SUBCLINICAL POSTNATAL CARDIAC CHANGES IN ASYMPTOMATIC INFANTS OF DIABETIC MOTHERS

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ABSTRACT

Background: *Maternal diabetes mellitus carries several significant risks to the fetal heart, even in the absence of structural abnormalities.*

Objectives: *To compare cardiac functions in asymptomatic infants born to mothers either with gestational diabetes (GDM) or pregestational diabetes (PGDM) and to observe changes in the cardiac functions in both groups over the first three months of life.*

Patients and Methods: *The current study was a prospective cohort that was conducted in Ain Shams University Children's Hospital Pediatric Cardiology Unit in conjunction with Obstetrics and Gynecology Hospital Outpatient Clinic during the period between January 2018 till June 2018.*

The study included forty-five infants born to mothers with diabetes; IGDM (Group 1) 13 patients (29%) and IPGDM (Group 2) 32 patients (71%). Transthoracic echocardiography was done to assess systolic functions and diastolic functions. The IDMs were compared to thirty healthy age and sex-matched controls.

Results: *After delivery, no significant difference was observed in cardiac dimensions or systolic functions between cases and controls. However, diastolic functions seemed to be worse in IDMs with significantly longer Tei index ($p = 0.014$) and lower E' ($p = 0.015$) and A' velocities ($p=0.049$). At one month follow-up, infants of PGDM mothers showed worse cardiac functions shown by worse Ejection Fraction (EF) ($p = 0.004$), Fractional shortening (FS) ($p =0.003$), Global Longitudinal strain (GLS) ($p =0.002$) and prolonged Tei index ($p=0.004$). These differences diminished at three months of follow-ups.*

Conclusion: *Asymptomatic infants of diabetic mothers may have diastolic dysfunction despite normal cardiac dimensions and normal systolic functions. Infants of pre-gestational diabetes have worse cardiac functions at one month of age compared to*

infants of gestational DM mothers. These differences in myocardial functions diminish at three months.

Keywords: *Infants of diabetic mothers, Global longitudinal strain, Tie index.*

INTRODUCTION

Diabetes mellitus is a well-established risk for many fetal morbidities and can adversely affect myocardial functions **(Jenny et al., 2017)**.

Although cardiac septal thickening in neonates born to diabetic mothers (IDM) has always been an alarming sign of possible cardiac compromise in these patients, recent evidence suggests subtle myocardial affection that may exist despite apparently normal cardiac dimensions **(Kozák-Bárány et al., 2004)**. Some studies have pointed out to subtle early to late filling velocity disturbances in IDMs denoting possible diastolic dysfunction **(Walther et al., 1985) (Çimen & Karaaslan, 2014)** as well as bidirectional flow across foramen ovale and ductus arteriosus again suggesting the presence of subclinical dysfunction in these patients that may precede myocardial hypertrophy or occurs independent of it **(Katheria & Leone T, 2012) (Hatém et al., 2008) (Zielinsky & Piccoli, 2012)**. Hyperglycemia, even for short periods during pregnancy, is a possible cause of cardiac dysfunction in these patients, probably due to the delirious effects of fetal hyperinsulinism that ensue **(Jenny et al., 2017)**.

AIM OF THE STUDY

The aim of this work was to assess and monitor progression of systolic and diastolic functions in healthy asymptomatic neonates born to diabetic mothers with gestational diabetes or pregestational diabetes.

PATIENTS AND METHODS

I. Ethical considerations:

1. Prior to conducting the study, the ethical approval of Ain Shams University ethical committee was obtained ensuring that the work complies with the principles of the Declaration of Helsinki in 1975.
2. Written informed consent was signed by caregivers before enrolment.
3. All patient's data were kept confidential and care givers had the right to keep them.
4. No conflict of interests existed regarding the research or the publications.

5. No Funds were received to conduct the research.

II. Sample size:

The sample size estimation was done using the Epi Info7 program for sample size calculation, setting the confidence level at 95% and margins of error at 10% and based on the work done by **Sobeih et al., (2020)**, a total of 45 patients was estimated to be sufficient sample size.

III. Inclusion Criteria:

1. Healthy full-term neonates born > 37 weeks gestational age.
2. Neonates born to mothers diagnosed with gestational or known pregestational diabetes were included.

IV. Exclusion Criteria:

1. Preterm neonates born less than 37 weeks of gestation.
2. Full terms born to mothers with complicated pregnancy by elevated blood pressure, cardiac disease, drug intake other than oral hypoglycemic drugs and insulin were excluded.
3. Neonates with structural cardiac abnormalities.

V. Methods:

This comparative cohort was conducted in Ain Shams University Children's Hospital Pediatric Cardiology Unit in conjunction with Obstetrics and Gynecology Hospital Outpatient Clinic during the period between January 2018 till June 2018.

The study was conducted on 45 neonates born to diabetic mothers who were further subdivided into two groups:

Group I: Neonates born to mothers with gestational onset of diabetes (IGDM) (13 patients).

Group II: Neonates born to mothers with pregestational diabetes (IPGDM) (32 patients).

These were compared to:

Group III: Thirty sex and age matched controls.

All patients were randomly selected.

All the studied neonates were subjected to:

A. Full perinatal history was obtained.

B. Full neonatal examination.

C. Echocardiographic examination which was done three times; at <7 days, then at the age of 1 month and again after three months of life. The control group were examined once in the first week of life.

- Conventional Transthoracic echocardiography was performed by a single echocardiographer expert in this field and blinded to subjects. Echocardiography was done using General Electric (GE vivid 9) system with probe 6 MHZ multifrequency transducer; the ECG cable was connected to define and time cardiac cycle.
- Left ventricular M-mode measurements were taken in parasternal long-axis view. Left ventricular dimensions and mass were measured with calculation of left ventricular ejection fraction and fractional shortening **(Lai et al, 2006) (Jafary F., 2007) (Lang et al., 2005)**.
- Tissue Doppler imaging of left ventricle was done to estimate different tissue Doppler velocities including peak systolic S', early and late diastolic velocities E' and A', and accordingly E'/A' were calculated **(Cui & Roberson, 2006)**.

Tei index was calculated as isovolumic relaxation time plus isovolumic contraction time divided by ejection time. Normal range of Tei index in neonates is 0.37 ± 0.06 and 0.35 ± 0.09 from 1 month to 1 year **(Cui & Roberson, 2006)**.

- For 2 D Longitudinal strain, images were obtained using three apical views (long apical axis, apical 4 chambers, & apical two-chamber view), 17 segments were presented, and automated function imaging (AFI) was used that enabled assessment of average LV global systolic strain in the three standard apical views **(Al-Biltagi et al., 2015)**.

Normal values of GLS known from previous literature were taken into consideration. It is reported by **Al-Biltagi et al. (2015)** that GLS in the first two days of life was −19±2%. While in the study of **Bulbul et al. (2015)** GLS was −20.9±2.8 % in the first four days of life.

VI.Statistical analysis:

Analysis of data was done using the software SPSS version 20.0. Data was presented as mean± standard deviation. Categorical data was expressed as percentage. Means were compared by t-test. ANOVA test was used to analyze difference between the means of groups with post hoc analysis in case of significance. Cut off value for significance was P-value <0.05.

RESULTS

Our results are displayed in the following tables:

Table (1): Comparison between control group and infants of diabetics regarding perinatal history

		Control group n = 30	IDM n= 45	P-value	Sig.
GA(weeks) ($\bar{x}\pm$ SD)		38.27 ± 1.11	37.67 ± 1.06	**0.037**	**S**
Birth weight (Kg) ($\bar{x}\pm$ SD)		2.91 ± 0.66	3.08 ± 0.54	0.264	NS
Body surface area (m^2)($\bar{x}\pm$ SD)		0.20 ± 0.03	0.20 ± 0.02	0.373	NS
Mode of delivery	NVD	25 (83.3%)	6 (20.0%)	**0.000**	**HS**
	CS	5 (16.7%)	24 (80.0%)		
Apgar score (Median)		9(8 – 10)	9(8 – 10)	0.073	NS

IDM: infants of diabetic mothers, GA: Gestational age, NVD: normal vaginal delivery, CS: Caesarean section

Table (1) showing highly significant difference between the IDMs and controls regarding mode of delivery, significant difference in gestational age, and no difference in birth weight, surface area or APGAR score at birth.

Table (2): Comparison of Cardiac dimensions between control, IGDM and IPGDM groups at birth

At birth	Control group n = 30	Group I n= 13	Group II n = 32	P-value	P1	P2	P3
IVS (mm) (x̄± SD)	0.58 ± 0.08	0.56 ± 0.05	0.56 ± 0.09	0.733	0.66	0.451	0.904
LVED (mm) (x̄± SD)	1.73 ± 0.31	1.68 ± 0.25	1.64 ± 0.29	0.58	0.67	0.299	0.738
PWT (mm) (x̄± SD)	0.56 ± 0.1	0.57 ± 0.09	0.56 ± 0.09	0.996	0.93	0.972	0.950
LV mass (gm/m^2) (x̄± SD)	8.6 ± 2.63	8.03 ± 3.09	7.89 ± 2.16	0.49	0.67	0.354	0.28
LVFS (%) (x̄± SD)	37.87 ± 5.59	40 ± 5.34	40.43 ± 13.03	0.57	0.53	0.317	0.90
EF (%) (x̄± SD)	70.87 ± 7.06	73.78 ± 6	69.9 ± 13.88	0.30	0.44	0.297	0.14
GLS (%) (Median, IQR)	-15 (-16.8 – -12.7)	-16.1 (-17.8 – -14.2)	-15.9 (-17.9 – -14.3)	0.49	0.37	0.319	0.81
Tei Index (x̄± SD)	0.47 ± 0.12	0.49 ± 0.13	0.58 ± 0.15	**0.014**	**0.026**	**0.018**	**0.004**
LVE`(mm/s) (x̄± SD)	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	**0.015**	**0.035**	**0.035**	0.736
LVA`(mm/s) (Median, IQR)	0.07 (0.06 – 0.07)	0.05 (0.04 – 0.06)	0.05 (0.04 – 0.07)	**0.049**	**0.020**	**0.022**	0.680
LVE`/A (x̄± SD)	0.87 ± 0.24	0.92 ± 0.42	0.92 ± 0.42	0.892	0.988	0.649	0.773
LVS` (mm/s) (Median, IQR)	0.04 (0.04 – 0.05)	0.04 (0.03 – 0.04)	0.04 (0.03 – 0.04)	0.173	0.063	0.281	0.421

IVS: interventricular septum, LVED: left ventricular end diastolic diameter, PWT: posterior wall thickness, LV mass: left ventricular mass, LVFS: Left ventricular fractional shortening, EF: ejection fraction, GLS: global longitudinal strain, LVE`:left ventricular Annular peak velocity during early diastole, LVA`: left ventricular Annular peak velocity during late diastole, LVS`: left ventricular Annular peak velocity during systolic, IGDM: Infants of gestational diabetic mothers, IPGDM: Infants of pregestational diabetic mothers

P1: control group vs group I, P2: control group vs group II, P3: group I vs group II, P value: of P1, P2 and P3

Table (2) showing significantly longer Tei index in IDM (more prominent in infants of PGDM) as well as significantly slower mitral inflow velocities.

Table (3): Comparison of cardiac dimensions between IGDM group and IPGDM groups at the age of 1 month

1 Month	Group I n = 13	Group II n= 32	P-value	Sig.
IVS(mm) ($\bar{x}\pm$ SD)	0.63 ± 0.14	0.62 ± 0.08	0.867	NS
LVED(mm) ($\bar{x}\pm$ SD)	2.14 ± 0.24	2.06 ± 0.32	0.498	NS
PWT(mm) ($\bar{x}\pm$ SD)	0.61 ± 0.09	0.68 ± 0.24	0.382	NS
LV mass (gm/m^2) ($\bar{x}\pm$ SD)	13.9 ± 3.35	13.36 ± 3.5	0.709	NS
LVFS (%) ($\bar{x}\pm$ SD)	41.78 ± 3.83	36.32 ± 4.32	**0.003**	**HS**
EF (%) ($\bar{x}\pm$ SD)	74.89 ± 3.37	68.95 ± 5.15	**0.004**	**HS**
GLS (%) (Median, IQR)	-16.5 (-17.2 – -14.8)	-15 (-16.8 – -12.7)	**0.002**	**HS**
Tei Index ($\bar{x}\pm$ SD)	0.37 ± 0.06	0.48 ± 0.09	**0.004**	**HS**
LVE` (mm/s) ($\bar{x}\pm$ SD)	0.07 ± 0.01	0.06 ± 0.01	**0.046**	**S**
LVA`(mm/s) (Median, IQR)	0.06 (0.06 – 0.07)	0.06 (0.06 – 0.09)	0.489	NS
LVE`/A ($\bar{x}\pm$ SD)	1.18 ± 0.32	0.98 ± 0.32	0.152	NS
LVS`(mm/s) (Median, IQR)	0.05 (0.05 – 0.06)	0.05 (0.05 – 0.06)	0.191	NS

Table (3) showing highly significant difference between IGDM (Group I) and IPGDM (Group II) at 1 month regarding LVEF, FS, GLS and Tei index.

Table (4): Statistical comparison of cardiac dimensions between IGDM group and IPGDM groups at the age of 3 month

At 3 months	Group I n = 13	Group II n = 32	P-value	Sig.
IVS (mm) (x̄± SD)	0.77 ± 0.09	0.69 ± 0.1	0.05	NS
LVED (mm) (x̄± SD)	2.49 ± 0.34	2.28 ± 0.38	0.174	NS
PWT(mm) (x̄± SD)	0.78 ± 0.15	0.72 ± 0.14	0.294	NS
LV mass (gm/m^2) (x̄± SD)	17.83 ± 4.12	16.35 ± 2.51	0.283	NS
LVFS (%) (x̄± SD)	35.22 ± 5.63	37.5 ± 3.98	0.249	NS
EF (%) (x̄± SD)	66.22 ± 7.28	69.69 ± 4.74	0.162	NS
GLS (%) (Median, IQR)	-18.6 (-20 – -14.8)	-17.2 (-18 – -15.55)	0.427	NS
Tei Index (x̄± SD)	0.42 ± 0.08	0.45 ± 0.14	0.668	NS
LVE`(mm/s) (x̄± SD)	0.09 ± 0.02	0.08 ± 0.02	0.199	NS
LVA`(mm/s) (Median, IQR)	0.07 (0.06 – 0.06)	0.07 (0.05 – 0.09)	0.223	NS
LVE`/A (x̄± SD)	1.43 ± 0.24	1.19 ± 0.45	0.162	NS
LVS`(mm/s) (Median, IQR)	0.06 (0.05 – 0.06)	0.06 (0.05 – 0.06)	0.269	NS

Table (4) shows no significant difference between the two groups at 3 months regarding cardiac dimensions and functions.

DISCUSSION

Cardiac functions in fetuses and infants born to diabetic mothers with evidence of septal hypertrophy and increased left ventricular masses have been studied before. Little is known about the cardiac functions of IDMs with apparently normal cardiac dimensions **(Jenny et al., 2017)**. In the current study, a group of forty-five infants of diabetics was compared to thirty age and sex-matched controls of neonates born to non-diabetic mothers. The IDMs were further divided into infants born to diabetic mothers with gestational diabetes (n=13, 28%) and those born to mothers with pre-gestational diabetes (n=32, 72%). At birth, although cases were asymptomatic and completely healthy neonates with no evidence of cardiac hypertrophy, their diastolic functions were significantly lower than those observed in controls. On one month follow-up, infants of gestational diabetes mothers

seemed to recover at a faster rate with significantly better systolic and diastolic functions than that observed in infants of pregestational diabetics. This difference in cardiac functions diminished at six months of follow-up.

In our study, no significant difference was observed between cases and controls regarding left ventricular dimensions, septal wall thickness and LV mass, which gives the impression of normal cardiac structure in these neonates. On the Assessment of systolic functions, again, no significant difference was observed using the conventional method of assessment of EF and FS as well as with advanced assessment using Global longitudinal strain. This agrees with **Sevket et al (2014)** who compared infants of mothers with GD to controls and found no difference in systolic functions. However, our results contrast that of **Al-Biltagi et al (2015)** who compared infants of pregestational and gestational diabetes mothers to controls but selected a population with significantly higher septal thickness when compared to controls and consequently had worse global strain rate on speckle tracking, denoting worse systolic functions.

Unlike S' velocity, which reflects systolic functions, decreased E' velocity is an early indication of diastolic dysfunction **(Gulati et al. 1996) (Ichihashi et al., 2011)**. On assessment of diastolic functions, cases had significantly lower E' and A' velocities and a significantly longer Tei index denoting worse diastolic functions. In addition, on comparing infants with gestational to pregestational diabetes, the latter showed worse functions with a significantly longer myocardial performance index. The idea of worse diastolic functions in infants of diabetics has been studied before. However, the diastolic functions were associated with grossly hypertrophied septa and increased left ventricular masses in those neonates **(Gulati et al. 1996) (Çimen & Karaaslan, 2014)**. In his study, **Zablah et al. (2017)** found that IDMs had lower S' velocity ($p \leq 0.03$) and slower E' ($p < 0.001$) velocities with higher E/E' ratios ($p < 0.001$) than controls, signifying lower diastolic functions which comes in concordance to our results. Also, **Sevket et al. (2014)** suggested impaired diastolic functions in infants of GDM compared to controls, yet, there was no comparison to infants of pre-gestational diabetics. Slower velocity of E' is related to left

ventricular torsion and hence is an early indicator of diastolic dysfunction. Sometimes the decreased E' velocity is accompanied by increased A' velocity, resulting in decreased E'/A' ratio reflecting further affection of diastolic functions. Such changes have been observed in IDM in the study of **Çimen & Karaaslan (2014)**, who had one-third of involved cases showing evidence of septal hypertrophy, but this was not the case in our cases, denoting milder affection of diastolic functions.

Although cardiac functions in neonates born to diabetic mothers, either with or without left ventricular hypertrophy, have been an area of interest, very few studies followed up changes in cardiac function that ensue in these neonates over the first few months of life. In our study at one-month follow-up, cardiac functions of infants of gestational diabetes mothers seemed to improve, unlike infants of PGDM mothers who showed deterioration of cardiac functions evidenced by lower EF, FS, GLS, prolonged Tie index and slower E' velocity when compared to GD infants. On three months follow up, this difference in diastolic functions disappeared. The slow recovery of myocardial functions may be related to the fact that babies born to mothers with pre-gestational diabetes suffer the early effect of hyperglycemia when compared to gestational diabetes, which usually starts later in pregnancy. Also, the idea of transient prolongation of the Tei index in infants of diabetics has been observed by **Bogo et al. (2020)** who explained this by the dynamic changes in maturation and myocardial performance at the end of pregnancy.

CONCLUSIONS

Infants of diabetic mothers with no cardiac hypertrophy still suffer diastolic dysfunction. This occurs in infants of gestational or pregestational diabetic mothers. The latter suffer a more significant delay in the recovery of myocardial functions.

Recommendation

Echocardiographic examination of systolic and diastolic functions is mandatory in all infants born to diabetic mothers even in absence of hypertrophic cardiomyopathy. Close follow up over the first few months of life is needed in these infants for possible deterioration especially in presence of pre-gestational diabetes in mothers.

LIMITATIONS OF THE STUDY

The current study has been limited by small number of patients in the subgroups which

may have hindered exploring small differences in variables. Furthermore, lack of control group at 1 month and 3 months limited our ability to define progression of cardiac dimensions and functions in normal neonates. In addition to the limitations encountered in the different modalities used namely the tissue Doppler and speckle tracking in neonates with high heart rate.

REFERENCES

1. **Al-Biltagi M, Tolba O, Rowisha M, et al. (2015):** Speckle tracking and myocardial tissue imaging in infant of diabetic mother with gestational and pregestational diabetes. Pediatr Cardiol., 36(2):445–453.
2. **Bogo M, Pabis J, Bonchoski A, et al. (2020):** Cardiomyopathy and cardiac function in fetuses and newborns of diabetic mothers. J Pediatr (Rio J). ,97(5):520-524. doi: 10.1016/j.jped.2020.10.003. Epub 2020 Nov 8. PMID: 33176166; PMCID: PMC9432014.
3. **Bulbul Z, Issa Z, Siblini G, et al. (2015):** Normal Range of Left Ventricular Strain, Dimensions and Ejection Fraction Using Three-dimensional Speckle-Tracking Echocardiography in Neonates, Journal of Cardiovascular Echography. 25(3):67-71. doi: 10.4103/2211-4122.166074. PMID: 28465937; PMCID: PMC5353409.
4. **Çimen D and Karaaslan S (2014):** Evaluation of cardiac functions of infants of diabetic mothers using tissue Doppler echocardiography. Turk Ped Ars., 49:25–29.
5. **Cui W, and Roberson D (2006):** Left Ventricular Tei Index in Children: Comparison of Tissue Doppler Imaging, Pulsed Wave Doppler, and M-Mode Echocardiography Normal Values; Journal of the American Society of Echocardiography, 19(12):1438-45. doi: 10.1016/j.echo.2006.06.006. PMID: 17138026.
6. **Gulati V, Katz W, Follansbee W, Gorcsan J. (1996):** Mitral annular descent velocity by tissue doppler echocardiography as an index of global left ventricular function. Am J Cardiol. ,77: 979–82.
7. **Hatém M, Zielinsky P, Hatém D, et al. (2008):** Assessment of diastolic ventricular function in fetuses of diabetic mothers using tissue Doppler. Cardiol.

Young, 18(3):297–302.

8. **Ichihashi K, Sato A, Shiraishi H, et al. (2011):** Tissue Doppler combined with pulsed-wave Doppler echocardiography for evaluating ventricular diastolic function in normal children. Echocardiography, 28:93–6.
9. **Jafary F. (2007):** Devereux formula for left ventricular mass--be careful to use the right units of measurement. J Am Soc Echocardiogr.,20(6):783. doi: 10.1016/j.echo.2007.02.034. PMID: 17543757
10. **Jenny E, Dorota G, Guillaume S, et al. (2017):** Subclinical Decrease in Myocardial Function in Asymptomatic Infants of Diabetic Mothers: A Tissue Doppler Study Pediatr Cardiol., 38(4):801-806. doi: 10.1007/s00246-017-1584-y. Epub 2017 Feb 14. PMID: 28197645.
11. **Katheria A, Leone T (2012):** Altered transitional circulation in infants of diabetic mothers with strict antenatal obstetric management: a functional echocardiography study. J perinatol., 32:508–513.
12. **Kozák-Bárány A, Jokinen E, Kero P, et al. (2004):** Impaired left ventricular diastolic function in newborn infants of mothers with pregestational or gestational diabetes with good glycemic control. Early Hum Dev., 77(1–2):13–22.
13. **Lai W, Geva T, Shirali G, et al. (2006):** Task Force of the Pediatric Council of the American Society of Echocardiography; Pediatric Council of the American Society of Echocardiography. Guidelines and standards for performance of a pediatric echocardiogram: a report from the Task Force of the Pediatric Council of the American Society of Echocardiography. J Am Soc Echocardiogr.,19(12):1413-30. doi: 10.1016/j.echo.2006.09.001. PMID: 17138024.
14. **Lang R, Bierig M, Devereux R, et al. (2005);** Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification

Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. ,18(12):1440-63. doi: 10.1016/j.echo.2005.10.005. PMID: 16376782.

15. **Sevket B, Feyza A, I˙brahim E, et al. (2014):** Assessment of Cardiac Functions in Fetuses of Gestational Diabetic Mothers, Pediatr Cardiol., 35:30–37.

16. **Sobeih A, Sakr M& Abolmaaty R. (2020):** Assessment of cardiac diastolic function in infants of diabetic mothers using tissue Doppler echocardiography. Egypt Pediatric Association Gaz., 68, 10 https://doi.org/10.1186/s43054 -020-00021-3

17. **Walther FJ, Siassi B, King J, et al. (1985):** Cardiac output in infants of insulin-dependent diabetic mothers. J Pediatr., 107(1):109-14. doi: 10.1016/s0022-3476(85)80630-2. PMID: 4009327.

18. **Zablah J, Gruber D, Stoffels G, et al. (2017):** Subclinical Decrease in Myocardial Function in Asymptomatic Infants of Diabetic Mothers: A Tissue Doppler Study. Pediatr Cardiol. ,38(4):801-806. doi: 10.1007/s00246-017-1584-y. Epub 2017 Feb 14. PMID: 28197645.

19. **Zielinsky P and Piccoli A (2012):** Myocardial hypertrophy and dysfunction in maternal diabetes. Early Hum Dev., 88(5):273–278.