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Altered Right Portal and Umbilical Vein Doppler Parameters in Fetal Macrosomia Resulting from Pregestational and Gestational Diabetic Mothers: A Prospective Case-Control Study

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ABSTRACT Objective: To evaluate the blood flow of the umbilical vein and right portal vein in macrosomic fetuses of diabetic mothers and investigate the effect of maternal insulin treatment on these blood flows. **Material and Methods:** This prospective case-control study was conducted between March 2019 and December 2019. Fetuses of the 49 pregestational and gestational diabetic mothers who had an abdominal circumference percentile above 97% were evaluated as macrosomic and formed the study group. The study group was divided into two subgroups: patients treated with insulin and those who did not. In the control group, 48 non-diabetic pregnant women with matched gestational weeks whose fetuses are at the 10-90% percentile were included. Time-averaged maximum blood velocity (TAMXV) values of the right portal vein and the free loop of the umbilical vein were measured. **Results:** The median right portal vein TAMXV value and umbilical vein TAMXV value were found to be significantly higher in diabetic pregnancies (16.25 cm/s, and 15.28 cm/s, respectively) than in the control group (12.76 cm/s, and 13.38 cm/s, respectively, $p<0.001$). Umbilical and right portal vein flows were similar in macrosomic fetuses of diabetic mothers who were treated with insulin or those who did not. While umbilical vein flow in macrosomic fetuses increased as the gestational age progressed ($p=0.028$), it was observed steadily in normally growing fetuses. **Conclusion:** The umbilical and right portal vein flows are higher in macrosomic fetuses of diabetic mothers than in appropriately grown fetuses. Maternal insulin treatment does not affect fetal umbilical vein and right portal vein blood flow in macrosomic fetuses.

Keywords: Gestational diabetes mellitus; diabetes mellitus Type 2; portal vein Doppler parameters; fetal macrosomia

Since the umbilical vein is the only source that brings nutrients and oxygen from the placenta to the fetus, it deserves intense attention, and the unique blood distribution after entering the abdomen has been studied with great care by researchers who are highly experienced in this field. In these studies, firstly, the anatomical relation of the umbilical cord to the portal system and ductus venosus after entering the abdomen in normal fetuses, and then the functional blood distribution was investigated.[1-3] After explaining the physiologic blood distribution, Doppler investigation of these vessels has been performed in some fetal disorders such as fetal growth restriction (FGR) and macrosomia, where these vessels' blood flow may be theoretically affected.[4-8]

The left portal vein is dominant because it is the continuation of the umbilical cord in fetal life and portal vein studies have mostly focused on the left portal vein.[6,9] Fetal abdominal circumference (AC) is important in the diagnosis of fetal macrosomia and FGR and the estimation of fetal weight. The size of the AC is directly related to liver mass and the right liver lobe is also of great importance. Previous studies demonstrated that the venous perfusion of the

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liver is reduced in FGR cases. They also showed that in some extreme cases of FGR, the right portal vein received the blood from the main portal vein, and almost no blood was given from the umbilical vein.[10] In fetal life, the right portal vein receives blood from both the umbilical vein and the main portal vein. Therefore, in this study, we aimed to investigate the fetal umbilical vein and right portal vein blood flow in macrosomic fetuses of diabetic mothers and to investigate whether insulin treatment affects fetal umbilical vein and right portal vein blood flow.

MATERIAL AND METHODS

The prospective case-control study was conducted at the Kanuni Sultan Süleyman Training and Research Hospital between March 2019 and December 2019. Ethical approval for the study was provided by the Kanuni Sultan Süleyman Training and Research Hospital's institutional review board (date: 22.03.2019, no: 2019/03/58). This study was conducted in accordance with the Declaration of Helsinki ethical principles. We obtained written informed consent from all participants. Fetuses of the 49 diabetic mothers who applied to the perinatology clinic and had an AC percentile above 97% according to the week of gestation were evaluated as macrosomic and formed the study group. The study group was divided into 2 subgroups: patients treated with insulin and those who did not. Twenty-nine participants had gestational diabetes mellitus (GDM) and 20 participants had pregestational DM; of these pregestational DM cases, 3 patients had Type 1 DM and 17 patients had Type 2 DM. All pregestational DM cases and 8 GDM cases received gestational insulin treatment. In the control group, 48 pregnant women with matched gestational weeks whose fetuses with the AC percentiles between 10-90% were included.

Pregestational diabetes was defined as Type 1 or Type 2 DM that existed before pregnancy. GDM was defined as glucose intolerance that is first detected during the second trimester of pregnancy by a 75-g oral glucose tolerance test. We diagnosed GDM based on at least one abnormal glucose value, as follows: a fasting plasma glucose ≥92 mg/dL, a 1-hour value of ≥180 mg/dL, or a 2-hour value of ≥153 mg/dL.[11]

Cases with gestational hypertensive disorders were excluded from the study since this pregnancy complication might affect fetal growth.[12,13] All pregnant women with chronic diseases other than diabetes that may affect fetal growth were excluded from the study. Other exclusion criteria for all cases were multiple pregnancies, smoking, maternal anemia, ruptured amniotic membranes, fetal chromosomal abnormalities, and congenital fetal malformations.

We determined the gestational age by measuring the crown-rump length in ultrasound (US) examination at the first visit at approximately 9-10 weeks of gestation to accurately calculate the gestational age and AC percentiles at the later weeks of gestation, and thus, to make a correct diagnosis of macrosomia. Gestational age was calculated in days to minimize the margin of error. Second-trimester routine US scans did not reveal any fetal malformation entire the study cohort. Participants were examined using a Voluson E 6 (GE Healthcare US, Milwaukee, WI, USA) US machine equipped with a RAB 6D (2-7 MHz) probe by an expert maternal-fetal medicine specialist. In the Doppler US evaluation, we measured the time-averaged maximum blood velocity (TAMXV) values of the right portal vein and the free loop of the umbilical vein during the fetal quiescence, with the angle of insonation kept as small as possible, not exceeding 30º (median angle correction was 0, range 0-30º).[6] Estimated fetal weight (EFW) was calculated based on sonographic measurements of fetal biparietal diameter, head circumference, abdominal circumference, and femur length.[14] Amniotic fluid volume (AFV) was measured in each case simultaneously by the single deepest pocket.[15]

The initial gestational age of the study group coincided with the 200th day of pregnancy, i.e. approximately the 28th week of gestation. Since gestational diabetes screening was performed after the 24th gestational week and a certain period was required for macrosomia to develop, the data in the study include the period from this week to the end of pregnancy.

STATISTICAL ANALYSIS

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality. The factors that may correlate with the outcome (group) were analyzed inde-

pendently (univariate analysis) by either Student's t-test or Mann-Whitney U test, where applicable. ANOVA and/or Kruskal Wallis tests were used to compare more than 2 independent groups, and the groups that made the difference were determined by post-hoc multiple comparison tests. The differences in proportions between groups were compared by using chi-square or Fisher's exact test. Descriptive statistics were used to summarize the data and expressed as mean±standard deviation (std) for normally distributed continuous variables, median (range) for skewed continuous variables, and count with the percentage of the total for categorical variables. To define the risk factors of being patient, multiple logistic regression analysis and adjusted odds ratios; their confidence intervals were calculated. All covariates with missing data in less than 20% of observations and a p-value <0.2 in univariate testing were considered for inclusion in the final multiple regression model, but the correlations prevented them from evaluation altogether. Highly collinear covariates (defined as correlation coefficient >0.6) were not included together in the final multivariate model. The correlation coefficient of Spearman was used to examine the linear relationships between the variables and the results are given with their respective p values. All statistical analyses were performed by using IBM SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

The comparisons between macrosomic fetuses whose mothers are diabetic and the control group in terms of the maternal age, gestational age at the Doppler US examination, AC percentile, right portal vein and umbilical vein TAMXV values, and AFV are given in Table 1. Accordingly, the mean maternal age and gestational age at the time of the Doppler US examination were similar between diabetic mothers and control cases (p=0.812 and p=0.857, respectively). The median right portal vein TAMXV value, umbilical vein TAMXV value, and AFV were found to be significantly higher in diabetic pregnancies (16.25 cm/s, 15.28 cm/s, and 8.79 cm, respectively) than in the control group (12.76, 13.38, and 5.47 cm, respectively, p<0.001).

We compared the diabetic mothers whether they received insulin treatment in their pregnancies and summarized the findings in Table 2. The mean maternal age, median right portal vein and umbilical vein TAMXV values, and AFV were similar in cases that received gestational insulin treatment and those that did not. Both of the groups' median right portal vein and umbilical vein TAMXV values and AFV were significantly higher than those of the control group (p<0.001). The mean EFW of the group that did not receive insulin treatment (3037.33±576.51 g) was found to be significantly lower than the group that was treated with insulin (2423.89±759.04 g, p<0.001).

The comparisons between pregestational DM and GDM cases were presented in Table 3. There was no significant difference in macrosomic fetuses of diabetic mothers regarding maternal age, the median umbilical vein and right portal vein TAMXV values, and AFV. Both of the groups' median right portal

TABLE 1: Comparisons of variables between macrosomic fetuses whose mothers are diabetic and the control group.

	Diabetes mellitus group		Control group		
	Mean±SD	Median (range)	Mean±SD	Median (range)	p value
Maternal age, years	34.53±4.28	34.00 (18.00)	34.35±5.29	35.00 (19.00)	0.857
Gestational age, days	231.79±22.59	232.00 (82.00)	232.85±21.16	236.00 (80.00)	0.812
Abdominal circumference, %	-	-	52.62±19.96	49.90 (76.85)	N/A
Portal vein TAMXV, cm/s	16.23±3.00	16.25 (18.37)	12.76±1.59	12.48 (6.67)	**<0.001***
Umbilical vein TAMXV, cm/s	16.17±2.80	15.28 (14.51)	13.38±1.90	13.35 (8.68)	**<0.001***
Amniotic fluid volume, cm	8.83±1.57	8.79 (6.69)	5.47±1.62	5.09 (7.25)	**<0.001***
Estimated fetal weight, g	2686.80±746.09	2703 (2947)	2224.23±542.92	2312 (2244)	**0.001**

*Signed p-values express p-values for Mann-Whitney U test; others for Student's t-test; TAMXV: Time-averaged maximum blood velocity; N/A: Not available.
SD: Standard deviation.

TABLE 2: Comparisons between diabetes mellitus cases whether they received gestational insulin treatment and control group.

	Gestational insulin treatment (-) cases		Gestational insulin treatment (+) cases		Control group		
	Mean±SD	Median (range)	Mean±SD	Median (range)	Mean±SD	Median (range)	p value
Maternal age, years	34.57±3.64	34.00 (14.00)	34.50±4.78	34.50 (18.00)	34.35±5.30	35.0 (19.0)	**0.983***
Gestational age, days	242.19±17.11[a]	242.00 (62.00)	224.00±23.31[b]	225.00 (79.00)	232.85±21.16[ab]	236.0 (80.0)	**0.013***
Portal vein TAMXV, cm/s	16.37±2.80	16.82 (11.73)[a]	16.12±3.19	16.13 (18.37)[a]	12.76±1.59	12.48 (6.67)[b]	**<0.001**
Umbilical vein TAMXV, cm/s	16.29±2.70	16.01 (8.97)[a]	16.09±2.91	15.18 (14.44)[a]	13.38±1.90	13.35 (8.68)[b]	**<0.001**
Amniotic fluid volume, cm	9.06±1.78	8.90 (6.69)[a]	8.66±1.40	8.71 (5.06)[a]	5.47±1.62	5.09 (7.25)[b]	**<0.001**
Estimated fetal weight, g	3037.33±576.51	3018 (2138)[a]	2423.89±759.04	2424.5 (2639)[b]	2224.23±542.92	2312 (2244)[b]	**0.001***

[a,b,ab]; Mean/median denoted by the same letter index are the same and denoted by the same different letter statistically different;
*ANOVA p-value and all others from Kruskal Wallis test; TAMAXV: Time-averaged maximum blood velocity.
SD: Standard deviation.

TABLE 3: Comparisons between gestational diabetes mellitus, pregestational diabetes mellitus, and control groups.

	Pregestational diabetes mellitus cases		Gestational diabetes mellitus cases		Control group		
	Mean±SD	Median (range)	Mean±SD	Median (range)	Mean±SD	Median (range)	p value
Maternal age, years	33.90±4.77	34.5 (17.0)	34.97±3.95	34.0 (16.0)	33.35±5.30	35.0 (19.0)	0.738
Gestational age, days	222.65±23.32[a]	220.0 (79.0)	238.10±20.12[b]	241.0 (82.0)	232.85±21.16[ab]	236.0 (80.0)	**0.048***
Portal vein TAMXV, cm/s	15.54±2.12	15.73 (8.8)[a]	16.70±3.44	16.40 (16.83)[a]	12.76±1.59	12.48 (6.67)[a]	**<0.001**
Umbilical vein TAMXV, cm/s	16.18±3.30	14.99 (14.19)[a]	16.17±2.45	16.01 (8.97)[a]	13.84±1.90	13.35 (8.68)[b]	**<0.001**
Amniotic fluid volume, cm	8.63±1.51	8.71 (5.06)[a]	8.97±1.62	8.84 (6.69)[a]	5.47±1.62	5.09 (7.25)[b]	**<0.001**
Estimated fetal weight, g	2398.1±791.33	3018 (2138)[a]	2885.9±654.78	2931 (2919)[b]	2224.23±542.92	2312 (2244)[a]	**<0.001***

[a,b,ab]; Mean/median denoted by the same letter index are the same and denoted by the same different letter statistically different;
*ANOVA p value and all others from Kruskal Wallis test; TAMXV: Time-averaged maximum blood velocity.
SD: Standard deviation.

vein and umbilical vein TAMXV values and AFV were significantly higher than those of the control group (p<0.001). The mean EFW in the pregestational DM group (2398.1±791.33 g) and in the control group (2224.23±542.92 g) was found to be significantly lower than in the gestational DM group (2885.90±654.78 g, p<0.001).

The data regarding the variables examined in terms of the correlation coefficient are presented in Table 4. According to these results, a significant positive correlation was found between the gestational age and umbilical vein TAMXV value only in the fetuses of diabetic mothers (p=0.028). The scatter graph of this significant relationship is given in Figure 1.

DISCUSSION

Fetal liver dimensions are correlated with fetal size and weight, like other fetal biometric measurements, including biparietal diameter, head circumference, AC, and femur length.[16] In macrosomic fetuses, AC and therefore liver sizes are also large. The majority of the nutrient-rich blood carrying from the mother to the fetus through the umbilical vein in fetal life first comes to the liver.[17] Experimentally, when the ductus

TABLE 4: Spearman correlations between gestational age and other variables.

Spearman's rho (p)	Portal vein TAMXV	Umbilical vein TAMXV	Amniotic fluid volume
Control cases (n=48)	0.230 (0.115)	0.026 (0.863)	0.116 (0.433)
Fetuses of diabetic mothers (n=49)	0.223 (0.124)	**0.314 (0.028)**	0.107 (0.463)
All cases	0.168 (0.100)	0.140 (0.172)	0.078 (0.448)

TAMXV: Time-averaged maximum blood velocity.

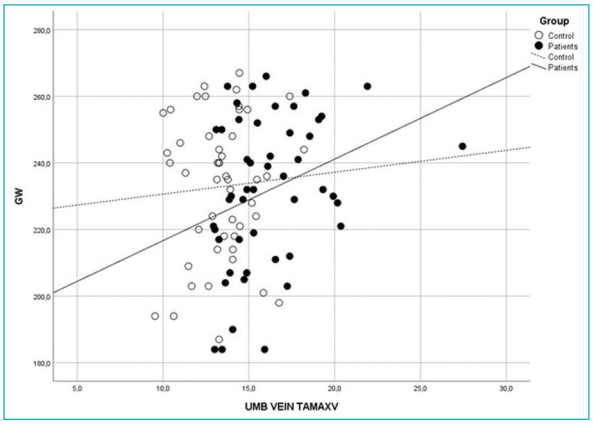

FIGURE 1: Scatter graph for gestational age and umbilical vein time-averaged maximum blood velocity.
TAMXV: Time-averaged maximum blood velocity.

venosus was narrowed, that is, when the blood flow to the liver increased indirectly, cell proliferation increased in the fetal liver, heart, kidney, and skeletal muscle.[18] These all indicate that the liver is the central organ in human development in fetal life.

In fetal life, the left portal vein has been used as an indirect determinant of the right portal vein flow, as it is considered the main tap of blood flowing to the liver.[2,5] There is a positive correlation between the umbilical vein blood flow and left portal vein, right portal vein, and total liver venous blood flow. When the umbilical vein flow increases, the left portal vein flow also increases because, in fetal life, the left portal vein is the continuation of the umbilical vein.[19] Also, since approximately 18-20% of the blood coming from the umbilical vein goes to the ductus venosus and from there to the heart, it directly passes into the systemic circulation without entering the portal system.[20] While this is the case in normal fetal development, in FGR, the venous flow to the liver is reduced because the blood coming from the umbilical vein gives priority to the systemic circulation, and this decrease is more pronounced in the right liver lobe.[10,19] While the right portal vein flow was decreasing in fetuses with FGR, how would it be in macrosomic fetuses? Also, as known, in pregnancies complicated with DM, the risk of macrosomia increases 2-fold to 3-fold, even with treatment.[21-24] In this study, we investigated how is the blood flow of the right portal vein, which has a more passive role in fetal life compared to the left portal vein, in macrosomic diabetic mothers' fetuses, and whether the maternal insulin treatment affects this blood flow.

In the study conducted by Haugen et al., the liver blood flow did not change in the fasting state, while the increase in the 2 hours after the glucose challenge test was associated with fetal size.[19] While the liver blood flow of macrosomic babies increased after glucose exposure compared to normal fetuses, no significant difference was observed in the fasting state. In our study, regardless of the fasting status or maternal glucose intake, our results of the random Doppler US analysis were consistent with the glucose exposure in the study of Haugen et al. Since all fetuses in our study group were macrosomic, the study group was divided into 2 subgroups whose mothers were treated with insulin and those who did not. Among these subgroups, TAMXV values were not significantly different between the umbilical vein and the right portal vein.

In the study of Kessler et al. and Ebbing et al. in macrosomic fetuses of nondiabetic mothers, they found that the blood flow to the liver in these fetuses was higher than in the control group. The increase in liver blood flow continued during the last trimester, but blood flow was observed to be stable in the normal growth control group.[4,5] Our results were similar to these studies. While the week of gestation increased in our control group, right portal vein and umbilical vein flows were observed constantly. Similar to these studies, we observed in the study group that the increase in the umbilical vein flow as the gestational age progressed was statistically significant. However, the slight increase observed in the right portal vein as the gestational age progressed was not statistically significant. The difference between our study group from these studies is that mothers of macrosomic fetuses were diabetic in our study, while were not diabetic in their studies. We observed that maternal insulin use did not affect fetal umbilical vein and right portal vein flow in macrosomic fetuses. The venous blood flow of macrosomic fetuses of pregestational diabetic mothers was similar to that of macrosomic fetuses whose mothers were diagnosed with GDM. Based on these findings, umbilical venous return increases in macrosomic fetuses, whether the mother is diabetic or not and whether she was treated with insulin or not. Also, in a recent

study, Grindheim et al. randomly prescribed metformin/placebo to pregnant women with polycystic ovary syndrome (PCOS) in the first trimester of pregnancy. They compared fetal venous liver blood flow in both metformin vs placebo-exposed fetuses of mothers of PCOS at 32 weeks of gestation. They concluded that metformin treatment during pregnancy did not affect fetal blood flow, as documented by TAMXV measurements of the umbilical vein, ductus venosus, and portal vein.[25] These results show that the venous blood flow to the liver is increased in macrosomic fetuses, regardless of the etiology.

CONCLUSION

TAMXV values of the right portal vein and umbilical vein were significantly higher in fetuses whose mothers were diabetic compared to the control group. While these values were approximately constant in the appropriately grown fetuses from 28 weeks to the end of the gestation, the umbilical vein TAMXV increased until the end of the gestation in the macrosomic fetuses of the diabetic mothers. Maternal insulin therapy did not affect these venous flows.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Salim Sezer, Süleyman Cemil Oğlak, Alev Atış Aydın, Sema Süzen Çaypınar, Başak Kaya, Melih Bestel;* ***Design:*** *Salim Sezer, Süleyman Cemil Oğlak, Alev Atış Aydın, Başak Kaya;* ***Control/Supervision:*** *Salim Sezer, Alev Atış Aydın, Sema Süzen Çaypınar;* ***Data Collection and/or Processing:*** *Salim Sezer;* ***Analysis and/or Interpretation:*** *Salim Sezer, Süleyman Cemil Oğlak, Alev Atış Aydın, Melih Bestel;* ***Literature Review:*** *Salim Sezer, Süleyman Cemil Oğlak;* ***Writing the Article:*** *Salim Sezer, Süleyman Cemil Oğlak;* ***Critical Review:*** *Süleyman Cemil Oğlak;* ***References and Fundings:*** *Salim Sezer.*

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