RESEARCH ARTICLE

Postnatal Histomorphometric Study of Umbilical Vessels and their Relationship with Neonatal Anthropometry in Low-risk Pregnancies

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Abstract

Background: Umbilical vessels are an extension of the fetal cardiovascular system, which are essential parts of fetal circulation and fetal wellbeing. Umbilical vessels are altered in maternal and fetal conditions, so they can be used to predict adverse pregnancy outcomes. Prenatal sonographic studies have developed nomograms of umbilical vessels in normal pregnancies and established their relationship with fetal biometry. However, there is a scarcity of such studies in the postnatal period.

Aim and objective: The aim and objective is to develop postdelivery histomorphometrical reference values for area and diameter of umbilical vessels across the available gestational age (GA) spectrum in low-risk pregnancies and secondly to examine the nature of its association with neonatal anthropometry.

Materials and methods: A cross-sectional study was carried out on 164 low-risk pregnant women between GA of 32 and 42 weeks. Umbilical cord (UC) samples were procured soon after delivery. Formalin-fixed paraffin-embedded tissue blocks were processed, stained, and histomorphometric measurements of umbilical vessels were carried out by Olympus microscope. Neonatal anthropometry was noted. The mean and percentile were calculated for each GA. Pearson's Correlation was used to assess the relationship between umbilical vessels parameters with neonatal anthropometry.

Results: Reference values and percentiles of diameter and area of umbilical vessels for each GA were calculated. Cross-sectional area and diameter of umbilical vein (UV) attained peak at 34 weeks of GA whereas both umbilical arteries (UAs) reached the peak at 36 weeks of GA and stabilized thereafter. A statistically significant positive correlation was observed between all umbilical vessels parameters with all neonatal anthropometric measurements (p <0.001). The regression equation for the prediction of newborn birth weight (y) according to the area (A) of umbilical vessels is 1.750 + 0.343(UA2A) + 0.248(UVA). It shows that the area of UA2 and UV are good predictors of newborn birth weight.

Conclusion: The study provides reference values of umbilical vessels area and diameter of post-delivery from 32 to 42 weeks of gestation in low-risk pregnancies. These reference values of umbilical vessels provide baseline values for pathological and perinatal studies in the future. The study showed a positive relationship between umbilical vessels measurements and neonatal anthropometry. These results may be useful during perinatal pathological examination of UC and can be used as a predictor for neonatal complications.

Keywords: Histomorphometry, Low-risk pregnancies and neonatal anthropometry, Umbilical arteries, Umbilical vein, Umbilical vessels.

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Introduction

The umbilical cord (UC) is organized in such a way that it provides ceaseless blood supply through the umbilical vessels to the developing embryo even though it is influenced by maternal systemic and uterine conditions throughout the pregnancy phase. Umbilical vessels have well-defined tunica intima, tunica media though tunica adventitia is not well organized. Wharton's jelly gives protective covering akin to the adventitial layer to the umbilical vessels. Umbilical vessels are considered as medium-sized vessels and they differ in structure and function from that of systemic vessels. The systemic artery has internal elastic lamina (IEL) as a characteristic feature, which is lacking in the umbilical artery (UA) instead the umbilical vein (UV) has IEL. Other unique features of umbilical vessels are arteries transport deoxygenated and vein oxygenated blood, and they are devoid of vasa vasorum and innervation.[1,2]

Prenatal evaluation of UC is restricted to noting the number of vessels and to some extent assessment of the impedance to blood flow of UA by Doppler waveform analysis. Many workers have investigated gross,[3] sonographic, and microscopic morphometric characteristics of umbilical vessels, which are altered in conditions, such as preeclampsia, pregnancy-induced hypertension (PIH),[4] diabetes mellitus,[5] and intrauterine growth restriction (IUGR), and showed its adverse effect on pregnancy outcome.[6–9] Adverse events during intrauterine life bring the altered fetal programming

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of organs. Early changes in vessels, mainly arterial stiffness may predispose to cardiovascular disease in adult life.[10–14] Hence, the normal anatomy and physiology of umbilical vessels are very crucial for the well-being of the fetus.

With the advancement in ultrasonography (USG) technology, prenatal sonographic studies have provided precise morphological knowledge of the development of UC and its relationship with fetal size by developing nomograms in normal pregnancies.[15–19] However, there is a dearth of such studies in the postnatal period. The structural composition of umbilical vessels is altered in maternal and fetal conditions, these alterations when measured can be used to predict adverse pregnancy outcomes. Hence, it is essential to establish standardized normal values of UC and its content for the given population. Proctor et al.[20] in 2013 for the first time developed a postdelivery nomogram for UC diameter on a fresh cord without considering umbilical vessels. An important aspect of this study was it was not limited to normal as it included high risks pregnancies also. They did suggest that uncomplicated pregnancies might provide a more reliable nomogram.

Hence to overcome the shortcoming of the previous study, the present study was designed to develop postdelivery histomorphometrical reference values for area and diameter of umbilical vessels across the available gestational age (GA) spectrum in low-risk pregnancies and secondly to examine the nature of its association with neonatal anthropometry.

Materials and Methods

A cross-sectional study was carried out on low-risk pregnant women having GA between 32 and 42 weeks at tertiary care KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. The institutional ethical committee approved the research project. According to the selection criteria study was conducted on 164 UC samples, out of 310 over 1 year and evaluated in the study.

Inclusion criteria were singleton fetuses from uneventful pregnancies with maternal age between 18 and 35 years from normal and cesarean delivery. Exclusion criteria include multiple pregnancies; maternal complications like diabetes mellitus, PIH, heart disease, renal disorders, intrauterine infections, oligohydramnios, and polyhydramnios; fetal complications like congenital anomalies, intrauterine deaths, IUGR babies, single umbilical artery; unknown GA and unavailability of history of pregnancy and delivery.

From the eligible subjects, relevant data were recorded in a prescribed pro forma. GA was determined by the last menstrual period or 1st-trimester USG. Newborn birth weight was recorded using a digital baby-weighing machine. Other anthropometry like mid-arm circumference (MAC) between the acromion process and olecranon process, abdominal circumference (AC) at the level of the umbilicus, chest circumference (CC) at the level of the nipple, and head circumference (HC) along the supraorbital ridge and occipital prominence were measured with a nonelastic tape in centimeter. soon after the birth.[21]

Umbilical cord tissue samples were procured soon after the delivery at the placental end. Formalin-fixed, paraffin-embedded tissue blocks were processed for Hematoxylin and Eosin and Masson's trichrome staining for light microscopy. UC cross-sections were examined and measured for different variables using an Olympus CX41 binocular microscope with a DP21 digital camera image analyzer. Then the reliability of the instrument was checked by the intraclass correlation coefficient test that showed very good agreement (0.935) between two examiners.

The umbilical vessel area was measured with the help of a polygonal area tool where the superimposed area was drawn over the vessel area. Vessel diameter was measured using a length tool and two readings were taken at right angles to each other.[20] All measurements were taken at 40 × magnification and results were displayed automatically on the screen. For each parameter, two to four readings were taken on every section and the average was calculated. Umbilical artery (UA) with the smaller area was considered as UA-1 and the larger one as UA-2. To avoid bias, all the measurements were taken from the same instrument and by the first author.

Statistical analysis was performed using SPSS version 20. Mean, standard deviation, and umbilical vessel's 10th, 50th, 90th percentiles were calculated. The normality of all parameters was tested by the Kolmogorov–Smirnov test. Normality was met and the parametric test like Karl Pearson's Correlation Coefficient was used to assess the relationship between UC variables with neonatal anthropometry. Stepwise multiple linear regression was performed to find out the best predictors of birth weight. The statistical significance was set at $p < 0.05$.

Results

The mean maternal age of the subjects was 24 years with a standard deviation of 3.17, and the mean GA at delivery was 38.76 ± 1.90. Out of total subjects, 56% of mothers were multigravida and out of all deliveries, 62% were vaginal deliveries. Male (49%) and female (51%) babies were nearly equal in number and mean birth weight was 2.89 ± 0.51. Mean values of AC, MAC, CC, and HC were 29.24 ± 2.10, 10.37 ± 1.07, 31.55 ± 2.05, and 33.17 ± 1.55, respectively.

Descriptive measurements and percentiles of diameter and area for each GA of UV in Tables 1 and 2 and for both UAs 1 and 2 in Tables 3 to 6 were presented respectively. Diameter and area of UV attained peak at 34 weeks of GA whereas both 1 and 2 UAs reached a peak at 36 weeks of GA and stabilized thereafter. These tables can be utilized to identify lean vessels that are less than 10th, average vessels between 10th to 90th and large vessels more than 90th percentile at different GA.

Table 1: Descriptive measurements and percentiles of umbilical vein diameter (UVD) for each gestational age (GA)

			95% CI of mean		*Percentiles*		
GA (weeks)	*n*	*Mean ± SD (mm)*	*Lower limit*	*Upper limit*	*10th*	*50th*	*90th*
32	3	1.50 ± 0.25	0.87	2.12	1.30	1.41	
33	3	1.57 ± 0.28	0.87	2.28	1.35	1.48	
34	3	1.79 ± 0.08	1.59	1.99	1.69	1.82	
35	4	1.64 ± 0.08	1.51	1.77	1.58	1.62	
36	6	1.63 ± 0.20	1.42	1.84	1.26	1.71	
37	22	1.55 ± 0.21	1.46	1.65	1.17	1.60	1.75
38	34	1.57 ± 0.21	1.50	1.65	1.36	1.58	1.90
39	39	1.58 ± 0.18	1.52	1.64	1.35	1.58	1.82
40	34	1.56 ± 0.53	1.49	1.62	1.31	1.55	1.81
41	13	1.58 ± 0.20	1.46	1.70	1.27	1.56	1.92
42	3	1.59 ± 0.20	1.10	2.07	1.44	1.51	

Table 2: Descriptive measurements and percentiles of umbilical vein area (UVA) for each gestational age (GA)

			95% CI of mean		*Percentiles*		
GA (weeks)	*n*	*Mean ± SD (mm²)*	*Lower limit*	*Upper limit*	*10th*	*50th*	*90th*
32	3	1.82 ± 0.66	0.17	3.47	1.22	1.72	
33	3	2.02 ± 0.69	0.30	3.74	1.38	1.93	
34	3	2.37 ± 0.15	1.99	2.74	2.20	2.40	
35	4	2.31 ± 0.08	2.18	2.45	2.23	2.31	
36	6	2.22 ± 0.52	1.67	2.77	1.25	2.42	
37	22	2.16 ± 0.46	1.95	2.36	1.64	2.12	2.84
38	34	2.14 ± 0.54	1.95	2.33	1.59	2.09	3.09
39	39	2.29 ± 0.47	2.14	2.44	1.78	2.18	2.76
40	34	2.17 ± 0.53	1.98	2.35	1.56	2.05	3.00
41	13	2.31 ± 0.58	1.96	2.67	1.72	2.04	3.49
42	3	2.20 ± 0.59	0.75	3.66	1.84	1.90	

Table 3: Descriptive measurements and percentiles of umbilical artery 1 diameter (UA1D) for each gestational age (GA)

			95% CI of mean		*Percentiles*		
GA (weeks)	*n*	*Mean ± SD (mm)*	*Lower limit*	*Upper limit*	*10th*	*50th*	*90th*
32	3	1.20 ± 0.18	0.76	1.65	1.09	1.11	
33	3	1.24 ± 0.16	0.84	1.64	1.07	1.26	
34	3	1.32 ± 0.02	1.27	1.37	1.30	1.32	
35	4	1.32 ± 0.04	1.26	1.38	1.27	1.33	
36	6	1.33 ± 0.26	1.05	1.60	0.97	1.45	
37	22	1.23 ± 0.17	1.15	1.30	1.01	1.23	1.47
38	34	1.28 ± 0.18	1.21	1.34	1.04	1.27	1.50
39	39	1.28 ± 0.17	1.23	1.34	1.06	1.26	1.52
40	34	1.29 ± 0.14	1.24	1.34	1.13	1.28	1.45
41	13	1.24 ± 0.18	1.14	1.35	1.01	1.22	1.55
42	3	1.26 ± 0.23	0.70	1.82	1.07	1.21	

Table 4: Descriptive measurements and percentiles of umbilical artery 1 area (UA1A) for each gestational age (GA)

			95% CI of mean		*Percentiles*		
GA (weeks)	*n*	*Mean ± SD (mm²)*	*Lower limit*	*Upper limit*	*10th*	*50th*	*90th*
32	3	1.17 ± 0.45	0.04	2.29	0.87	0.94	
33	3	1.23 ± 0.21	0.71	1.75	0.99	1.35	
34	3	1.29 ± 0.25	0.67	1.90	1.05	1.27	
35	4	1.46 ± 0.17	1.19	1.74	1.25	1.48	
36	6	1.49 ± 0.57	0.89	2.08	0.76	1.66	
37	22	1.18 ± 0.30	1.04	1.31	0.82	1.17	1.74
38	34	1.46 ± 0.49	1.28	1.63	0.89	1.42	2.05
39	39	1.46 ± 0.39	1.33	1.58	1.00	1.41	1.98
40	34	1.39 ± 0.32	1.28	1.50	1.05	1.32	1.91
41	13	1.38 ± 0.49	1.08	1.67	0.90	1.12	2.22
42	3	1.37 ± 0.58	–0.08	2.83	0.91	1.18	

Table 5: Descriptive measurements and percentiles of umbilical artery 2 diameter (UA2D) for each gestational age (GA)

			95% CI of mean		*Percentiles*		
GA (weeks)	*n*	*Mean ± SD (mm)*	*Lower limit*	*Upper limit*	*10th*	*50th*	*90th*
32	3	1.23 ± 0.11	0.95	1.51	1.11	1.25	
33	3	1.23 ± 0.01	1.21	1.26	1.23	1.23	
34	3	1.28 ± 0.09	1.05	1.51	1.18	1.32	
35	4	1.40 ± 0.19	1.10	1.71	1.14	1.45	
36	6	1.46 ± 0.28	1.17	1.75	1.01	1.54	
37	22	1.42 ± 0.36	1.26	1.58	1.10	1.29	2.13
38	34	1.40 ± 0.21	1.32	1.47	1.16	1.35	1.68
39	39	1.44 ± 0.21	1.38	1.51	1.13	1.44	1.70
40	34	1.44 ± 0.20	1.38	1.51	1.23	1.42	1.72
41	13	1.39 ± 0.22	1.26	1.52	1.17	1.32	1.79
42	3	1.45 ± 0.38	0.50	2.40	1.04	1.52	

Table 6: Descriptive measurements and percentiles of umbilical artery 2 areas (UA2A) for each gestational age (GA)

			95% CI of mean		*Percentiles*		
GA (weeks)	*n*	*Mean ± SD (mm²)*	*Lower limit*	*Upper limit*	*10th*	*50th*	*90th*
32	3	1.38 ± 0.27	0.71	2.05	1.12	1.35	
33	3	1.39 ± 0.06	1.25	1.53	1.32	1.41	
34	3	1.41 ± 0.10	1.18	1.65	1.32	1.42	
35	4	1.74 ± 0.20	1.41	2.07	1.54	1.71	
36	6	1.80 ± 0.64	1.13	2.47	0.81	1.97	
37	22	1.71 ± 0.64	1.43	1.99	1.00	1.62	2.72
38	34	1.78 ± 0.52	1.60	1.96	1.10	1.86	2.50
39	39	1.78 ± 0.39	1.66	1.91	1.30	1.76	2.44
40	34	1.79 ± 0.36	1.66	1.91	1.27	1.73	2.31
41	13	1.72 ± 0.56	1.39	2.06	1.10	1.58	2.65
42	3	1.78 ± 0.73	–0.02	3.59	1.37	1.37	

Table 7: Pearson correlation between umbilical vessels parameter with neonatal anthropometric measurements

Umbilical vessels parameter	*Birth weight*	*AC*	*MAC*	*CC*	*HC*
UV diameter	0.28[a]	0.25[a]	0.24[a]	0.21[a]	0.25[a]
UV area	0.36[a]	0.32[a]	0.32[a]	0.29[a]	0.33[a]
UA1 diameter	0.32[a]	0.31[a]	0.31[a]	0.24[a]	0.25[a]
UA1 area	0.38[a]	0.37[a]	0.32[a]	0.30[a]	0.26[a]
UA2 diameter	0.28[a]	0.28[a]	0.26[a]	0.21[a]	0.20[a]
UA2 area	0.36[a]	0.36[a]	0.34[a]	0.29[a]	0.27[a]

[a]$p \leq 001$. AC, abdominal circumference; MAC, mid-arm circumference; CC, chest circumference; HC, head circumference; UV, umbilical vein; UA, umbilical artery

A statistically highly significant positive correlation was observed (Table 7) between all umbilical vessels parameters with all neonatal anthropometric measurements. Hence, results indicate that neonatal anthropometry is a function of the umbilical vessel's area and diameter. Interestingly, neonatal anthropometry showed a higher R-value with an area of umbilical vessels.

Regression analysis was carried out to know the best and significant predictors like diameter and area of umbilical vessels, which affect the birth weight. The multiple stepwise linear regression was performed and the area of UA2 and UV are found to be significant predictors of newborn birth weight. Therefore, to predict birth weight the following regression equation was established. Newborn birth weight = 1.750 + 0.343(UA2A) + 0.248(UVA). This model was found to be significant with R = 0.47, F = 22.53, p <0.001. Further R^2 is found to be 0.219 means the total contribution of parameters like the area of UA2 and UV on newborn birth weight is approximately 21.9%. In future research, the area of UA2 and UV can be used as good predictors of newborn birth weight.

Discussion

In the present study, we have developed reference values of the postdelivery area and diameter of umbilical vessels from 32 to 42 weeks of gestation in low-risk pregnancies. The study showed a significant positive relationship between umbilical vessel's measurements with neonatal anthropometry.

Weissman et al.[17] first introduced the UC nomogram between 15 and 41 weeks of gestation. Later Togni et al.[16] and Barbieri et al.[18] constructed nomograms for diameter and area of umbilical vessels using sonographic measurements in normal pregnancies. Weissman et al. and Barbieri et al. observed that values increased consistently according to GA and reached the peak at 32–33 weeks, whereas Togni et al.[16] observed UV area increasing up to 34 and artery till 36 weeks after which they remained stable.[21] Recently, Afroze et al.[22] conducted a study for the Indian population and noted that the UV area increased up to 37 and UA until 36 weeks of GA. In the present study, UV attained peak at 34 and UAs at 36 weeks of GA followed by a plateau and these results are comparable to prenatal studies of Togni and Afroze et al. There is a lack of literature about detailed postnatal umbilical vessel histomorphometry for each GA. We have come across one study carried out in the Chinese population on UV diameter where they observed that it reached a peak at 37–40 weeks. In this study, the observations were made at the interval of 4 weeks of GA and not every week, and also they have not defined the subject selection criteria.[23] The difference of 1 or 2 weeks may be due to racial differences, measuring methods, selection criteria, and sample size. Proctor et al.[20] have constructed the postdelivery nomogram using fresh UC samples only for UC diameter but did not include umbilical vessels.

Since anthropometry is always a gold standard method to assess fetal growth whether it is *in utero* or *in vivo*. The present study has attempted to reveal the nature of the association between umbilical vessels measurements and neonatal anthropometry and observed significant positive correlations between all umbilical vessel's diameter and area with all neonatal anthropometric measurements. Prenatal studies[16,19] found a significant correlation of the area of UV and UA with fetal biometry that is in accordance with the present study. Even after an exhaustive search, the postdelivery nomogram of umbilical vessels and its relationship with all neonatal anthropometry parameters was inadequate in the literature. Only the postnatal study of Peyter et al.[8] reported a correlation of cross-sectional area of UV with birth weight. More postnatal studies are needed to explore the relation of vessels with body weight as well as other anthropometric parameters. Previous studies[15,17,19] have given regression equations for UC parameters according to GA. The present study has attempted to explore the association of multiple predictors on newborn birth weight and given a regression equation that is more of practical use in future research. We found that areas of UA2 and UV are predictors for newborn birth weight. This indicates that areas of umbilical vessels are better parameters to measure than the diameter, as UC is not always having a geometrically perfect circular shape.

Umbilical vessels are an extension of the fetal cardiovascular system that is an essential part of fetal circulation and fetal wellbeing. According to microscopic structural studies, developing human umbilical vessels have abundant smooth muscle cells (SMCs) in tunica media that form the main component of vessels along with moderate amounts of collagen and elastin. SMCs of umbilical vessels structurally and functionally acquire fully differentiated contractile phenotype during the third trimester.[1,23] Since umbilical vessels are devoid of innervation, the tone of vessels is regulated mainly by contraction and relaxation of SMCs induced by the action of vasoactive agents like nitric oxide (NO) secreted by endothelial cells, which are sensitive to alteration in blood flow.[1,24] Blood vessels arise from mesoderm derived hemangioblasts (angioblast) which are mediated by vascular endothelial growth factor that induces differentiation of endothelial cells. Blood vessel's myogenesis and maturation are controlled by platelet-derived growth factor and transforming growth factor (TGFβ).[25] When these genes show altered expression, which is exhibited as maldeveloped vasculature leading to uteroplacental insufficiency that is the most common impediment for fetal growth leading to inadequate transport of nutrients.[26,27] These adverse events during intrauterine life may lead to circulatory adoption mainly increasing arterial stiffness that is considered as a risk factor for vascular aging and cardiovascular pathology in adult life.[10–13] Elastin is one of the major determinants for vessel compliance. Reduced elastin synthesis leads to increased arterial stiffness that affects UA compliance, mechanical properties along with smaller vessel areas.[6] Umbilical vessels are more vulnerable to altered hemodynamic and hypoxic conditions, which leads to impaired activity of NO that causes degenerative structural changes which were well established in IUGR and preeclamptic conditions and even worsening with abnormal UA blood flow.[8,9,28–30] Continuous blood flow through the vessels is necessary to maintain the vascular functions and structural integrity of umbilical vessels.[23] Hence, any pathological conditions may have the potential to affect the structure of vessels. Descriptive histomorphometric study of umbilical vessels in normal conditions would facilitate to differentiation between normal and abnormal conditions.

The limitation of this study is it had fewer samples in 32–36 and 42 weeks of GA group. We have collected samples from a tertiary hospital, where they receive most of the high-risk pregnancies. Even though samples from premature delivery of less than 37 weeks were available, but most of them were associated with maternal complications or IUGR babies. Hence, we found it difficult to get UC samples of less than 37 weeks in normal conditions. A higher number of samples may give a more reliable result.

Conclusion

In the absence of availability of postnatal nomograms of umbilical vessels, our study provides more precise reference values of postdelivery area and diameter of umbilical vessels from 32 to 42 weeks of gestation in low-risk pregnancies by the histomorphometric method. These reference values of umbilical vessels provide baseline values for pathological and perinatal studies in the future. Secondly, the study showed a significant positive relationship of postdelivery measurements of umbilical vessels with neonatal anthropometry. These results may be useful during perinatal pathological examination of UC and can be used as a predictor for neonatal complications.

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