

Clinico-morphological aspects and outcomes of the lean umbilical cord

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Manuscript received April 07, 2020; revised manuscript May 27, 2020; published online June 10, 2020

Abstract

Background: The umbilical cord forms connecting link between the fetus and placenta through which the fetal blood flows to and from the placenta. Wharton's jelly is a specialized tissue which acts as supportive and protective structure substituting for the adventitia of the umbilical vessels. The aim of the study was to reveal the clinical and morphological features of the lean umbilical cord for improving its outcomes.

Material and methods: The study included 190 patients divided into 2 groups: L₁ – 95 patients with UC abnormalities and L₀ – 95 with normal UC. Umbilical cord assessment was based on macro- and microscopic examinations. An entire umbilical cord was available from all patients and examined for diameter. Three full thickness sections of the UC were fixed in 10% formalin and stained with hematoxylin and eosin, Van Gieson's, Alcian blue for histological examination.

Results: A study of the association between the absence of Wharton's jelly and an unfavorable pregnancy outcome was undertaken. The lean umbilical cord results in reduced fetoplacental circulation, thus resulting in intrauterine growth restriction (p<0.0001), fetal distress and hypoxia, which require the neonatal intensive care (p<0.0001). Morphological examination of the umbilical cord revealed changes in Wharton's hard and fibrous jelly.

Conclusions: This study shows the importance of the knowledge of cord diameter. Clinico-morphological examination of the umbilical cord, including the study of the lean forms is of great importance in the diagnosis of the causes of adverse perinatal outcomes of fetuses and newborns in the obstetrical practice. Therefore, our study confirms that all umbilical cords should be submitted for complete examination.

Key words: lean umbilical cord, Wharton's jelly, diameter, morphology, perinatal outcome.

Cite this article

Alsatou A, Petrovici V, Corolcova N. Clinico-morphological aspects and outcomes of the lean umbilical cord. *Mold Med J.* 2020;63(2):25-30. doi: 10.5281/zenodo.3865990.

Introduction

One of the most important parts of the fetoplacental unit is the umbilical cord (UC) [1]. It is the lifeline that connects and provides vascular flow between the fetus and the placenta. The fully developed umbilical cord is pearly white, 50-60 cm long with an average diameter of 1-2 cm, optimal protection which is provided by Wharton's jelly (WJ) [2]. Other studies have found that at birth, the average diameter and circumference of the umbilical cord in a normal term infant is 1.5 cm and 3.6 cm, respectively [3,4]. The ultrasound average vein diameter is 8 mm with an average artery diameter of 4 mm at term [5]. The "lean cord" is a rare structural abnormality, characterized by reduced or completely absent Wharton's jelly, which has seldom been described in the medical literature. Umbilical cord is lean if the middle diameter is less than 1.0 cm and the lean index is less than 0.55 g/cm in male fetus and less than 0.49 g/cm in female fetus [6].

Wharton's jelly is a specialized tissue serving many purposes for the developing fetus. The WJ is the umbilical cord stroma that originates from the extraembryonic mesoderm of allantois. It is rich in mucopolysaccharides such as hyaluronic acid and chondroitin sulfate and thus protects

umbilical vessels from compression [7]. It is surrounded by myofibroblasts, which are mesenchymal cells with the characteristics of both fibroblasts and smooth-muscle cells. Myofibroblasts have both fibrogenesis and contractile functions and produce increasing amounts of type I, II, and V collagen fibrils during the pregnancy, giving Wharton's jelly elastic and contractile properties as well as microfibrils. Hyaluronic acid is the most common glycosaminoglycan – a hydrophilic component of Wharton's jelly that absorbs water and electrolytes. It has been suggested that diameter of the umbilical cord is determined by the water content of Wharton's jelly. Umbilical cord elasticity confers resistance to external pressure, and acts as a physical buffer in the regulation of fetoplacental blood circulation and umbilical vessels [8]. It has been speculated that the cells of Wharton's jelly may participate in the regulation of umbilical blood flow. In some cases, the reduction in fetal growth could be directly associated with Wharton's jelly decrement, leading to hypoplasia of the umbilical vessels. If Wharton's jelly is poorly developed, or if the vessels remain unprotected, they become more prone to compression [9]. Cord compression may be a stimulus to induce such a compromise. It is theorized that if the umbilical blood flow is slowed, then placental blood flow is also slowed. When this happens, blood

thickens in the small spaces in the placenta called the villous vessels and clots like gelatin. This, in turn, causes thromboses of the intervillous space that contains blood flow from the mother. The result is devitalized placental tissue and loss of that placental nutritional space [10, 11]. The development of multiple capillaries in the periphery and fibrosis of Wharton's jelly may be secondary consequences of the thin UC, and the capillaries can be considered collaterals for compensating for chronically compromised umbilical circulation. Thus, loss of protection by the Wharton's jelly can lead to compromised fetoplacental circulation and subsequent fetal death [12, 13].

It is believed that males have more Wharton's jelly content than do females and that good nutrition increases the amount [6]. Wharton's jelly tends to reduce with gestational age and can disappear when pregnancies go beyond forty weeks. Because these cases tend to have fetal heart rate changes, the level of Wharton's jelly is a consideration when obstetricians plan the deliveries of pregnancies low on amniotic fluid [5].

Umbilical cord is vital to fetal development and its alterations are related to perinatal complications. Though the pathogenesis of variability of umbilical cord diameter remains unclear, this study would provide information about the thin umbilical cord and its association with adverse outcomes.

There is a huge arena for research in this field as what we are seeing is just the tip of an iceberg. The challenge should be taken up, and newer equipment and strategies should be developed to analyze and avoid cord complications. This would decrease the incidences of the perinatal morbidity and mortality due to cord complications in the future and help in realizing the expectations for the delivery of a healthy baby.

Material and methods

It was performed a prospective cohort study in the Department of Obstetrics and Gynecology at the clinical base of Municipal Clinical Hospital No 1, *Nicolae Testemitanu* State University of Medicine and Pharmacy. The control group (L_0) included 95 patients with normal umbilical cord and the study group (L_1) included 95 patients with umbilical cord abnormalities of which 24 had a lean UC.

Clinical details from all patients and their newborns consisted of the evaluation of patient's complaints, the anamnesis, general physical and obstetrical examination which were obtained along with the cord specimens. Umbilical cord assessment was based on macro- and microscopic examinations. The umbilical cord was available from all patients and examined for diameter (in centimeters) immediately after delivery. Abnormality included in the study group was thin UC. Three full thickness sections of the UC were fixed in 10% formalin and stained with hematoxylin and eosin (H&E), selectively histochemical staining – Van Gieson's (VG), Alcian blue pH 2.5 (AB) for histological examination.

The *inclusion* criteria in the research were: gestational age between 22⁺⁰–41⁺⁶ weeks, spontaneous and singleton pregnancy, maternal age ≥ 18 years, research participation agreement. The *exclusion* criteria were: gestational age ≤ 21 ⁺⁶ weeks and ≥ 42 ⁺⁰ weeks, pregnancy, which occurred as a result of assisted reproduction technologies, multifetal gestation, decompensated somatic pathology of the patient, age of the patient ≤ 18 years, patients who refused voluntary participation in the research.

Statistical analysis was performed using *Statistical Package for Social Sciences* for Windows (SPSS Version 23.0), *Statistical Analysis System* (SAS Version 9.4) and Microsoft Excel 2016. The significance was tested by using a Chi-square test, the Cramer V coefficient, and the Fisher's exact test. For all quantitative characteristics in the compared groups were evaluated the arithmetic means and mean-square (standard) errors of the mean, coefficient of variation, median, mode, and quartiles. To analyze the differences among group means in a sample was used a collection of statistical model's ANOVA. *P* value of less than 0.05 was regarded as statistically significant.

Results

In our study no demographic differences could be detected between the study and control groups. The rate of lean UC was 12.63% (24) in all singleton pregnancies and the cord diameter varied from 0.4 to 0.7 (0.55 \pm 0.01) cm. The gestational age in the patients with lean UC ranged between 26-41 (38.25 \pm 0.78) weeks, there was no difference in this parameter in the studied groups ($p > 0.05$). There were 2 times more primiparous women than multiparous ones – 16 (8.42%) vs 8 (4.21%) cases. Patients of the study group had an imminent delivery at different periods: 4-16 weeks in 10 (5.26%) cases, 23-35 weeks in 5 (2.65%) cases, IUGR – in 4 (2.11%) cases by 2-6 weeks. The findings suggest that 19 (10%) women underwent vaginal delivery and 5 (2.63%) women had a cesarean delivery.

All children were born alive. Out of all neonates, 15 (7.89%) were male and 9 (4.74%) were female babies. The birth weight in the control group (L_0) was 2460–4780 g (mean 3470.21 \pm 463.80 g); in the study group (L_1) – 1030–3740 g (mean 2890 \pm 146.8 g) ($p < 0.01$) (fig. 1). The newborn length in the L_0 = 45–57 cm (52.37 \pm 1.99 cm) vs 34–54 cm (49.37 \pm 1.04 cm) in the L_1 ($p < 0.01$) (fig. 2). APGAR score at 1 min L_0 = 7-10 points (8.66 \pm 0.69) vs L_1 = 4-9 points (7.45 \pm 0.24) ($p < 0.05$). APGAR score at 5 min L_0 = 8-10 points (9.13 \pm 0.67) vs L_1 = 5-10 points (8.12 \pm 0.23) ($p > 0.05$).

In our study thin cords were found to be significantly associated with maternal outcome such as woman's obstetrical history (primiparity), somatic diseases, TORCH-infection ($p < 0.05$) and perinatal outcome. The lean umbilical cord in the long run results in reduced fetoplacental circulation, thus resulting in intrauterine growth restriction ($p < 0.0001$), fetal distress and hypoxia, which required the neonatal intensive care ($p < 0.0001$) (tab. 1). The neonatal morbidity in the study group was observed in 16 (8.42%) cases and was

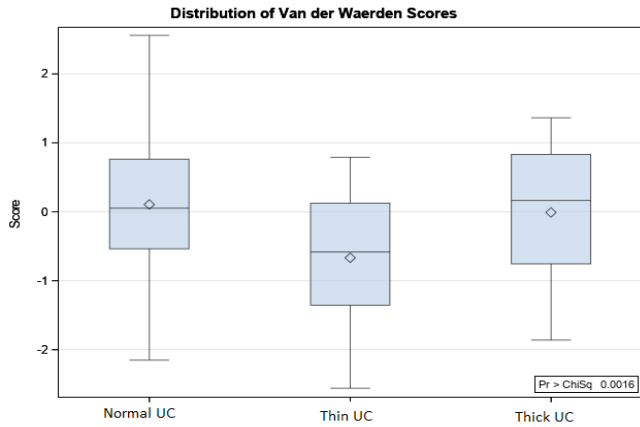


Fig. 1. Distribution of groups according to the birth weight.

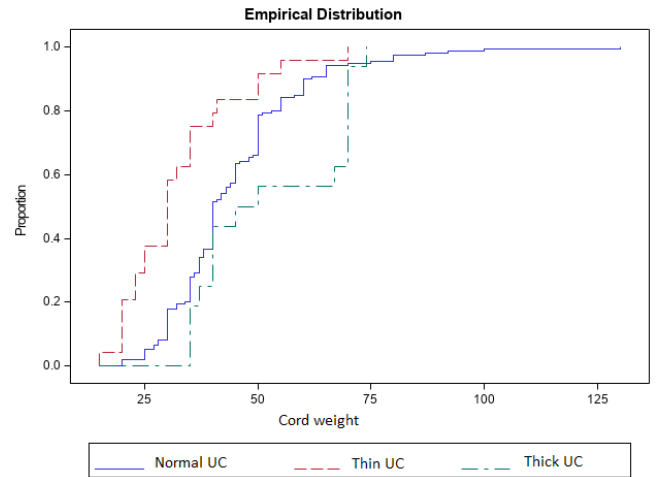


Fig. 3. Distribution of groups according to the cord weight.

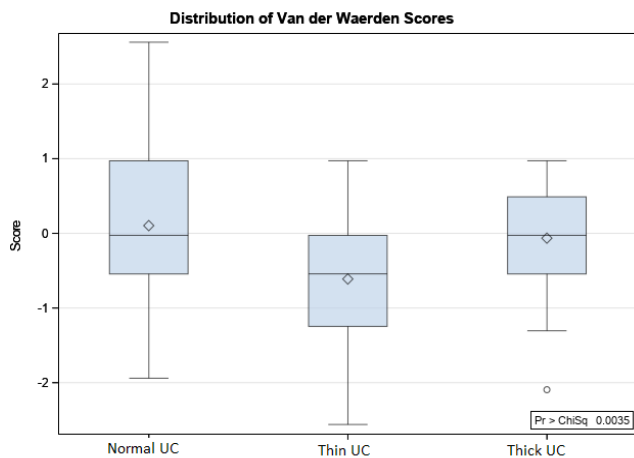


Fig. 2. Distribution of groups according to the newborn length.

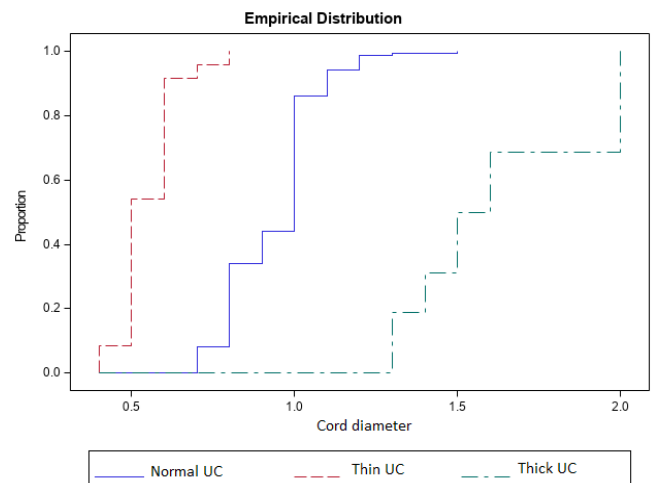


Fig. 4. Distribution of groups according to the cord diameter.

presented as infectious complications (intrauterine infection – 2 (2.53%), pneumonia – 3 (3.80%)), respiratory distress syndrome (RDS) in 5 (2.65%) cases, IUGR and anemia in 2 cases each (2.53%), metabolic disorders – 4 (5.06%), central nervous system diseases – 2 (2.53%), respiratory

disorders – 10 (12.66 %). No association was found among disorders from other organs and systems.

Analysis of the morphological proprieties of the UC demonstrated that the length in the L_0 ranged between

Table 1

Maternal and perinatal factors of the lean umbilical cord

The evaluated characteristics	χ^2	P value	Cramer's V
Primipara	9.56	0.04	0.16
Extragenital pathology:			
- ENT diseases	21.04	0.02	0.9
- diseases of the urinary system	7.10	0.02	0.2
- endocrine system diseases	37.76	0.0006	0.4
TORCH-infection (Mycoplasma)	33.55	0.006	0.3
Insufficiency of placental circulation	15.29	0.0005	0.3
IUGR	23.32	<0.0001	0.35
Fetal bradycardia	18.32	0.001	0.2
Pathological CTG	30.89	<0.0001	0.3
Fetal hypoxia	30.02	<0.0001	0.4
Pathological adaptation period	19.27	<0.0001	0.32
Neonatal morbidity	8.61	0.01	0.2
Transfer to other medical facilities	13.98	0.0009	0.3

Note: UC – umbilical cord; ENT – ear, nose, and throat; CTG – cardiocotography; IUGR – Intrauterine growth restriction.

42-69 (55.6±7.29) cm, but in the $L_1 = 25-83$ (53±3.37) cm ($p>0.05$) frequently with a rectilinear or slightly spiral normoform appearance and only segmentally being attested some varicose or trajectory disorders of the vascular device in cross sections. The weight of the UC varied between 20-130 (44.72±1.27) g in the control group vs 15-70 g (32.6±2.6) in the study group ($p<0.01$) (fig. 3). The diameter of the umbilical cord was ≤ 10 mm ($p<0.01$), which was lower than the 10th percentile of the normal range (fig. 4).

Histological examination in cross sections found the form disorders of the UC and structural abnormalities of the cell-matrix component of the Wharton's jelly. It showed a decrease in differentiation of the areas (perivascular, intermediate and subepithelial), being presented by a homogeneous structure, hypocellular or acellular perivascular with low or high density (fig. 5, 6).

The Van Gieson's method was used to assess the physical and chemical properties of the Wharton's jelly. It is the simplest method of differential staining of collagen and

other connective tissue showed a close correlation with the umbilical vein muscles, the presence of variable density of the Wharton's connective tissue in the peripheral muscle layer without the strict differentiation of the cells and the presence of scattered myocytes (fig.7). The evaluation of the Wharton's jelly by Alcian blue (pH 2.5), which stains acid mucosubstances and acetic mucins, designated the positive features of the stroma's persistence penetration and absorption capacities. The mesenchymal mucin in the stroma of the Wharton's jelly is more pronounced compared to the vascular one (fig.8).

Thus, the macroscopic and microscopic examination in the study group attested some particularities of the thin umbilical cord such as the presence of disorders in the stromal (Wharton's jelly) and vascular components. No less significant is the presence of segmental muscle hypoplasia or vascular muscles with frequent aneurysmal deformation of the umbilical vein. The formation of capillary vessels was also detected in the peripheral region of Wharton's jelly.

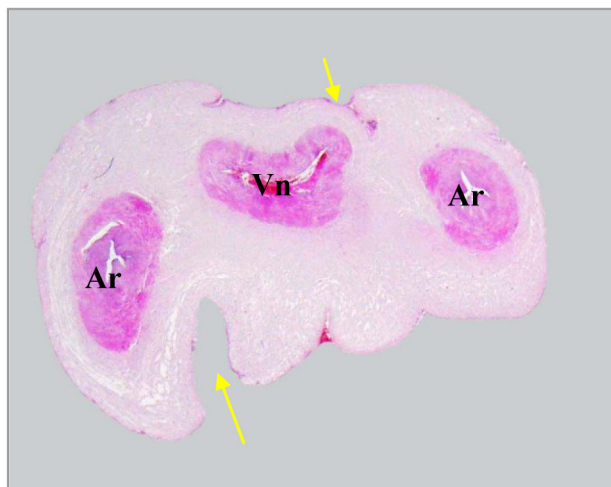


Fig. 5. Folded scalloped surfaces, reduced differentiation of the Wharton's jelly, variable density of the matrix cellular component. $\times 6$, H&E.

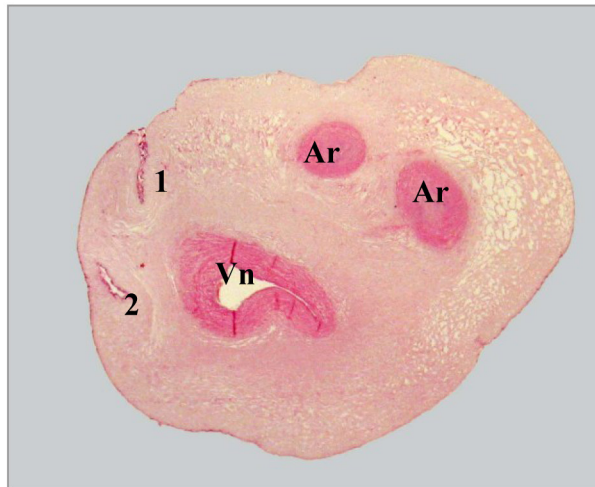


Fig. 6. Oval shape of the UC, central device with variable thickness of the Wharton's jelly, hernia of the epithelial tissue (1) in the intermediate area with formation of the cysts (2). $\times 6$, H&E.

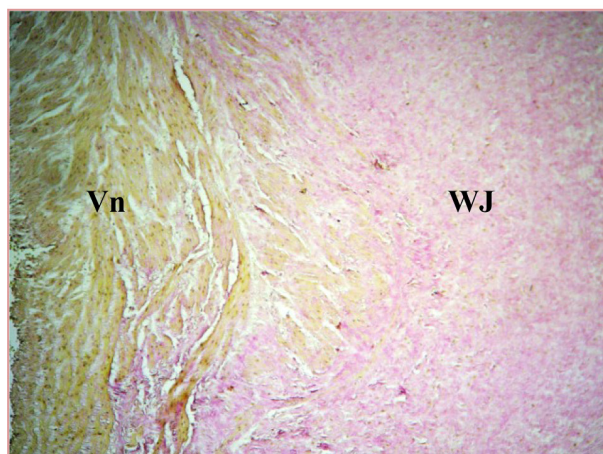


Fig. 7. Features between the collagen component of the connective tissue of the WJ and the muscle component of the umbilical vein. $\times 100$, VG.

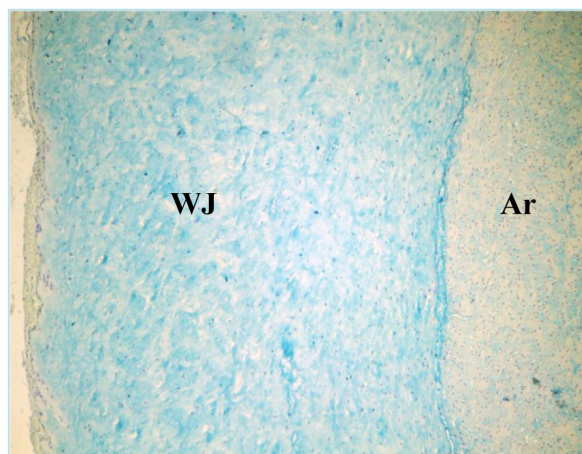


Fig. 8. Positive test for mesenchymal mucins of the WJ and vascular mucin of the umbilical artery. $\times 100$, Alcian blue.

Discussion

Previous studies have found an association of thin cord with fetal growth restriction and other poor fetal outcomes [14,15]. Very often, a lean umbilical cord is combined with hypocoiling, which also renders umbilical cord vessels susceptible to kinking and acute obstruction. Wharton's jelly reductions have also been recognized as a possible cause of fetal death in the presence of single umbilical artery, which is the most common abnormality of the umbilical cord [16].

Proctor et al. [17] studied 497 umbilical cords of gestational ages ranging from 18 weeks to 41 weeks. They found that the umbilical cord diameter increases as the gestational age progresses until 28 weeks when it reaches a plateau at approximately 1.0 cm. These findings are in agreement with the antenatal ultrasound assessment of the umbilical cord that describes an increase in diameter with gestational age until the third trimester. Di Naro et al. [9] obtained a similar result demonstrating the sonographic umbilical cord diameter and area increase as a function of gestational age until the 32nd week of pregnancy. After that, a reduction in the diameter of the umbilical cord can be observed due to the water content of Wharton's jelly at the end of the pregnancy [9].

Using Proctor's nomogram, they identified and classified the umbilical cord diameter as thin (< 10th percentile), average (10th–90th percentile) and thick (> 90th percentile), and concluded that the umbilical cord components were responsible for the diameter variation. Their findings show that a significant increase in the vessel area (specifically an increase in the umbilical artery wall area) is responsible for a thick umbilical cord diameter, while a significant decrease in Wharton's jelly area is responsible for a thin umbilical cord diameter. Proctor et al. [17] showed that there was a relationship between the umbilical cord diameter and gross placental pathologic features. A thin umbilical cord was associated with low placental weight percentile, a single umbilical artery, and a marginal umbilical cord insertion [17]. Baergen et al. [18] demonstrated that an abnormally thin umbilical cord is associated with adverse pregnancy outcomes such as oligohydramnios, fetal growth restriction, and fetal distress.

Filiz et al. [8] investigated the relationship between the amount of Wharton's jelly and its protective role in umbilical cord vessels, and hence, in fetal growth. Their study concluded that the "quality" and characteristics of Wharton's jelly were both important in its protective role. Abnormal situations, such as a decrease in the hyaluronic acid content of Wharton's jelly and Wharton's jelly fibrosis, may affect the mechanical characteristics of the cord, which leads to impaired fetal circulation, anoxia, and fetal death.

Silver et al. [19] reported that in post-term pregnancies, the umbilical cord diameter is smaller in patients with oligohydramnios compared with normal amniotic fluid. In addition, these authors found a higher incidence of antepartum variable decelerations in patients with a small umbilical cord diameter compared with those with a normal umbilical cord. Raio et al. [20] found an association between the

presence of a thin umbilical cord and the delivery of an infant who is small for its gestational age.

The possible physiopathologic mechanisms for this anomaly could be an incomplete fusion of the amniotic covering and the mesenchyme of the umbilical cord during early development, or a hypoplasia of this amniotic covering with a secondary loss of Wharton's jelly [21]. Decreased WJ area is associated with clinically-significant placental pathology and WJ area scales proportionally with placental size. These findings suggest that WJ area correlates with functional capacity of the placenta and thus merits further evaluation alongside currently-available tests of placental function in clinical practice [16].

Pathologic studies and case reports demonstrated that a thin umbilical cord is associated with oligohydramnios, fetal distress, and adverse pregnancy outcome. Careful umbilical cord examination often reveals significant lesions which may be associated with these processes. As obstetricians, we realize this when a heavy toll of fetal life is due to cord complications. Suspected fetal distress is not uncommon. Often no explanation for such intrapartum complication is apparent. Complications associated with lean umbilical cord may explain this enigma [1].

Conclusions

The present study showed that the diameter of umbilical cord is variable, but cases which had thin UC constituted abnormal cord diameter. The findings suggest that the clinico-morphological aspects of the lean umbilical cord were associated with a high risk of maternal and perinatal outcomes ($p < 0.05$). The changes in the quantity or quality of Wharton's jelly affect the diameter of the umbilical cord and the hemodynamics of its vessels, leading to impaired fetal blood flow and consequently low weight gain and fetal demise. Morphometric parameters of the umbilical cord are considered as markers of fetal development disorders, and their early assessment allows to predict risk of adverse outcomes in children. In case of the thin umbilical cord, rather expressed dystrophic and degenerative changes of all the umbilical cord structures are detected. These pathomorphological changes of umbilical cord structures are supposed to play a great part in the development of fetal hypoxia. Therefore, our study attests that all umbilical cords should be submitted for complete examination.

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Authors' contributions

AA designed the trial and interpreted the data, drafted the first manuscript; VP described morphology; NC revised the manuscript. All the authors approved the final version of the manuscript.

Funding

It was provided by *Nicolae Testemitanu* State University of Medicine and Pharmacy and Mother and Child Institute. The trial was the authors' initiative. The authors are independent and take responsibility for the integrity of the data and accuracy of the data analysis.

Ethics approval and consent to participate

The protocol of the study was approved by the Ethics Committee No 95/110 21.06.2017 of *Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova. It was obtained an informed consent from all participants in the study.

Conflict of Interests

There are no known conflicts of interests and financial or non-financial support associated with this publication.