Female*	28(70%) 12(30%)	25(62.5%) 15(37.5%)	0.478
gestational age in weeks	*Range Mean ± SD*	(37-40) 37.6±0.8	(37-40) 37.8±0.8	0.176
birth weight in kg	*Range Mean ± SD*	(4-6) 4.4±0.4	(2-3.4) 3±0.3	<0.001*
Length in cm	*Range Mean ± SD*	(49-61) 54.1±3	(42-48) 45.9±1.2	<0.001*
Body surface area(sq.m2)	*Range Mean ± SD*	(0.4-0.6) 0.5±0.03	(0.3-0.4) 0.4±0.01	<0.001*
Admission to NICU	*Yes No*	39(97.5%) 1(2.5%)	0(0%) 40(100%)	<0.001*

*P value based on Student's t-test or Fisher's exact test used to compare groups * P value significant <0 .05, IQR: inter quintile range, NICU neonatal intensive care unit.*

Table (1) shows demographic data of the studied groups**, out** of forty macrosomic neonates, twenty-eight (70%) were males and twelve (30%) were females. Thirty nine (97.5%) of macrosomic neonates were admitted to NICU while none of neonates of control group were admitted to NICU. Regarding gestational age, there were no significant difference between macrosomic neonates and controls. As shown in table **(1)** there was significant difference in weight, length, body area surface of macrosomic neonates at p <0.001 than control.

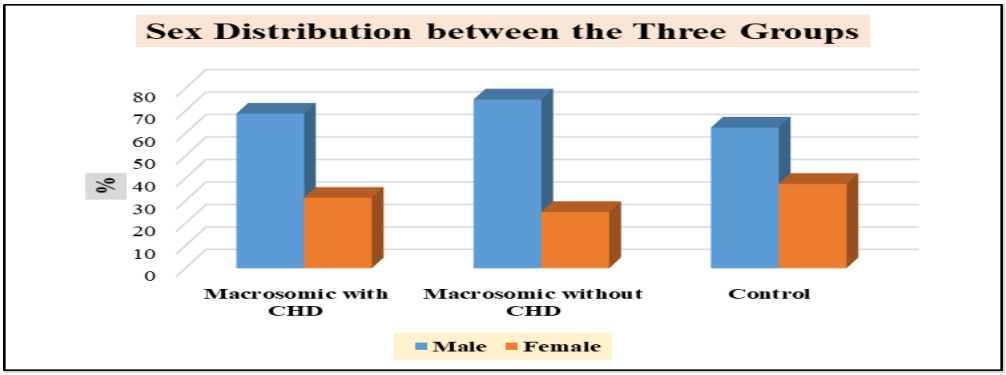

Figure (1): sex distribution in the studied groups

Table (2) Echocardiographic measurements in the studied group and control:

		Cases	Control	P value
		N=40	N=40	
RVD	*Range* *Mean ± SD*	(0.5-1.2) 0.9±0.2	(0.5-0.8) 0.6±0.1	<0.001*
IVSD	*Range* *Mean ± SD*	(0.3-0.9) 0.6±0.2	(0.3-0.5) 0.4±0.1	<0.001*
LVESD	*Range* *Mean ± SD*	(0.5-1.9) 1.1±0.3	(0.8-1.5) 1.2±0.2	0.369
LVEDD	*Range* *Mean ± SD*	(0.7-2.4) 1.7±0.3	(1.4-2.2) 1.8±0.2	0.486
LVPWD	*Range* *Mean ± SD*	(0.2-0.7) 0.4±0.1	(0.3-0.4) 0.3±0.04	<0.001*
EF	*Range* *Mean ± SD*	(56-82) 70.1±5.7	(62-72) 67.4±2.8	0.009*
FS	*Range* *Mean ± SD*	(27-48) 37.3±4.4	(32-39) 35.7±2.2	0.035*
Lt Atrium	*Range* *Mean ± SD*	(0.3-2.2) 1.5±0.4	(1.4-1.9) 1.7±0.1	0.006*
AORTA	*Range* *Mean ± SD*	(0.4-1.7) 1.1±0.4	(0.9-1.5) 1.2±0.1	0.035*
main Pulmonary	*Range* *Mean ± SD*	(0.4-1.7) 1.1±0.3	(0.8-1.4) 1.1±0.2	0.664
RT pulmonary	*Range* *Mean ± SD*	(0.3-0.9) 0.6±0.14	(0.4-0.7) 0.5±0.1	0.023*
LT pulmonary	*Range* *Mean ± SD*	(0.2-0.8) 0.57±0.15	(0.4-0.7) 0.5±0.1	0.063

*Values are presented as mean SD unless otherwise specified. *P value based on Student's t-test , RVD, right ventricle end-diastole diameter, IVDS, interventricular septum dimension in diastole, LVEDD, left ventricle dimension end-diastole; LVEDS, left ventricle dimension in systole; LVPWD, left ventricle posterior wall dimension in diastole EF, ejection fraction FS ,fractional shortening ,RT ;right ,LT left . p value significant* <0 .05.

Table (2) summarizes echocardiographic measurements in studied group, the increase in IVSD was highly significant in macrosomic neonates compared to control (*Mean ± SD* 0.6±0.2 versus 0.4±0.1 respectively p <0.001). RVD was statistically significantly increased in macrosomic neonates compared to control (*Mean ± SD* 0.9±0.2 vs 0.6±0.1 p <0.001), also LVPWD, EF, FS, Lt Atrium, AORTA, RT pulmonary were significantly higher in macrosomic neonates compared to control. No differences between the groups were observed in LVESD, LVEDD, main pulmonary dimensions and LT pulmonary.

Table (3) Echocardiographic finding in the studied macrosomic sub groups:

		Macrosomic of diabetic mothers	Macrosomic of Non-diabetic mothers	P value
		N=26	N=14	
RVD in cm	*Range* *Mean ± SD*	(0.5-1.1) 0.9±0.2	(0.6-1.2) 0.9±0.1	0.488
IVSD in cm	*Range* *Mean ± SD*	(0.3-0.9) 0.6±0.2	(0.3-0.7) 0.5±0.1	0.089
LVESD in cm	*Range* *Mean ± SD*	(0.5-1.9) 1.2±0.3	(0.7-1.7) 1.1±0.3	0.173
LVEDD in cm	*Range* *Mean ± SD*	(0.7-2.4) 1.8±0.4	(1.3-2.2) 1.7±0.3	0.337
LVPWD in cm	*Range* *Mean ± SD*	(0.3-0.7) 0.4±0.1	(0.2-0.6) 0.4±0.1	0.073
EF percentage	*Range* *Mean ± SD*	(58-82) 69.7±5.4	(56-81) 70.8±6.4	0.584
FS percentage	*Range* *Mean ± SD*	(30-48) 37.3±4.1	(27-46) 37.3±4.9	0.967
LT atrium in cm	*Range* *Mean ± SD*	(0.3-2.2) 1.6±0.4	(0.7-1.9) 1.4±0.4	0.083
AORTA in cm	*Range* *Mean ± SD*	(0.4-1.7) 1.2±0.4	(0.4-1.6) 1±0.4	0.086
main Pulmonary in cm	*Range* *Mean ± SD*	(0.4-1.7) 1.2±0.3	(0.5-1.6) 1±0.3	0.222
RT pulmonary in cm	*Range* *Mean ± SD*	(0.3-0.8) 0.6±0.1	(0.3-0.9) 0.6±0.2	0.600
LT pulmonary in cm	*Range* *Mean ± SD*	(0.2-0.8) 0.6±0.2	(0.3-0.8) 0.6±0.2	0.352

Independent samples T test for parametric quantitative data between the two groups
**: Significant difference at P value < 0.05, RVEDD, right ventricle end-diastole diameter, IVDS, interventricular septum dimension in diastole, LVEDD, left ventricle dimension end-diastole; LVEDS, left ventricle dimension in systole; LVPWD, left ventricle posterior wall dimension in diastole EF, ejection fraction FS ,fractional shortening ,RT ;right ,LT left*

Table (3) shows echocardiographic findings in subgroups analysis of macrosomic neonates, IVSD, LVPWD, LT atrium, AORTA were relatively increased in IDM at (p= 0.089, p =0.073, p =0.083, p=0.086) respectively, while there was no significant differences in RVD, LVESD, LVEDD, EF, main Pulmonary and its branches between infant of diabetics mothers and other macrosomic neonates of non IDM .

Table (4) plasma cardiotrophin-1 level in studied groups:

		macrosomic N=40	Control N=40	P value
CT-1 level (pg. /mL)	*Median IQR*	226 (130 -383.7)	59 (37-66.8)	<0.001*

Mann Whitney test for non-parametric quantitative data between the two groups, *CT-1; cardiotrophin-1, IQR: inter quintile range*

Table (9) shows significant increase in cord blood Cardiotrophin-1 level in macrosomic neonates than control group (p<0.001)

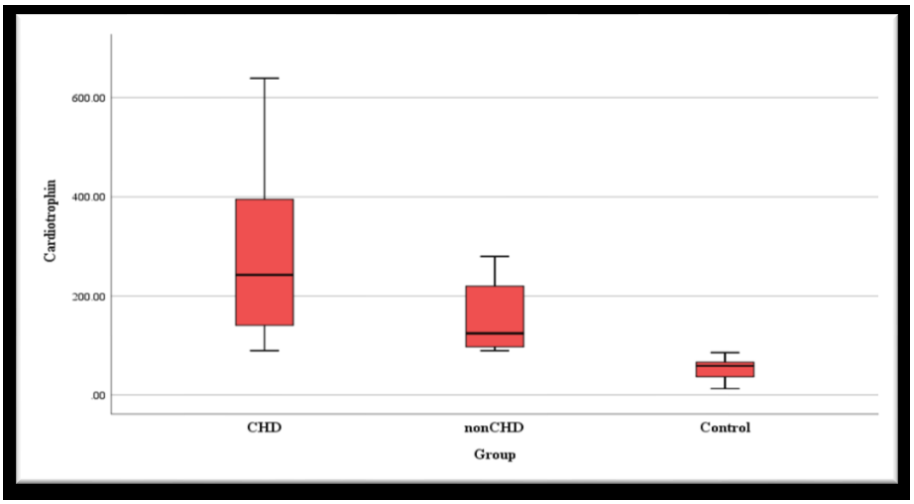

Figure (2) Plasma cardiotrophin-1 level in studied subgroups

CT-1 concentrations in cord blood were significantly higher in macrosomic neonates with CHD and Macrosomic without CHD, as compared to Control group (p2 <0.001, p3 <0.001 respectively), A subgroup analysis (in the macrosomic group) showed increased cord blood CT-1 concentrations in Macrosomic neonates with CHD, as compared to Macrosomic neonates without CHD (p1 =0.029) .

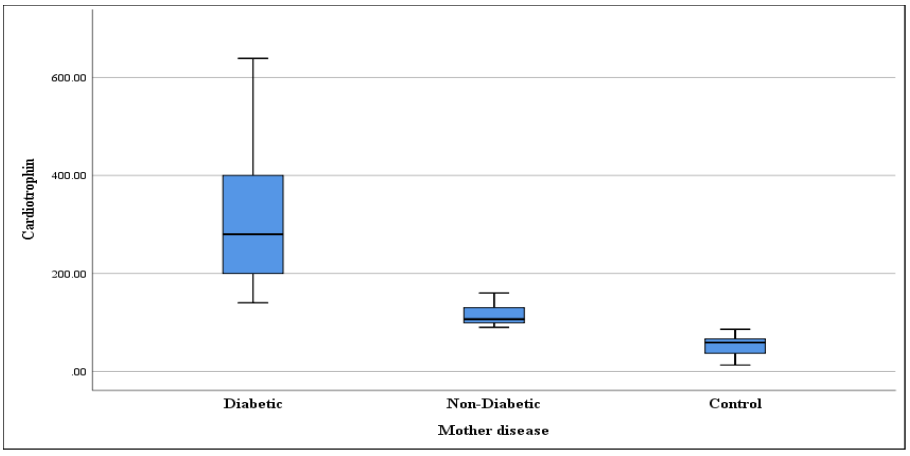

Figure (3) plasma cardiotrophin-1 level in infant of diabetic mother

Subgroup analysis (in the macrosomic group) showed increased cord blood CT-1 concentrations in IDM median 280(pg. /mL) as compared to controls median 59(pg./mL) p2 <0.001, CT-1 concentrations was significantly elevated in Macrosomic of IDM Median 280(pg. /mL) as compared to macrosomic of Non-diabetic mothers p1<0.001, but still significantly high in macrosomic neonates of Non-diabetic mothers than control Median was 280 (pg. /mL) versus(59) p3<0.001. **Table (7)**

Table (8) Correlation between cardiotrophin-1 and Infant RBS

CT-1 level (pg./mL)	All Macrosomic		Macrosomic with CHD		Macrosomic without CHD	
	R	P value	R	P value	R	P value
Infant RBS	*0.791*	*<0.001**	*0.949*	*<0.001**	*0.948*	*<0.001**

Vs, versus, *Pearson's correlation, CT-1; cardiotrophin-1, RBS; random blood sugar.*

CT-1 concentrations were similar in Macrosomic neonates with CHD and Macrosomic without CHD, and positively correlated with Infant RBS (r =*0.949*, r = *0.948* respectively p<*0.001)*. **Table (8), figure (2)**

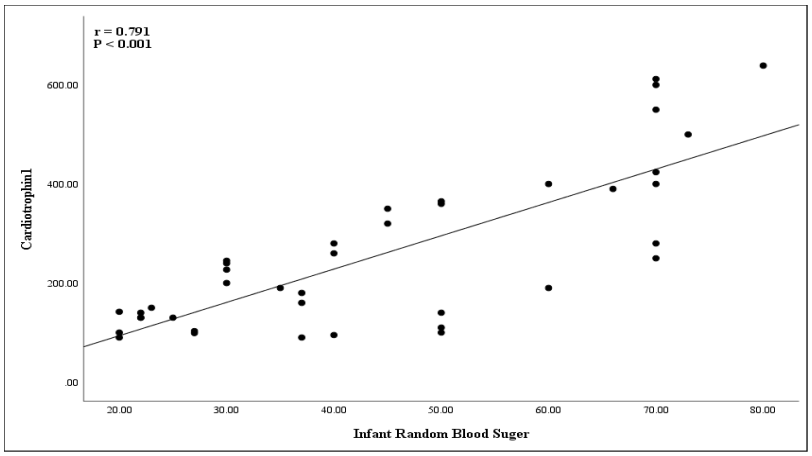

Figure (4) Correlation between cardiotrophin-1 and Infant RBS in macrosomic neonates

Table (9) Correlation between plasma cardiotrophin-1 level and body surface area and birth weight in the studied macrosomic neonates:

CT-1 level (pg./mL)	All Macrosomic		Macrosomic with CHD		Macrosomic without CHD	
	R	P value	R	P value	R	P value
Body surface area	*0.770*	*<0.001**	*0.888*	*<0.001**	*0.917*	*0.001**
BW	*0.726*	*<0.001**	*0.800*	*<0.001**	*0.920*	*0.001**

Pearson's correlation, *CT-1; cardiotrophin-1*, CHD; congenital heart disease

Table (9) shows that: CT-1 concentrations are positively correlated with body surface area and birth weight in Macrosomic neonates with CHD (r =0.888, r =0.800 respectively) and Macrosomic neonates without CHD (r =0.917, r =0.920 respectively). **Table (9)**, **Figure (2,3)**

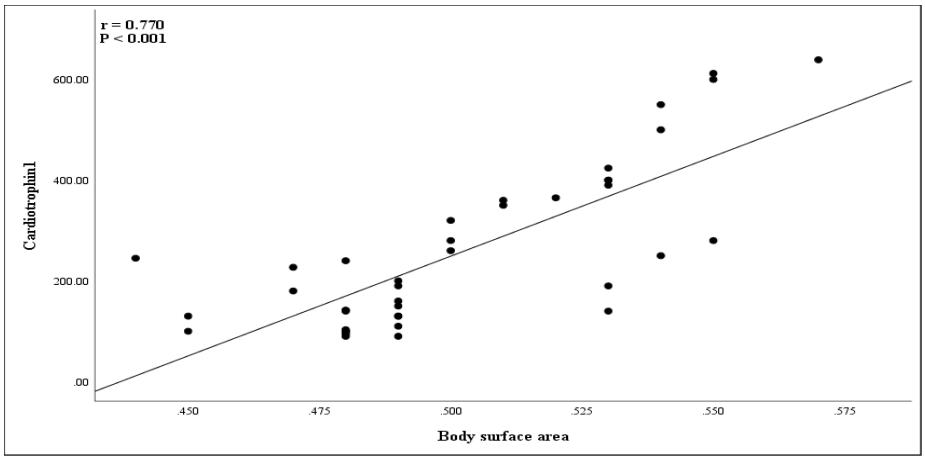

Figure (5) Correlation between cardiotrophin-1 and body surface area in macrosomic neonates

Discussion

Fetal macrosomia, or otherwise large-for-gestational - age (LGA) neonates are applied to a birth weight (BW) between 4000 and 4500g, and BW > 90th percentile for gestational age [1] In developed world the percentage of macrosomia is ranging from 5 to 20% of all births, percentage of fetal macrosomia varied from region to region.[6]

Cardiotrophin-1(CT-1) is member of the interleukin- 6 cytokine family, produced by cardiac myocytes, and plays a fundamental role in fetal heart development; this is up-regulated by hypoxia and inflammation and makes potent hypertrophic action on cardiac cells. It mediates the hyperglycemia/ hyperinsulinemia-induced myocardial hypertrophy, and is actively involved in cardiovascular pathology.[5] Hyperglycemia and hyperinsulinism in utero may lead to fetal hypertrophic cardiomyopathy, affect-ting the interventricular septum and possibly the myocardium, occasionally severely impacting morbidity and mortality. [4]

This is a prospective study that was conducted on 80 full term neonates, 40 of them were macrosomic, and the other were apparently healthy 40 neonates as control. In the current study: in macrosomic neonates males were (28) represent of cases 70% of cases while females were (12) represented 30%; All neonates in our study were full term with range from 37 to 40 week of gestational age, Our results are in accordance with results of [7].

In another study conducted in 2012, on maternal and neonatal outcome of pregnancy with macrosomic neonates, the number of male macrosomic neonates was more than females significantly. Gestational age at birth was significantly higher in macrosomic neonates, and most of macrosomic neonates were post term.[8]

In our study; thirty-two cases (80% of macrosomic neonates) were with congenital heart disease. ASD was the commonest defect, it was present in eighteen cases (56.3%) of macrosomic neonates, PDA in eleven cases (34.4%) of macrosomic neonates, PFO was present in fourteen cases (35%), TR was present in sixteen cases (40%) of macrosomic neonates, Aortic coaractation present in three cases (9.4%), MR five cases (12.5%) of macrosomic neonates. In Controls echo study were normal apart from PFO, trivial TR which are considered normal finding in neonates.

In a retrospective study that was done to confirm the association between birth weight and congenital anomalies in infants, it revealed a significant association where,

macrosomic neonates were more likely to have congenital anomalies than others of AGA (appropriate for gestational age). Infants born with ventricular septal defects, atrial septal defects, ventricular hypertrophy, or anomalies of the great vessels were 1.5–2.5 times more likely to weight ≥4,000 g than were infants without birth defects.[9]

In our study, Echocardiography evaluation of cases, showed a significantly higher **IVSD** in macrosomic neonates compared to control (*Mean ± SD* 0.6±0.2 versus 0.4±0.1 respectively p <0.001) as showed in **.**In a retrospective study done by Pike et al., 2013 on neonates with atrial flutter or ectopic atrial tachycardia,it was found that macrosomic neonates and IDM were the more vulnerable group, in addition to ventricular hypertrophy and left ventricular diastolic dysfunction.[10]

Regarding RVD, it was statistically significantly increased in macrosomic neonates compared to control (Mean ± SD 0.9±0.2 vs. 0.6±0.1 p <0.001), also LVPWD, EF, FS, Lt atrium, Aorta, RT pulmonary were significant higher in macrosomic neonates compared to control. while no differences between the studied groups regarding LVESD, LVEDD, main pulmonary dimensions and LT pulmonary.

This is in agreement with[11] who observed that cardiac diameters were more in macrosomic than control ,also more in macrosomic of IDM than those of non IDM. To the contrary to our results, a study was done by[12] on 9 healthy full term AGA neonates and 15 macrosomic neonates; Echocardiography was done, and showed a similar cardiac measurement in macrosomic neonates and control except mean LVES volume was smaller in macrosomic neonates than in control which resulted in increased FS (fractional shortening),and this could be attributed to a small sample size in their study.

In this study; among macrosomic neonates, IDM represented 65% of cases, whereas those of non-diabetic mother represented 35%. There were no significant differences in cardiac diameters and function between macrosomic neonates of diabetic mothers and non-diabetic mothers. while in a study done on 119 pregnant women whom were divided into three groups; group 1 included 47 pregnant patients with pre gestational diabetes mellitus (DM), group 2 included 40 patients with gestational diabetes and group 3 included 32 non-diabetic pregnant women and echocardiography was done to their neonates, it was found that; IVSD was significantly thicker in the pre gestational diabetes group(mean±SD was 4.49 ± 0.93,4.01 ±0.78, 3.63 ± 0.42 respectively) compared with other groups, but The right and left ventricular shortening fractions were similar in the three groups**.**[13]

On the contrary to our study, IVSD was significantly higher in neonates of uncontrolled diabetic mothers (P < 0.05) while there was no difference found between neonates of controlled diabetic mothers and control group.[14]

Another study was done by[15]**,** and revealed a strong association between maternal diabetes and hypertrophic cardiomyopathy (HCM), especially IVS hypertrophy.

In our study; plasma cardiotrophin-1 level was significantly higher increase in macrosomic neonates compared to +control group p<0.001. This is in agreement with another study on macrosomic neonates, where CT-1 and Titin concentrations were higher in LGA than AGA pregnancies (p<.001 and p¼.023, respectively**).**[1]

In another study, Plasma CT-1 levels in neonates with myocardial injury were significantly higher than those without myocardial injury (249±35 pg/mL vs. 177±26 pg/mL; P<0.01), also it was significantly increase in neonates with hypoxic ischemic encephalopathy (HIE). [16]

Macrosomic was considering as a hypoxic and inflammatory state, and given that CT-1 is up-regulated by both hypoxia and inflammation.[1]

In this study: CT-1 concentrations in cord blood were significantly higher in macrosomic neonates with CHD and

macrosomic neonates without CHD, as compared to Control group (p2 <0.001, p3 <0.001 respectively), A subgroup analysis (in the macrosomic group) showed significant increase in cord blood CT-1 concentrations in macrosomic neonates with CHD, as compared to macrosomic without CHD (p1 =0.029). In previous study that was done in 2010; it showed up regulation of CT-1 in plasma not only in the heart diseases, but also in the pulmonary, renal, gastrointestinal, cerebral, and muscular tissues. It was postulated that CT-1 could also be synthesized and secreted from vascular endothelial cells and adipocytes.[17]

CT-1 has hypertrophic actions on the cardiac myocytes, skeletal muscle cells, and smooth muscle cells. Concentration is increased in various cardiovascular and renal diseases such as hypertension, congestive heart failure, myocardial infarction, valvular heart disease, metabolic syndrome, and chronic kidney disease.[17]

In our study: Subgroup analysis (in the macrosomic group); CT-1 concentrations was significantly elevated in macrosomic neonates of diabetic mothers (Median 280(pg. /mL) as compared to macrosomic of non-diabetic mothers p1<0.001, but still significantly higher in macrosomic neonates of non-diabetic mothers (Median was 280 (pg. /mL)) than in control group p3<0.001. on the other hand[1] observed that a subgroup analysis (in the LGA group) revealed increased CT-1 concentrations only in diabetic pregnancies.

In our study: CT-1 concentrations were positively correlated with Infant RBS at birth R=*0.791*.

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