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Biomechanical Properties of the Umbilical Cord and Its Relationship with Perinatal Outcomes

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ABSTRACT

Purpose: The aim of this study was to determine the elasticity modulus of umbilical cord (UC) using biomechanical tests in diabetic, preeclamptic and control groups and to investigate the relationship with perinatal outcomes.

Methods: Patient data from diabetic, preeclamptic and healthy control group women, who gave birth in a single center between September and December 2019 were collected. Prenatal demographic data, pregnancy outcome, and ultrasound Doppler pulsatility index (PI) was obtained. Cord samples were taken at birth and newborn morphometric parameters were measured. The diameter of UCs were measured. The samples then underwent biomechanical testing. By calculating strain and stress, the elasticity modulus of samples were derived.

Results: There were thirty subjects in each group. Mean UC radius was significantly greater ($p<0.01$) in the diabetic group (1.03 ± 0.29 cms) compared to control group (0.86 ± 0.21 cms) and preeclamptic group (0.74 ± 0.14 cms). Median (range) elasticity modulus was highest in the preeclamptic vs. the diabetic and control groups [0.28 (0.22-0.34) vs. 0.12 (0.8-0.30) vs. 0.14 (0.12-0.34), respectively; $p<0.01$]. Increase in birth week ($r=-0.26$, $p=0.01$), birthweight ($r=-0.42$, $p<0.01$), newborn height ($r=-0.38$, $p<0.01$), and UC diameter ($r=-0.78$, $p<0.01$) were all negatively correlated with elasticity modulus. Umbilical artery Doppler PI values had weak positive correlation with elasticity modulus ($r=0.21$, $p=0.4$).

Conclusion: Morphological, mechanical and histological studies were performed on the UC. It appears that the UC its characteristics are changed in disease processes affecting pregnancy. We believe that if ultrasonographic, histological, biochemical and immunohistochemical data are combined with biomechanical data, larger serial studies may provide new parameters with which we can evaluate fetal well-being based on UC characteristics.

Keywords: Umbilical cord, preeclampsia, diabetes, elasticity

INTRODUCTION

The umbilical cord (UC) is a structure that provides the vital connection between the fetus and the mother.[1] The placental-fetal relationship is conducted through the UC. The UC continues develops from the third week of embryonic life until the twelfth week and, starting from the first trimester, the UC can be visualized through ultrasonography, generally for its entire length. The primitive umbilical ring, the precursor of the primitive UC, originates from the ventral reflection line of the amnio-ectodermal junction.[1] It is a mesoblastic structure approximately 50-60 cm long and 1.5-2 cm thick at term.[2]

In section, the UC contains two umbilical arteries (UA) transferring fetal blood to the placenta, an umbilical vein (UV) transferring oxygenated blood from the placenta to the fetus, and the amnion membrane around the outside. In addition, within the lamellar structure filling the inside of the cord, there is the tissue known as Wharton's jelly (WJ), which consists of structural support from the mesodermal formation and connective tissue.[3] The UC usually contains 10-11 full turns from the fetus to the placental insertion site.[1,2] The UC, a vital component of the fetoplacental unit, is the only structure that plays a decisive role in the beginning of extrauterine life, but is unnecessary after life begins.[2] Evidence obtained through

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clinical experience and experiments has shown that the morphology and components of the UC affect the course of pregnancy, mode of delivery and pregnancy outcome.[4-6]

As anatomical, histological, and ultrasonographic studies, and thus UC-related data, has increased, the importance of the UC has became more clear. The relationship between sonographic UC thickness and fetal growth in early trimesters has been recently published. Many groups have reported that altered UC morphology in the second and third trimesters is associated with poor perinatal outcomes, including fetal distress, fetal growth restriction, gestational diabetes, hypertensive disorders, intrapartum complications, and altered UV blood flow.[3-7] In addition, in the second trimester, the presence of a thin UC is associated with the fetus having a lower birth weight for gestational age and being more likely to show signs of distress during birth.[8,9] Studies conducted in the second trimester have concluded that the interrelationship of umbilical vessels and WJ components may affect pregnancy prognosis.[4,7-9]

Studies have shown that UC diameter and UC area is correlated with fetal macrosomia, fetal weight and fetal biometric parameters.[6,10,11] The results of these studies indicated the importance of UC morphometry in terms of possible risks to the fetus during pregnancy and birth in diabetic pregnancies.

Studies conducted with pregnant women diagnosed with intrauterine growth restriction (IUGR) and preeclampsia showed a decrease in the area of WJ and umbilical vessels as the earliest finding.[5,12] Importantly, these changes are present in the absence of fetal growth disorders and altered UA Doppler parameters. It was reported that in fetuses in pregnancies affected by preeclampsia and in IUGR fetuses, the decrease in umbilical vessel area may be due to vasoconstriction of these vessels through an altered function of locally acting factors. Since human UC vessels lack neural innervation, the action of vasoactive substances may be crucial for vascular control of the UC.

Comparison of clinical outcomes and UC thickness measured ultrasonographically and pathologically has shown that the diameter of the UC and the arteries and veins within it are important indicators of the intrauterine development of the fetus, birth and perinatal complications and general well-being.[13]

The current study aimed to identify the relationship between the diameter and biomechanical properties of the cord and perinatal outcomes, based on the assumption that the UC is a structure that surrounds the outside of the artery and vein that circulate oxygenated blood, providing nutrition to the fetus, and also creates resistance, and that such measurements can provide information for the evaluation of fetal development and fetal well-being in the intrauterine period.

METHODS

In the present study, the UCs of patients who gave birth in the 22nd-41st week of pregnancy in a single center between September 2019 and December 2019 were prospectively evaluated. After obtaining consent from the patients, UC sections were prepared. These sections were divided into three groups: samples from diabetic pregnant women, preeclamptic pregnant women and healthy pregnant women without known additional diseases. Ethical committee approval was received from the local ethics committee for the study.

The inclusion criteria were patients who gave birth to a healthy baby weighing over 500 grams between 22-41 weeks of gestation; diabetic pregnant women, pregnant women diagnosed with preeclampsia and healthy pregnant women without comorbidities; babies without genetic or systemic abnormalities; no high blood pressure (systolic <140 mmHg, diastolic <90 mmHg) in the diabetic group; normal UC morphology (two arteries and one vein); and singleton pregnancy. Exclusion criteria were multiple pregnancies; maternal infection, preterm rupture of membranes, latent labor phase, pregnancies with a single umbilical artery; and those who were diabetic and also developed preeclampsia or high blood pressure.

Demographic characteristics, physical examination results, umbilical artery findings of Doppler ultrasonography, laboratory values such as hemoglobin level and blood gas pH and birth records of the patients were recorded. Obstetric ultrasonographic examination of patients before birth were recorded and umbilical artery pulsatility index (PI) values were measured. umbilical artery blood gas sampling values at 0 minutes postpartum were noted. First and five-minute Apgar scores, birth weight and length were noted. Information on whether there was a need for neonatal intensive care unit admission in the postnatal period was noted.

During birth, 10 cm of the UC was cut in the delivery room and instantly stored in 5% formaldehyde solution. Each UC sample was soaked in formaldehyde for approximately 20 days and then taken to the biomechanics laboratory to be studied.

To determine the UC thickness, the circumference of the cord was measured, and the radius value was used by calculating r (radius) with the formula $2\pi r$. The cord area was calculated with the formula πr^2 (mm^2) and used in the elasticity modulus calculation.

Each cord was subjected to uniaxial pulling without undergoing any physical processing in the biomechanics laboratory. All cords were tested at room temperature (22 °C) at single tension, parallel to the long axis of each sample. Tensile testing was performed for each cord sample using a universal testing machine and the load was measured with a 20kN load cell. The samples were placed on both jaws of the testing device from both ends and an average distance of 2 cm was set between them. A preload tension of 5 N was applied to pre-stress the loose cords and remove any residual mis-shappeness when placed between the jaws. For stress-strain testing, samples were tested at a displacement rate of 60 mm/minute until failure. Displacement (mm) and load (maximum force, N) of the cords were obtained from the test device. A force-displacement curve was obtained for each tensile test performed.

To calculate the elastic modulus, all samples were examined by the same scientist, under the same room conditions, and at postpartum 20th day to avoid data error. The stress-strain diagram of each tested sample was obtained, and the

tangent modulus and elastic modulus were calculated. While calculating the elasticity modulus, the unit displacement value (ε) in the formula was taken as the distance (mm) extended by the cord in our tensile test. The tension (б) was taken as the force [1 Megapascal (MPa)=1 newton per square millimeter] at the moment of breaking of the cord. The elasticity module value was found for each data using the formula E=б/ε.

Statistical Analysis

Statistical evaluation was performed with SPSS, version 23.0 (IBM Corp., Armonk, NY, USA). The conformity to normal distribution was evaluated with the Shapiro-Wilk test. Numerical variables with normal distribution (age, height, fasting blood sugar value, cord diameter) are shown as mean ± standard deviation while numerical variables that do not show normal distribution (gestational age, weight, body mass index, birth length, hemoglobin, blood pressure, hemoglobin A1c (HbA1c), birth weight, umbilical artery Doppler PI, proteinuria, maximum cord force value, cord displacement, and elasticity value) are shown as median (interquartile range). Finally, categorical variables are given as frequency (%). For normally distributed numerical variables, the difference between groups was analyzed by One-Way Analysis of Variance (ANOVA) and Tukey's multiple comparison test. Non-parametric data sets were compared using the Kruskal-Wallis, ANOVA and Dunn's multiple comparison tests. The Yates and Monte Carlo chi-square test were used for categorical variables. A $p<0.05$ was considered sufficient for statistical significance.

RESULTS

Samples were taken from 90 patients, including 30 women with gestational diabetes, 30 preeclamptic pregnant women and 30 healthy pregnant women and the elastic modulus of all samples were calculated by the same scientist, under the same room conditions, and at postpartum 20th day to avoid data error.

Demographic characteristics of the women are presented in Table 1. The preeclamptic women were significantly younger than the women in the diabetic group ($p=0.01$). Gestational age at birth was significantly earlier in the preeclamptic group compared to both control group and diabetic group ($p<0.01$). Maternal weight of the diabetic group was significantly heavier in the diabetic group than the preeclamptic and control groups ($p<0.01$).

Comparisons of the fetal parameters between the study groups are given in Table 2. First minute Apgar scores, fifth minute Apgar scores, mean birth weight, and mean fetal birth length of the preeclamptic group were significantly lower than the diabetic and control groups ($p<0.01$ for all).

Comparison of UC radii, umbilical artery PI, strain, maximum stress and modulus of elasticity values are presented in

Table 1. Demographic characteristics of patients according to groups

	Diabetic (n=30)	Preeclamptic (n=30)	Control (n=30)	p-value
Age	33.1±5.1	28.9±5.3	30.7±5.6	**0.01**θ
Birth week	37 (36-38)	35 (28-36)	38 (37-39)	**<0.01**θμ
Gravida	3 (2-3)	2 (1-3)	2 (1-3)	0.13
Parity	1 (0.75-2)	0 (0-2)	1 (0-2)	0.19
Abortus	0 (0-1)	0 (0-0.25)	0 (0-0)	0.54
Living child	1 (0-2)	0.5 (0-1.2)	1 (0-2)	0.52
Height	1.62±5.84	1.61±5.50	1.63±6.40	0.32
Weight	86 (76-100)	73 (66-83)	75 (67-87)	**<0.01**θł
BMI	33.5 (23-49)	28.9 (25.3-32.1)	28.3 (24.8-34.0)	**<0.01**θł

θ: There is significant difference difference between diabetes and preeclampsia. One-Way ANOVA, Tukey test.
ł: There is significant difference between diabetes and control group One-Way ANOVA, Tukey test.
μ: There is significant difference between preeclampsia and control group. One-Way ANOVA, Tukey test.
BMI: Body mass index

Table 2. Comparison of fetal parameters between the study groups

	Diabetic	Preeclamptic	Control	p-value
Apgar first minute	8 (7-8)	7 (4-7)	8 (7-8)	**<0.01**θμ
Apgar fifth minute	9 (9-9)	8 (7-9)	9 (9-9)	**<0.01**θμ
Birth weight (g)	3178±599	2194±1042	3206±554	**<0.01**θμł
Birth length (cm)	50 (49-51)	45 (38-48)	50 (48-51)	**<0.01**θμ
Haemoglobin (g/dL)	18.4±1.4	17.1±2.8	18.4±2.2	0.09
Blood gas pH	7.35 (7.32-7.37)	7.33 (7.29-7.38)	7.37 (7.33-7.38)	0.078

θ: There is a difference between diabetes and preeclampsia. One-Way ANOVA, Tukey test.
ł: There is a difference between diabetes and control group. One-Way ANOVA, Tukey test.
μ: There is a difference between preeclampsia and control group. One-Way ANOVA, Tukey test.

Table 3. Umbilical artery Doppler PI values of the patients were compared using prenatal US images. The median (range) PI was 1.07 (088-1.28) in the preeclampsia group, 0.80 (0.73-0.94) in the diabetic group, and 0.7 (0.58-0.87) in the control group. PI was significantly greater in preeclamptic pregnant women ($p<0.01$). The smallest radius of UC was observed in the preeclamptic group. The mean value was found to be 0.74±0.14 cm. The average value of the control group was 0.86±0.21 cm, the diabetic group was 1.03±0.29 cm, and it was statistically significant that the cord radius of diabetic patients increased, and the cord was thinner in preeclampsia ($p<0.01$).

The elasticity modulus values were compared between groups. These values were found to be 0.12 (0.8-0.30) mPa/mm (in the diabetic group, 0.28 (0.22-0.34) mPa/mm in the preeclamptic group, and 0.14 (0.12-0.34) mPa/mm in the control group. A higher value for elasticity modulus indicates less flexibility and greater fragility, and this value was significantly lower in the preeclampsia group compared to the diabetic and control groups ($p<0.01$). No difference was found between the diabetic and the control groups ($p=0.84$). Maximum stress value was lowest and maximum stress value was highest in preeclamptic group compared to diabetic and control groups, but it was not significantly different.

Every unit increase in birth week ($r=-0.26$, $p=0.01$), birthweight ($r=-0.42$, $p<0.01$), newborn length ($r=-0.38$, $p<0.01$), and UC diameter ($r=-0.78$, $p<0.01$) was negatively correlated with elasticity modulus. UA Doppler PI values had a weak positive correlation with the elasticity modulus ($r=0.21$, $p=0.4$).

When correlation analysis was conducted in the preeclamptic group, birth week ($r=-0.37$, $p=0.03$), birthweight ($r=-0.542$, $p<0.01$), newborn length ($r=-0.60$, $p<0.01$), and UC diameter ($r=-0.55$, $p<0.01$) were negatively correlated with elasticity modulus. However, in this group UA Doppler PI values did not show correlation with elasticity modulus.

DISCUSSION

The UC is one of the most important parameters that indicates us the welfare of fetal life.

In biomedical and multidisciplinary studies have shown that differences from the norm of the UC and its components will have an effect on the pregnancy process and neonatal outcomes.[4-6] Intrauterine loss, gestational diabetes, preeclampsia, intrauterine growth retardation, fetal distress during birth, and the relationship between fetuses with meconium and the UC have recently attracted the attention and interest of many researchers.[4-7,14] Multisystemic diseases such as preeclampsia and diabetes remain the main focus of studies. It is undeniable that there are important conditions in the perinatal period that can negatively affect both fetal life and maternal life. As has been shown, biomolecular structures in the cord structure cause changes in the cords by affecting their histological, biomechanical and anatomical properties.[15]

Raio et al.[4] found that the rate of low birth weight and fetal distress increased depending on the gestational week in fetuses with a thin UC. They suggested that the presence of a thin UC be used as a marker for low birth weight and fetal distress. Goodlin reported that babies who underwent caesarean section due to fetal distress and also had meconium had a thinner UC.[7]

In contrast, Ghezzi and Weissman, investigated the relationship between thick UC, gestational diabetes and macrosomia and reported that the birth weight was higher in fetuses with thick UC. They suggested that the thickness of the UC increased significantly in patients with gestational diabetes compared to the control group, and that gestational diabetes should be investigated in pregnant women whose UC was measured to be thick.[6,10] In the current study, cord thickness was significantly higher in diabetic pregnant women ($p<0.01$).

Although there was a significant relationship between cord components and fetal macrosomia, no difference was observed between the diabetic group and the non-diabetic control group. Cromi et al.[10] stated that the cord area, and especially the WJ area, was larger in diabetic pregnant women than in non-diabetic pregnant women, and especially in those who give birth to macrosomic babies. Similarly, in the study conducted by Weissman and Jakobi,[6] it was concluded that there was a significant association between birth weight and cord radius in diabetic pregnant women it was suggested that by combining these two variables, macrosomic fetuses would be predicted with a high degree of accuracy.[3,6] In our study, there was a significant positive correlation between cord radius and birth weight in diabetic pregnant women ($p<0.05$).

Barbieri et al.[16] constructed reference curves for the WJ area in low-risk pregnancies between 13-40 weeks and its relationship with estimated fetal weight (EFW) was evaluated. In 2,189 low-risk pregnancies, estimated WJ area was calculated as

Table 3. Comparison of umbilical cord radii, umblical artery pulsatility index and modulus of elasticity

	Diabetic	Preeclamptic	Control	p-value
Umbilical artery PI	0.84±0.18	1.09±0.36	0.71±0.14	**<0.01**[θm]
Cord radius (cm)	1.03±0.29	0.74±0.14	0.86±0.21	**<0.01**[θǂ]
Strain (mm)	28.7±9	31±9.3	26.3±9.9	**0.1**
Maximum stress (mPa)	61±16.8	54.3±17	62±18	**0.1**
Elasticity modulus	0.12 (0.8-0.30)	0.28 (0.22-0.34)	0.14 (0.12-0.34)	**<0.01**[θm]

[θ]: There is a difference between diabetes and preeclampsia. One-Way ANOVA, Tukey test.
[ǂ]: There is a difference between diabetes and control group. One-Way ANOVA, Tukey test.
[m]: There is a difference between preeclampsia and control group. One-Way ANOVA, Tukey test.

the 10th, 50th, and 90th percentile using USG and a third-order polynomial regression procedure. EFW and WJ area measured by USG were correlated. WJ area increased linearly according to the gestational week (R^2=0.64) and stabilized from the 32nd week. There was a significant linear correlation (r=0.782) between WJ area and EFW until the 26th gestational week. In addition, it has been reported that the UC diameter increases significantly with gestational age until the 32nd-36th week, and then this value decreases.[4,6,17] In their respective nomograms, Weissman and Jakobi[6] reported this limit as the 36th week and Raio as the 34th week. In our research, a statistically significant positive correlation was found between gestational age and UC diameter in all groups.

Raio et al.[12] reported the first finding that WJ morphometric changes were present in the cord of fetuses with early-onset preeclampsia. The WJ area was smaller in the group diagnosed with preeclampsia. The most important aspect of these changes is that they are present in the absence of fetal growth disorders and altered UA Doppler parameters.[12]

In biochemical studies, changes were observed in the UC extracellular matrix of preeclamptic women. Bańkowski et al.[18] and Pawlicka et al.[19] found a significant increase in WJ, sulphated glycosaminoglycans and type III collagen and a decrease in hyaluronic acid in preeclamptic women. These findings suggest that in preeclampsia, WJ is characterized by reduced hydration. The second finding was that the cord thickness was smaller in preeclamptic women than in healthy pregnant women. In our research, cord thickness was significantly different between diabetic and preeclamptic pregnant women ($p<0.01$). The decrease in thickness in preeclamptic pregnant women compared to normal pregnant women was significant.

Antepartum fetal monitoring with UA Doppler has shown significant diagnostic effectiveness in determining fetal risk in complicated pregnancies, such as IUGR and preeclampsia. A significant relationship was observed between abnormal Doppler indices and fetal hypoxia, fetal acidosis and adverse perinatal outcomes.[20] However, its effectiveness in reducing perinatal mortality has been demonstrated in randomized clinical trials and meta-analyses. Among the tests performed to understand fetal well-being, the most effective is the antepartum fetal test.[21] In our study, we compared the UA PI value in all three groups and the PI value was significantly higher in the preeclamptic group. Bilateral correlations were examined in the preeclamptic group, and a significant negative correlation was found between PI values, and birth weight. Although in preeclamptic and diabetic groups blood gas pH value was lower than in the control group, the difference was not significant.

Ferguson and Dodson[3] performed biomechanical, histological and biomolecular tests in preeclamptic pregnant women and showed that the elasticity modulus was increased (i.e., the elasticity decreased) due to the decrease in collagen and elastin in the extracellular matrix in the cord. In the present study, there was a significant increase in elasticity modulus in preeclamptic pregnant women compared to the diabetic and control groups. This suggests that cord flexibility is reduced in preeclamptic pregnant women. Interestingly, no significant difference was found in elasticity modulus values between diabetic pregnant women and the control group.

The limitation of our study is the formaldehyde solution processing of the UC which may have caused alteration in the elasticity of the UC samples.

CONCLUSION

The UC is critical for normal fetal development during most of pregnancy. Therefore, defining the changes and differences in the cord and its multifactorial features will be beneficial in understanding fetal life. It is clear that the morphological, physical and developmental changes occurring in the UC should be investigated by multidisciplinary (including bioengineering and medicine) teams.

We suggest that predicting macrosomia in diabetic pregnant women in the future or screening for diabetes in pregnant women with a large cord radius can be done, once there is sufficient evidence to validate this approach. A limited number of patients were included in our study, and therefore we were unable to investigate the relationship between macrosomia, fetal outcomes and cord elasticity and diameter in the diabetic pregnant group. We believe that conducting studies in larger series may provide additional and more conclusive data. That the US-measured cord diameter and area, and diameters and elasticity data of the UA and veins were not included in the study are further limitations of the current study.

Larger-scale studies combining biomechanical data with ultrasonographic, histological, biochemical and immunohistochemical data may provide new insights into monitoring fetal well-being together with a better understanding of cord morphology and thus help prevent cord pathologies leading to serious fetal and maternal complications, such as preeclampsia, in terms of treatments at the molecular level, in the coming years.

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Ethics

Ethics Committee Approval: The approval of Alanya Alaaddin Keykubat University Clinical Research Ethics Committee (decision dated: 16.11.2022 and numbered: 12/05).

Informed Consent: Participation in the study was voluntary and all participants read and approved the informed consent form.

Authorship Contributions

Surgical and Medical Practices: S.K.Ö., T.Ç., A.Ç., Concept: S.K.Ö., M.Ç.K., L.A., H.D., A.Ç., Design: S.K.Ö., A.Ç., Data Collection or Processing: S.K.Ö., M.Ç.K., T.Ç., L.A., H.D., A.Ç., Analysis or Interpretation: S.K.Ö., M.Ç.K., T.Ç., H.D., A.Ç., Literature Search: S.K.Ö., M.Ç.K., T.Ç., L.A., A.Ç., Writing: S.K.Ö., L.A., H.D.

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