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*Corresponding author

*Andrea Surányi, M.D., Ph.D, Department of Obstetrics and Gynecolgy, Albert Szent-Györgyi Medical School, University of Szeged, Szeged,(Csongrád-Csanád), Hungary
Email: gaspar-suranyi.andrea@med.u-szeged.hu

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Cardiac Function, Fetus, Gestational Diabetes Mellitus, Pregnancy, Prenatal Ultrasound

*List of Abbreviation

BMI: body mass index
EDV: end-diastolic volume
EWF: estimated fetal weight
GDM: gestational diabetes mellitus
IRDS: infant respiratory distress syndrome
IUGR: intrauterine growth restriction
NIC: neonatal intensive centre
OGTT: oral glucose tolerance test
PI: pulsatility index
PSV: peak systolic velocity
SD: standard deviation
UH: ultrasound
Vmean: mean volume of systolic and diastolic velocities
WHO: World Health Organisation

Original Research

The Examination of Fetal Myocardium and Maternal and Fetal Features of Pregnancy Complicated by Gestational Diabetes Mellitus

Zoltán Pál[1], Zsófia Kádas[1], Zoltán Kozinszky [1,2]*, Andrea Surányi [1]*

[1]*Department of Obstetrics and Gynecolgy, Albert Szent-Györgyi Medical School, University of Szeged, Szeged,(Csongrád-Csanád), Hungary*
[2]*Capio Specialized Center for Gynecology, Solna, 171 45, Stockholm, Sweden*
**These authors contributed equally*

Abstract

Purpose: We examined the morphological factors affecting the growing foetus' heart, the fetal and maternal relations of pregnancies complicated by diabetes mellitus. We seaked the severity of myocardium hyperplasia is in correlation with infant respiratory distress syndrome and cardiac failure. Our study was a prospective case- control study of pregnancies complicated by diabetes mellitus produce fetal myocardium hyperplasia.

Methods: Two ultrasound examinations were carried out on 84 pregnant women, in accordance with the selection criteria (different types of diabetes mellitus and controll cases).

The first ultrasound examination was carried out between the 24-28th weeks, the second between the 33-38th weeks of pregnancy. During the examinations we measured and averaged the fetal sizes, the estimated fetal weight, the quantity of amniotic fluid and the thickness of the ventricles and interventricular septum. Besides, we collected data from pregnant women in connection with the symptoms of diabetes mellitus, plus followed the outcome of these pregnancies. We compared these data against the our control group and a literature reference group.

Results: Regarding the fetal myocardium and the interventricular septum, significantly higher values were registered compared to the control group, and 21% of the infants are macrosomic, 16% of them were born with intrauterine growth restriction.

Conclusions: Based on the examinations we concluded that more complications occurred to foetuses and infants of obese pregnant women and those with diabetes mellitus than in the control groups. Thus, following the fetal myocardium's parameters in the perinatal outcome of the mother's glucose system's discrepancies can be a well-applicable filtering method.

Introduction

Diabetes mellitus has become an endemic disease. While the occurrence of Types 1 and 2 in fertile women is 0,5-1,0% [1,2], gestational diabetes mellitus(GDM) diagnosed during pregnancy is present in 10-30% in Europe [1,2], making it the most common medical complications during pregnancy [3,4,5]. Showed an increase in the GDM incidence from 12.4% in 2009 to 18.5% in 2017 in Hungary [5].

In our research we highlighted the examination of the relation between the fetal myocardium and the GDM. In case of GDM, the development of temporary fetal myocardium hyperplasia occurs in approximately 25%, the severity of which is in direct proportion to infant respiratory distress syndrome (IRDS), as well as to atonic cardiac failure [6].

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The mail goals of study are:

1) Our main objective is the examination of fetal myocardium, since we wished to examine he prevalence in case of diabetic pregnant women in Hungarian population, too. We prepared the ultrasound examinations twice: in 2nd and 3rd trimester. Therefore we want to seek the first detection date of myocardial problem.

2) Follow-up of fetal biometric parameters and complications.

3) Analysis of circulatory relations of uterinal and umbilical arteries.

4) Registration of infancy adapting phenomena.

Consequently, in our study we wish to elaborate on and summarise the experiences and findings registered during our research: the effects of various forms of obesity and diabetes mellitus on fetal myocardium compared to pregnancies without complications, including our control group and ones listed in the literature. With the help of our research, we would like to call attention to these, possibly severe pathological processes and to help preserve the health of pregnant women and their children to be born.

Material and method

As a result of our research, altogether 84 pregnant women were included in our examinations during a year period. We looked for participants amongst prenatal care- and hospitalised patients at the Obstetrics and Gynaecology Clinic, University of Szeged, based on the criteria set. The pregnancies were separated into two groups: a normal control group (n=44) and an GDM group (n=40).

Material and method/ Documentation

After orientation and reading an Ethical Committee-approved patients' guide, the participating pregnant women signed a document of consent, then they filled in a datasheet related to their pregnancy and diabetes mellitus, while having an in-depth conversation.

Material and method/ Ultrasound examination

Two ultrasound examinations were carried out: one between the 24-28th, and one between the 32-38th weeks of pregnancy. The abdominal ultrasound examination in the 2nd and 3rd trimesters in two-dimensional B and M mode.

Material and method/ Ultrasound examination/Fetal parameters, biometry

For two-dimensional ultrasound a Voluson E10 ultrasound machine (GE Medical Systems), and a RAB 2-5 MHz convex transducer were applied. The estimated fetal weigh : with Hadlock B formula [7], with a computer programme, based on the values of biparietal diameter, fronto-occipital diameter , head circumference, abdominal circumference, femur length .

Material and method/ Ultrasound examination/Quantity of amniotic fluid

Its measuring takes place by applying the amniotic fluid pocket method, i.e., the distance between the body and the uterus muscle is measured in accordance in four quadrants. This provides the amniotic fluid index, according to which 1 cm distance equals the quantity of 30 cm3 amniotic fluid [8].

Material and method/ Ultrasound examination/ Fetal cardio-ultrasound

The targeted time of the fetal cardio-ultrasound is dated between the 18-23rd weeks of pregnancy [9]. Nevertheless, the focus of this research is gestational diabetes mellitus and obesity as risk factors making the fetus' heart susceptible to development disorders, which can basically be mostly detected from the end of the second trimester [6], measurements were implemented from the 24th gestational week.

The basic heart-examination happens in 4-chamber view flat, when M-mode shaft is perpendicular to the interventricularis septum, at the height of the apex of bi- and tricuspid valves. The thickness of the interventricularis septum and the cardiac chamber can also be defined with this method [6,9].

The two atriums are around the same size in physiological cases, just as the two ventricles are approximately of the same size. The ventricular septum widens towards the apex cordis. In a healthy fetus its thickness grows proportionately with the advance of pregnancy, however, in pathological cases like maternal diabetes mellitus it may thicken [6].

Material and method/ Ultrasound examination/ Flowmetria

We examined the flow parameters of the uterinal and umbilical arteries by analysing the wavelength appearing on screen, especially the pulsatility index (PI) [10].

Material and method/ Selection criteria of pregnant women who meet GDM criteria

Hungary accepted the FIGO2013/AIDPSG 2013/ WHO 2013 guidelines for diagnosing GDM [5,11,12]. They are in the 18-45 age range, singular pregnancy, no anatomic development disorder detected by ultrasound, no chromosome mutation

Material and method/ Exclusion criteria

Mother's age under 18 or over 45, multiple pregnancy, anatomic development disorder detected by ultrasound.

Material and method/Data collection about newborns

Collecting data from MedSolution's registered data of patients prospectively.

Material and method/ Data analysis

Analysing the received data with PSPP computer programme (version: 0.10.2, year of release: 2016), descriptive statistics and calculations with the help of single-sample t-probe. Furthermore, making charts with Microsoft Office Excel 2016 and Plotly 2016 programmes. The significancs level was p=0.05.

Results

In the following subpoints we am going to review our results and findings based on the examinations carried out during the research. We applied percentage- and average calculations, the sign ± indicated after the average score means standard deviation (SD).

Results/ Description of pregnant women based on the completed datasheets

Altogether 84 pregnant women were examined. The maternal data see in Table 1a.

In GDM cases 5% of the pregnant woman included in our examinations, on the basis of BMI-classification defined by the [13], were slightly thin, 35% of them of normal weight, 15% overweight, 30% first-degree obese and 15% second-degree obese.

Regarding insulin therapy, it must be mentioned that 75% of pregnant women received medication in addition to being on a carbohydrate diet. As for the remaining pregnant women, in 50% of the cases pathological complications occurred, such as IUGR, pathological flow of uterinal artery and premature birth.

100% of them apply a carbohydrate diet, while 75% of them also need insulin therapy.. Also, 75% of them can register diabetes mellitus in their family anamnesis.

Results/ The results of ultrasound examinations

Comparing the interventricular septum's average and standard deviation (0,42cm±0,13), examined by fetal cardio-ultrasound in gestational weeks 24-28, to the average and standard deviation (0,25cm±0,07) of the our control goup, we found significant discrepancy (p=0,045). We compared our control group with control group mentioned in the literature,[14], there was no significantly alteration (p=0,092). (see Figure 1)

Simultaneously measuring average and standard deviation (0,65cm±0,25) of the left ventricle's muscle's thickness, we did not find significant discrepancy (p=0,053) compared to the average and standard deviation (0,26cm±0,07) of the our control group. We compared our

Table 1a: *Maternal characteristics*

Maternal characteristics	normal cases (N=40)	GDM cases (N=44)	p value
Maternal age (years)	30.6 ± 4.95	33.85±5,90	N.S.
BMI (kg/m^2)	23.4 ± 4.25	28,34±5,91	0,05
Nulliparous women (%)	50,00	27,00	0,01
Gestational age at 2nd trimester ultrasound examination (weeks)	26.8 ± 2.22	27.2 ± 2.87	N.S.
Gestational age at 3 rd trimester ultrasound examination (weeks)	34± 2.17	35± 3.87	N.S.

Table 1b: *Neonatal characteristics*

Neonatal characteristics	Normal cases (N=40)	GDM cases (N=44)	p value
Gestational age at birth (weeks)	38.9 ± 3.20	36.7 ± 5.15	0,04
Birth weight (grams)	3355.7 ± 517.15	3253,16±848,42	0,00
Birth weight (percentile)	52,00	86,00	0,00
5-minute Apgar score < 7 (%)	2,00	15,00	0,00
Umbilical cord arterial pH <7.2 (%)	3,30	21,00	0,00
Admission to NICU[1] (%)	11.33	39,70	0,00
Short-term adverse perinatal outcome[2] (%)	12.67	32,00	0,00
caesarean section. (%)	12,00	85,00	0,00
gender of newborn (female(%))	47,00	63,00	0,03

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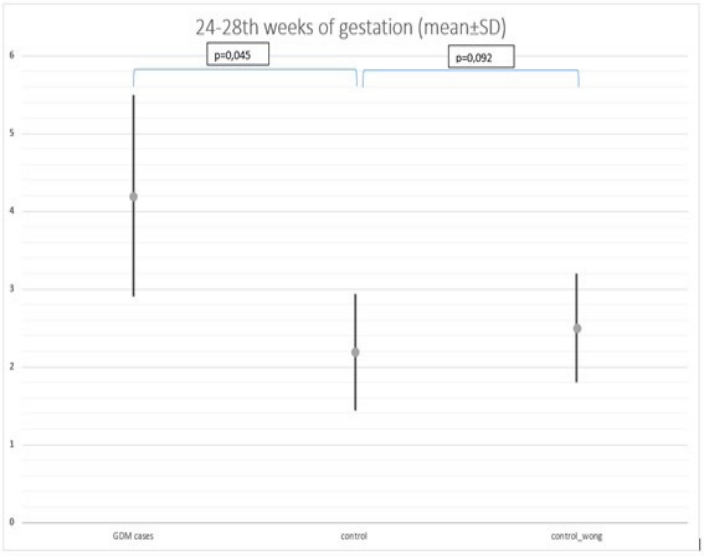

Figure 1: *Measurement of intraventricular septum in four-chamber view using M-mode (24-28th gestational weeks). Control_Wong [14].*

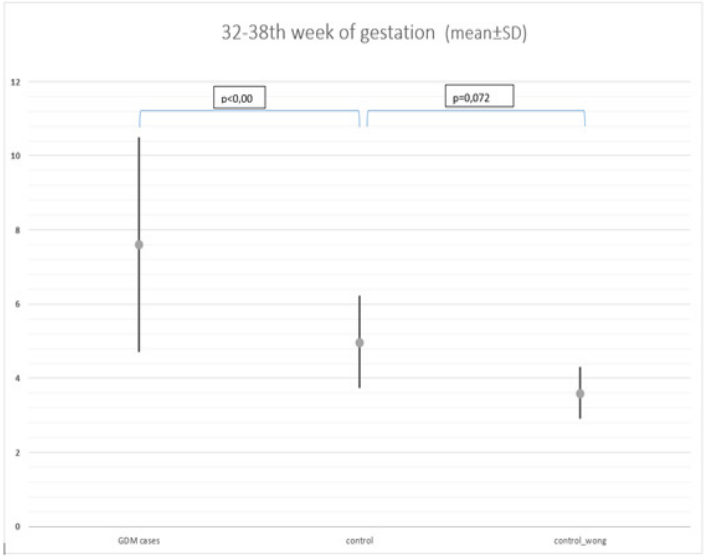

Figure 2: *Measurement of intraventricular septum in four-chamber view using M-mode (32-38th gestational weeks). Control_Wong [14]*

control group with control group mentioned in the literature [14], there was no significantly alteration (p=0,067).

The interventricular septum's average and standard deviation (0,76cm±0,29) examined in gestational weeks 32-38 significantly differs (p<0,001) from the average and standard deviation (0,36cm±0,07) of the our control goup and the control group (N=44) mentioned in the literature[14] (see Figure 2). We compared our control group with control group mentioned in the literature[14], there was no significantly alteration (p=0,072).

Simultaneously measured average (0,99cm±0,53) of the left ventricle's muscle's thickness (N=14) shows significant discrepancy (p=0,001) compared to the average (0,42cm±0,12) of the control group (N=41) mentioned in the literature by Wong et al [14].

During the first ultrasound examinations (24-28th weeks), neither the quantity of the amniotic fluid, nor pathological flow of umbilical and uterinal arteries could be registered.

However, during the examinations in the 32-38th gestational weeks 11% of the GDM cases showed an increased amount of amniotic fluid and 16,67% showed pathological flow of uterinal artery.

Results/ Results regarding infants

The newborns characteristics data are in Table 1b. We realized higher frequency in caesarean section (85% vs normal 12%) and the female gender (63% vs normal 47%) in GDM cases.

Comparing the birth weights to the given gestational week, they fall into three categories: IUGR below 10 percentiles, macrosomia over 90 percentiles, between the two ranges the infant is of normal weight [15,16].

63% of them were born with normal weight, 21% were macrosomic infants and 16% were born with IUGR.

Based on their weight before pregnancy, out of first-degree obese pregnant women, 50% were diagnosed with GDM. 33% of ones with GDM gave birth in due time to normal-weight infants, while in cases (16%) of the pathological flow of uterinal artery was registered and gave birth as a premature infant needing transportation to neonatal intensive centre.

In summary, 75% of the newborns with IUGR had pathological Apgar-scores, while 25% of the macrosomic infants received a score of 7 in the first minute, but on the whole, their condition was stabilised after 5 and 10 minutes of the delivery.

The average value of their umbilical cord's pH is 7,24±0,14.

15% of them had to be transported to NIC due to perinatal complications (meconium aspiration, acute intrauterine distress).

Discussion

During the measuring process we utilised many advantages of the ultrasound equipment: all structures to be examined could be placed into the field of vision quickly and precisely, without invasion or danger.

Discussion/ Fetal cardio disorders

Measurements were implemented in the two indicated intervals, because in case of gestational diabetes mellitus,

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visible thickening of the interventricular septum in the fetus can be expected from the end of the second trimester, which may result in hypertrophic cardiomyopathy [6].

During our measurements we did register thicker interventricular septum and left chamber hypertrophy in the second trimester, but the mutations became more significant in the third trimester. In that period, we registered a significantly greater average value regarding the intraventricular septum, however, as opposed to [6,14] description.

The consequence of fetal hypertrophic cardiomyopathy was that 15% of the new-born infants had to be transported to NIC, and they received the worst Apgar-scores.

Discussion /Other disorders connected to maternal diabetes mellitus

The eastern region presented the highest GDM prevalence (14-31%) in Europe. GDM prevalence was 2.14-fold increased in pregnant women with maternal age ≥30 years (versus 15-29 years old), 1.47-fold if the diagnosis was made in the third trimester (versus second trimester), and 6.79- fold in obese and 2.29-fold in overweight women (versus normal weight) [17].

Diabetes already diagnosed before or during pregnancy, or greater than 28 kg/m2 BMI before pregnancy imposes triple risk on the development of congenital growth disorder. The risk of this is further enhanced by the increase of BMI [18].

In the second and third trimesters of pregnancy, the most common complication of pathologically high maternal blood-sugar level is macrosomia. As opposed to this, the occurrence of IUGR infants is more likely for mothers already diagnosed with diabetes mellitus before their pregnancy, the reason of which is the existence of maternal vascular damage for years [19].

However, during our measurements 75% of macrosomic infants, occurrent in 25%, were delivered by a mother with GDM. 100% of the IUGR infants, occurrent in 16%, were delivered by mothers with GDM.

The flow of umbilical artery was within normal range in all cases. In connection with the pathological flow of uterinal artery all of the notches was complicated by IUGR.

We measured a pathological excess of amniotic fluid in some in 3rd trimester.

Complications concerning pregnant women and fetuses alike were present amongst, according to BMI-categorisation, normal weight, overweight and first-degree obese individuals.

Complication can be caused by GDM [6], its appearance can mostly be expected from the end of the second trimester. The cardiac thickening is asymmetric, and primarily concerns the interventricularis septum's left ventricle-side. Its danger is that it may obstruct the left heart ventricular outflow. However, the mutation is mostly benign and regresses by the sixth month after birth [6].

All pregnant women gave birth at the Obstetrics and Gynaecology Clinic of the University of Szeged, therefore, after analysing the deliveries we can conclude, taking the pre-pregnancy BMI-values into consideration, that 100% of the pregnant women of normal body weight presented some kind of complication during pregnancy, in case of overweight pregnant women, a pathological state was registered in 66,67%, while amongst first-degree obese women an occurrence of complication was experienced in 50%.

Based on a research by Yeh et al. [20], the ideal pH-value of the umbilic artery's blood is 7.26-7.30, when the risk of unfavourable neurological outcome is the lowest. The worst umbilical pH were measured in GDM group, 31 % were in obes pregnancies with GDM.

Conclusion

Based on our examination, we can conclude that although we experienced conditions differing from physiological among normal body weight pregnant women with diabetes mellitus many times, but when diabetes is present with obesity, there is a greater risk of complications concerning the pregnant woman, the fetus and the infant.

The low number of elements between gestational weeks 24-28 is probably the explanation to why we did not experience significant discrepancy regarding intraventricular thickness, but during the measurements between gestational weeks 32-38, the average thickness of interventricular septum and left chamber walls are significantly greater in fetuses of pregnant women with complicated by GDM.

The notion that complications occurred, even cumulatively, in case of pregnant women treated with insulin just as much as to those not treated with insulin, further supports the fact that maternal blood sugar level must be kept under regular control and modified by therapy if any complication is detected during fetal cardio-ultrasound examinations.

Thus, following the fetal myocardium's parameters in the perinatal outcome of the mother's blood glucose system's discrepancies can be a well-applicable filtering method. It is suitable for early detection of complications, therefore their degree and proportion can be favourably influenced in prenatal existence.

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What is Known

It is already known that carbohydrate intolerance develops often during pregnancy. In diabetic pregnancies, the high serum glucose level can affect fetal carbohydrate metabolism and have influence on fetal heart growth.

What is New

It is the first prospective case-controll study to investigate the fetal myocardiumin in second and third trimesters in pregnancies complicated by gestational diabetes mellitus. Our puropuse was to determine the early detection intervall for fetal myocardial disfunction.

Ethics approval: Our study protokoll has been reviewes and approved by the institutional research ethics committee (Human Investigation Review Board, University of Szeged, Szeged, Hungary, H-6701 P.O.Box:427). Ethical registration number: 237/2015-SZTE.

All procedures followed in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000.

Consent to participate: Written informed consent to participate in the study were obtained from all participants.

Conflict of Interest Statement: The authors report no conflicts of interest.

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Author Contributions: Each author's participation in the manuscript. All authors have read and approved the manuscript.

Z.P: ultrasound investigation, data collectin, manuscript editing and revision

Zs.K. data collection, statistical analysis, manuscript revision

G.N: project development, manuscript revision

A.S: project development, study design, ultrasound investigation, manuscript writing and editing

Data Availability Statement: All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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