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ORIGINAL RESEARCH

Maternal Fetal Medicine

Umbilical cord structural changes in Kenyan women with anemia diagnosed within the first 20 weeks of pregnancy: A retrospective cohort study.

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Abstract

Background: Gestational anemia is a global health concern. The initial 20 weeks of pregnancy are critical for the development and prevention of negative pregnancy outcomes related to low hemoglobin levels.

Objective: To compare the structural characteristics of the umbilical cord (UC) in women diagnosed with anemia in the first 20 weeks of pregnancy with those without anemia.

Methods: This was a retrospective cohort study conducted at the Kenyatta National Hospital. Thirty-six umbilical cords were collected and examined for differences in gross and histological features. Comparisons were also made between the fetal and placental ends of the UC for these features.

Results: Significant differences were observed in the diameter of the umbilical cord, the volume of Wharton's jelly, and the intima-media thickness of the umbilical vein (all $p<.05$) between the anemic and nonanemic group. Disruption of the internal elastic lamina and intimal thickening of the umbilical vein were more prominent toward the fetal end of the UC in the anemia group. However, the increased risk of low birth weight in this group was not statistically significant, with a relative risk (RR) of 4.0 (95% CI: 0.49-32.39).

Conclusion: Anemia within the first 20 weeks is associated with structural changes in the UC that may contribute to adverse outcomes. Improving hemoglobin levels before conception and during early pregnancy is therefore critical.

Keywords: adverse pregnancy outcomes, anemia, gestational anemia, low birth weight, umbilical cord.

Introduction

According to the World Health Organization, anemia in pregnancy is defined as hemoglobin (Hb) levels <11 g/dL in the first and third trimester or <10.5 g/dL in the second trimester (1). Iron deficiency anemia is the most common cause of anemia in pregnancy and results from hemodilution due to expanded plasma volume, combined with increased iron requirements for both the mother and the developing fetus (2). Gestational anemia (GA) disproportionately affects low- and middle-income countries (LMICs), including Kenya, with prevalence rates as high as

56%, compared with 17.4% in high-income countries (3). The prevalence of GA in Kenya was 55.1% in 2013 (4). When the prevalence of GA in a population reaches 40% or higher, it is considered a severe public health problem (5).

Gestational anemia is associated with adverse fetomaternal outcomes such as low birth weight (LBW), fetal growth restriction, preterm birth, and postpartum hemorrhage (6). Anemia during the early stages of pregnancy may have a greater negative impact on fetal growth than anemia developing later, and restoration of Hb levels after 20 weeks does not appear to improve pregnancy outcomes (6,7). Iron supplementation and restoration of Hb during the periconceptual period may reduce the risk of adverse pregnancy outcomes (APOs) (8). The first 20 weeks of pregnancy may therefore represent the critical window during which low Hb exerts its greatest impact on pregnancy outcomes (7). These findings therefore emphasize the importance of timing in the manifestation and prevention of anemia-related adverse pregnancy outcomes.

A plausible biological mechanism linking early-onset anemia to APOs is oxidative stress. Anemia contributes to oxidative stress by reducing oxygen delivery and promoting compensatory increases in free radical generation (9). Oxidative stress is a central mechanism in the pathogenesis of several pregnancy-related complications, including preeclampsia, which is thought to arise from early placental ischemia-reperfusion injury and endothelial dysfunction (10). Correcting anemia before 20 weeks of gestation may therefore have added benefits beyond improving maternal hematologic status, as it could mitigate the oxidative imbalance that predisposes to APOs, such as preeclampsia. Although direct interventional evidence is limited, observational studies consistently link early anemia with higher APO risk, suggesting that timely correction may play a preventive role.

During pregnancy, the umbilical cord is the vital conduit for transport of oxygen, nutrients, and waste products between the fetus and the placenta (11). Because of its critical role in fetal development, any functional or structural alteration in the umbilical cord properties could adversely affect pregnancy outcomes (12). The umbilical cord achieves its final form by the 12th week of gestation (13). Thus, its structural and functional maturation occurs during the same critical period when anemia may exert adverse effects. Anemia may alter the structural features of the umbilical cord, such as vascular architecture, by modifying the hemodynamic properties of blood flow and elevating levels of angiogenic factors (14,15). These structural alterations in the umbilical cord contribute to APOs associated with anemia during the first 20 weeks of pregnancy.

This study therefore, aimed to compare the structural features of the umbilical cord in women diagnosed with anemia in the first 20 weeks of pregnancy with those without anemia. To the best of our knowledge, this area of study has remained unexplored both locally and globally. This study also aligns with the second WHO global nutrition target of achieving a 50% reduction in anemia among women of reproductive age by 2025 (16).

Methods

Study design and setting

This was a retrospective cohort study conducted at the Kenyatta National Hospital labor ward. Umbilical cord samples were examined and collected immediately after delivery. Processing and subsequent analysis were performed at the Department of Human Anatomy, University of Nairobi, Chiromo Campus.

Study population

The study population comprised women admitted to the labor ward at KNH. Participants were Kenyan women aged between 20 and 40 years. The study was conducted between March 2021 and June 2021.

Inclusion and exclusion criteria

Umbilical cords were collected from women aged 20-40 years without underlying pathology other than low Hb levels during the first 20 weeks of pregnancy. Low Hb levels were defined according to revised WHO criteria: <11 g/dL in the first trimester and <10.5 g/dL in the second trimester. Eligible study participants were identified by the principal investigator using antenatal care (ANC) booklets and medical records. Normal Hb levels for the non-anemic group were defined as 11-16 g/dL. Only live births were included.

Women older than 40 years were excluded because this age group is associated with higher risks of comorbidities and obstetric complications (17). Women younger than 20 years were excluded because adolescent pregnancy is associated with improper fetal development, growth

restriction, and obstructed labor (18). Umbilical cords from deliveries before 32 weeks of gestation were also excluded, since cord diameter and vessel size increase progressively until 32 weeks, after which they plateau (19).

Sample size calculation and sampling technique

The sample size was calculated using OpenEpi program (version 3.04.04, Open Source Epidemiologic Statistics for Public Health, www.OpenEpi.com) with a power of 80%, 95% confidence interval (CI) and an anemic-to-non-anemic ratio of 1:1. Expected proportions were obtained from Koech et al. (20). Using Fleiss' formula (21), a total sample size of 36 was determined. Consecutive sampling was employed, whereby the first 18 anemic and 18 nonanemic participants who met the inclusion criteria were recruited following acquisition of informed consent.

Data collection, tissue harvesting, and processing

Newborn weights were recorded immediately after delivery using a Detecto™ electronic baby scale. Low birth weight was defined as <2500g per WHO criteria (21). Immediately after delivery, umbilical cords were collected for tissue harvesting.

Morphometric and morphological analysis

Measurement of umbilical cord diameter

The gross diameter of each cord was measured twice using a digital vernier caliper with a precision of 0.01 mm. The reported value was the average of the fetal and placental end diameters.

Determination of Wharton's Jelly volume density and absolute volume

Photomacrographs of each cord segment were taken using a 16-megapixel (f/1.8) camera. Images were loaded into Fiji ImageJ software (version 1.53f, Wayne Resband, National Institute of Mental Health, USA). A 300-point grid was applied to estimate Wharton's jelly volume density using the point-counting method (**Figure 1**). The absolute volume of Wharton's jelly of each 5-cm cord segment was calculated by multiplying the volume density by the absolute volume of the 5-cm cord segment, measured using Scherle's method (23).

From each tissue block, one of five stained slides was selected for histomorphometric analysis. Photomicrographs were obtained using a Richter Optica™ UX-1 digital photomicroscope connected to Motic Images Plus™ software and analyzed using Fiji ImageJ. Parameters assessed included disruption and reduplication of the internal elastic lamina, intima-medial thickness (IMT) of the umbilical vein, and IMT of the umbilical artery.

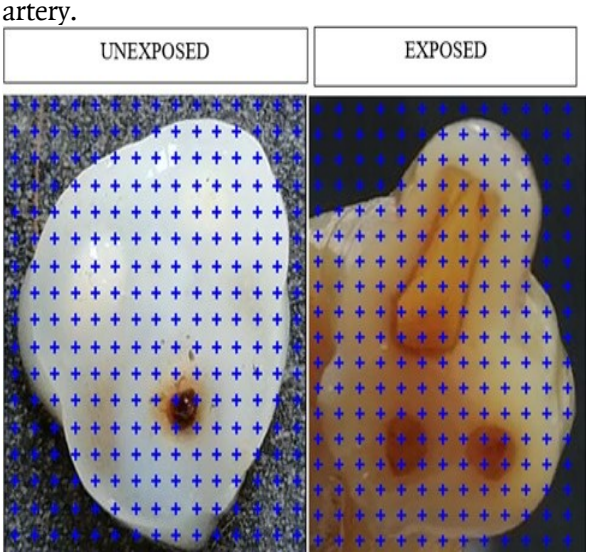

Figure 1: Determination of Wharton's Jelly volume density using the point-counting method

Intimal-medial thickness of umbilical vessels

Measurements were taken at four random points along the umbilical vessel wall and averaged to obtain the approximate IMT (**Figure 2**). For the umbilical artery, the IMT was taken as the average IMT of both arteries.

$IMT_V = (IMTa + IMTb + IMTc + IMTd) / 4$

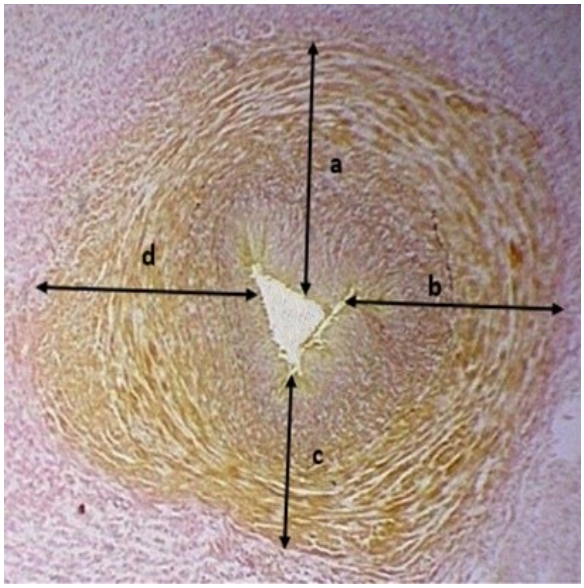

Figure 2: Estimation of intima-medial thickness of an umbilical vessel. Points a, b, c, and d indicate four random measurement sites along the wall.

Data analysis

Morphometric data were entered into the SPSS software (version 25.0, IBM, Illinois) for analysis. Dependent variables included umbilical vein IMT, umbilical artery IMT, cord diameter, Wharton's jelly volume density, Wharton's jelly absolute volume, Hb levels, and fetal birth weight. Data were summarized as means ± standard deviation, medians, and quartiles.

Data were categorized into anemic versus nonanemic groups, based on Hb levels during the first 20 weeks of pregnancy, and fetal versus placental cord segments. Anemic status was analyzed as an independent variable, and the cord segment as a dependent variable. Normality was assessed using the Shapiro-Wilk test ($p<.05$). Since most parameters were non-normally distributed, non-parametric tests were applied. The Mann-Whitney U test compared differences between the anemic and nonanemic groups, and the Wilcoxon signed-rank test assessed differences between the fetal and placental cord segments. A p-value of ≤.05 was considered statistically significant.

Ethical consideration

Ethical approval was obtained from the KNH/University of Nairobi Ethics and Research Committee (Registration No. KNH-ERC/UA/85). Informed consent was obtained from all participants.

Results

Differences in the clinical parameters

In this study, 36 participants (18 anemic; 18 nonanemic) were recruited. The median age in the anemic group was 26.5 years (IQR, 22 -33 years) and 29 years (IQR, 24-35 years) in the nonanemic group (p .521). The median Hb level was 10.1 g/dL (IQR, 8.4-10.4 g/dl) in the anemic group and 12.0 g/dL (IQR, 11.1 - 12.6 g/dL) in the nonanemic group (p <.001). The median infant birth weight was 2846g (IQR, 2488–3270 g) in the anemic group and 3150g (IQR, 2768- 3565g) in the nonanemic group (p .085). Four of 18 anemic participants (22.2%) had LBW infants (<2500g) while only 1 of 18 nonanemic participants (5.6%) had LBW infants. However, the relative risk (RR) of LBW in the anemic group was not statistically significant at a 95% CI (RR, 4.0; 95% CI, 0.494–32.39).

Difference in the internal elastic lamina structure

The internal elastic lamina of the umbilical vein in the anemic group was observed to be fragmented and reduplicated, whereas the nonanemic group did not show fragmentation or reduplication (**Figure 3**).

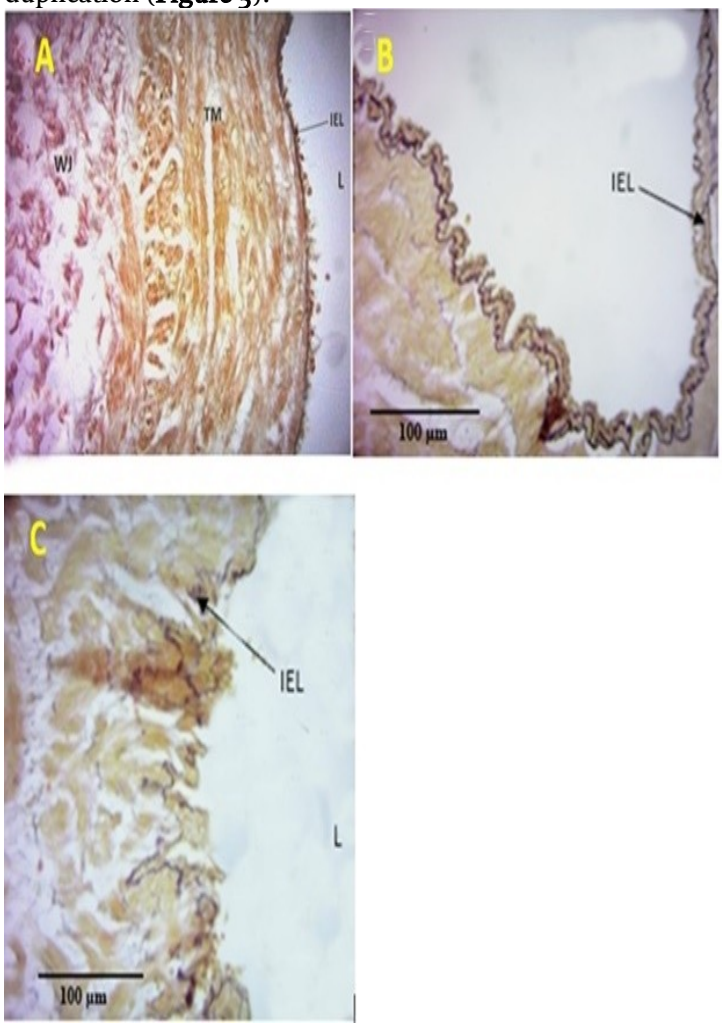

Figure 3: Internal elastic lamina duplication and disruption. IEL: internal elastic lamina; L: Lumen. (Weigert's Van Gieson stain, magnification X400). **3A**: Normal continuous internal elastic lamina (black arrow) in the nonanemic group. **3B**: Reduplication (black arrow) of the internal elastic lamina in the anemic group. **3C**: Disruption (black arrow) of the internal elastic lamina in the anemic group.

Difference in umbilical vein intima-medial thickness

The intima-medial thickness of the umbilical vein was significantly increased in the anemic group compared to the nonanemic group (p <.001) (**Figure 4**). The mean, median, and interquartile range for the UC vein IMT were 0.516±0.085, 0.496, and 0.448-0.572, respect-

ively, in the anemic group, and 0.365±0.116, 0.371, and 0.301-0.425, respectively, in the non-anemic group (**Table 1**).

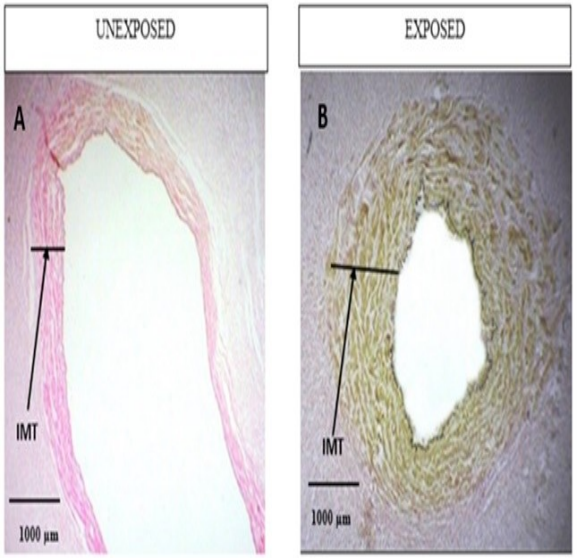

FIGURE 4: UMBILICAL VEIN IMT. (WEIGERT'S VAN GIESON STAIN, MAGNIFICATION X40). IMT: INTIMA-MEDIAL THICKNESS. **4A:** A PHOTOMICROGRAPH ILLUSTRATING THE UMBILICAL VEIN WALL WITH SMALLER IMT (BLACK ARROW) IN THE NONANEMIC GROUP. **4B:** A PHOTOMICROGRAPH ILLUSTRATING THE UMBILICAL VEIN WALL IN ANEMIC GROUP. NOTE THE LARGER IMT (BLACK ARROW) IN THE ANEMIC GROUP.

Difference in umbilical artery intima-medial thickness

The difference in the umbilical artery IMT between the two groups was not statistically significant (p = .308) (**Figure 5**). The mean, median, and IQR of the umbilical artery IMT were 0.654 ± 0.101, 0.630, and 0.571-0.733, respectively, in the anemic group; and 0.598 ± 0.152, 0.602, and 0.505-0.690, respectively (p <.308) in the non-anemic group (**Table 1**). Fragments of elastic fibers in the tunica media of some of the umbilical arteries were observed in the anemic group.

Differences in the umbilical cord diameter between anemic and non-anemic groups

The umbilical cord diameter was significantly smaller in the anemic group compared to the nonanemic group (p <.001). The mean, median, and interquartile range were 9.135 ± 1.359, 10.216, and 7.971-0.462, respectively, in the anemic group; and 11.073 ± 1.221, 10.815, and 10.198-11.736, respectively, in the nonanemic group (**Table 1**).

Difference in Wharton's jelly volume

Wharton's jelly absolute volume was significantly lower in the anemic group compared to the nonanemic group (p <.001). No significant difference in Wharton's jelly volume density was observed (p = .864) (**Table 1**).

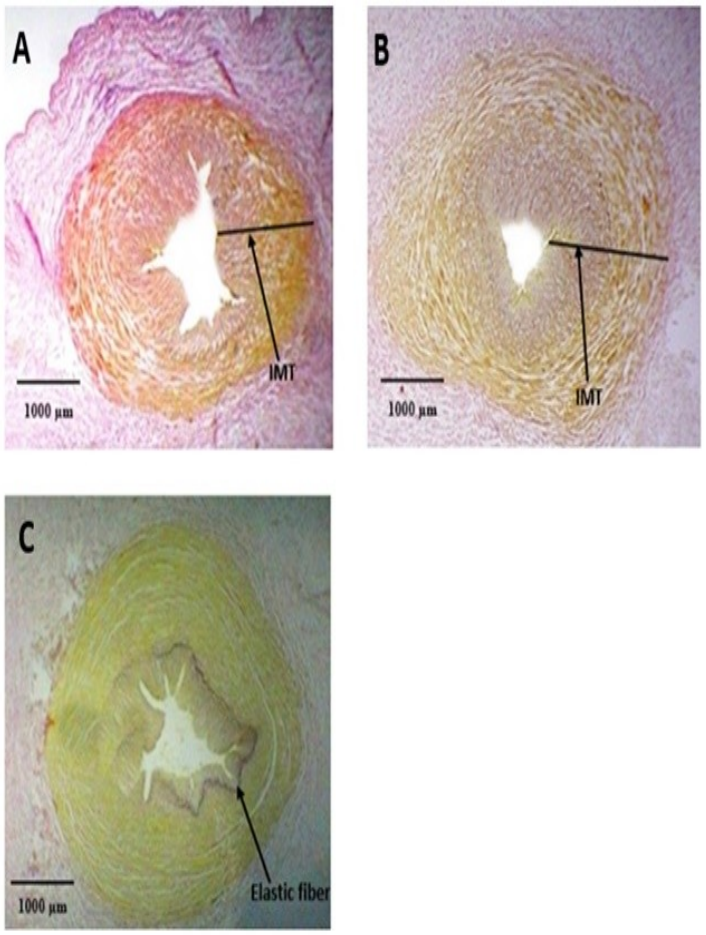

FIGURE 5: UMBILICAL ARTERY IMT AND ELASTIC FIBER. (WEIGERT'S VAN GIESON STAIN, MAGNIFICATION X40) IMT: INTIMA-MEDIAL THICKNESS. **5A:** A PHOTOMICROGRAPH ILLUSTRATING THE IMT (BLACK ARROW) OF THE UMBILICAL ARTERY IN THE NONANEMIC GROUP. **5B:** A PHOTOMICROGRAPH ILLUSTRATING THE IMT (BLACK ARROW) OF THE UMBILICAL ARTERY IN THE ANEMIC GROUP. NOTE THE RELATIVELY SIMILAR IMT IN BOTH GROUPS. **5C:** A PHOTOMICROGRAPH ILLUSTRATING AN ELASTIC FIBER (BLACK ARROW) FRAGMENT IN THE TUNICA MEDIA OF THE UMBILICAL ARTERY IN THE ANEMIC GROUP.

Segmental differences in the observed parameters

The IMT of the umbilical vein differed significantly between the placental and fetal ends of the umbilical cord in the anemic group (p = .001). No significant segmental differences were observed in the nonanemic group (p >.05). The increase in IMT was more pronounced toward the

fetal end of the umbilical cord. The disruption and reduplication of the internal elastic lamina were also more prominent on the fetal end (**Table 2**).

Table 1: Mean, median, and interquartile ranges of umbilical cord parameters in the anemic and non-anemic groups

Parameter	Anemic			Nonanemic			p-value
	Mean	Median	IQR	Mean	Median	IQR	
ImtUV	0.516 ± 0.085	0.496	0.448–0.572	0.365 ± 0.116	0.371	0.301–0.425	<.001*
ImtUA	0.654 ± 0.101	0.630	0.571–0.733	0.598 ± 0.152	0.602	0.505–0.690	.308
UCD	9.135 ± 1.359	10.216	7.971-10.462	11.073 ± 1.221	10.815	10.198-11.736	<.001*
WjVd	0.928 ± 0.050	0.949	0.897–0.968	0.943 ± 0.024	0.946	0.923–0.965	.864
WjAbsV	3.893 ± 0.375	3.865	3.589–4.270	4.717 ± 0.455	4.631	4.327–5.164	<.001*

*UCD: Umbilical cord diameter; WjVd: Wharton's jelly volume density; WjAbsV: Wharton's Jelly absolute volume; ImtUV: Umbilical vein intima-medial thickness; ImtUA: Umbilical artery intima-medial thickness. *significant difference*

Table 2: Mean and median values in the fetal and placental segments in the anemic group.

Parameters	Fetal			Placental			p-value
	Mean	Median	IQR	Mean	Median	IQR	
IMT Umbilical vein (mm)	0.554 ± 0.091	0.524	0.480–0.611	0.479 ± 0.096	0.484	0.400–0.530	0.001*
Wharton's jelly absolute volume (cm^3)	3.814 ± 0.435	3.815	3.603–3.925	3.973 ± 0.555	3.870	3.674–4.600	0.322
Umbilical cord diameter (mm)	9.204 ± 1.644	9.322	8.073-10.594	9.067 ± 1.254	9.069	8.080–9.962	0.597

Discussion

The intima-medial thickness of the umbilical vein was observed to be higher in the anemic group compared to the nonanemic group. This could be due to compensatory wall thickening resulting from altered blood flow dynamics in anemia. Geometric changes in the vessel wall, such as an increase in wall thickness due to anemia, may cause vessel stiffness (14). In anemia, the increase in cardiac output is the main hemodynamic factor affecting blood flow. Anemia may result in an increased systolic peak velocity and a change in the umbilical vein blood flow pattern from continuous to pulsatile under Doppler ultrasonography (22). Sustained high blood flow causes compensatory IMT in the blood vessels (14). Anemia also causes an increase in the levels of angiogenetic factors, including vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (e-NOS), hypoxia-induced factor 1-alpha (HIF-1a), and placental growth factor (PlGF), which are associated with adaptive changes in vessels such as endothelial proliferation and increased smooth muscle mass in response to hypoxia (23). The umbilical vein is important for the transport of oxygen- and nutrient-rich blood to the fetus. Thickening and resultant stiffening may impair compliance of the umbilical vein and therefore limit its capacity to regulate blood flow to the developing fetus. This could contribute to the adverse pregnancy outcomes observed in anemia during the first 20 weeks of pregnancy.

This study did not observe a statistically significant change in the umbilical arteries wall thickness. This may be because blood flowing in the

umbilical arteries originates from the fetus, not from the maternal side affected by anemia. However, fragments of elastic fibers were observed in the tunica media of the umbilical arteries of the anemic group. This may be part of vascular remodeling in response to changes in vascular hemodynamics (24). The internal elastic lamina of the umbilical vein was observed to be reduplicated and fragmented in the anemic group. This could be due to excessive mechanical stretching of the umbilical vein caused by altered hemodynamics and increased blood flow in anemia (25,26). Internal elastic lamina disruption may also result from intimal thickening of the umbilical vein (24). Owing to the important role that the internal elastic lamina plays in vessel compliance and mass flow, disruption and reduplication may decrease umbilical vessel compliance. These factors could contribute to impaired fetal circulation and APOs such as LBW and intrauterine growth restriction observed in anemia during the first 20 weeks.

Wharton's jelly absolute volume and umbilical cord diameter were observed to be significantly lower in the anemic group compared to the nonanemic group. This may be because all the nutrients and oxygen supply to the Wharton's jelly are solely derived from umbilical blood vessels (27). Therefore, alteration of blood flow patterns and oxygen-carrying capacity in umbilical vessels due to anemia may potentially result in reduced fibroblast cell density in Wharton's jelly, leading to decreased production of its extracellular matrix. Poor development of the Wharton's jelly in the umbilical cord directly contribute to hypoplasia of umbilical vessels and an increased risk of compression of these vessels (28). Umbilical cord myofibroblasts are also speculated to participate in the regulation of umbilical blood flow, and their decrease due to decreased oxygen supply in anemia may lead to altered umbilical blood flow (28). Wharton's jelly plays vital adventitial roles in the protection of fetoplacental circulation through its ability to resist external pressure on the umbilical vessels (29). A decrease in Wharton's jelly volume in women with anemia in the first 20 weeks reduces the diameter of the umbilical cord and alters the hemodynamics of umbilical blood flow. These changes could contribute to impaired fetal circulation and APOs, such as LBW and intra-uterine growth restriction, observed in anemia during early pregnancy. Intima-medial thickening as well as elastic lamina disruption were more pronounced on the fetal end of the umbilical cord in the anemic group. This may be due to higher VEGF expression in the stromal cells near the fetal end of the umbilical cord (25). VEGF is responsible for vascular growth in response to hypoxia, and its higher expression near the fetal end may explain the significantly greater IMT of the umbilical vein. Increased intimal thickening consequently leads to increased internal elastic lamina disruption, as observed in this study.

The cumulative incidence of LBW in the anemic group was 22.2% and 5.6% in the nonanemic group. However, the relative risk of low infant birth weight in the anemic group was not statistically significant (RR, 4.0; 95% CI, 0.494 to 32.39). The lack of statistical significance may be due to the relatively small sample size in this study. Nevertheless, a relative risk of LBW in anemia of 1.38 (95% CI, 1.07 to 1.77) has been reported in a Brazilian population (30). According to the WHO, the general prevalence of LBW in Eastern Africa was 13.4% in 2015 (31). The relatively high prevalence of poor maternal nutritional status in Kenya may play a role in the occurrence of LBW as an APO (32).

Study limitations

This study is limited by the relatively small sample size and reliance on the antenatal clinic booklet as the primary data source. Hemoglobin levels were available as part of the antenatal profile, but red cell indices and other laboratory parameters were not included. Consequently, we were unable to determine the specific type of anemia present in early pregnancy and could only classify women as anemic or nonanemic. In interpreting our findings and making recommendations, we assumed that the cases largely represented iron deficiency anemia, as this is by far the most common cause of anemia in pregnancy in our setting. However, this assumption may have overlooked other possible etiologies such as folate deficiency, vitamin B12 deficiency, hemoglobinopathies, or anemia of chronic disease.

Conclusion

Anemia during the first 20 weeks of pregnancy was associated with changes in both the gross and histological characteristics of the umbilical cord. These structural changes may provide an anatomical basis for the adverse effects of early

pregnancy anemia on outcomes. It may therefore be prudent for clinicians to aim for correction of hemoglobin levels during the periconceptual period rather that later in pregnancy. Regular screening for anemia in women of reproductive age is also recommended.

Recommendations

We recommend conducting a prospective cohort study with a larger sample size to more conclusively determine the relative risk of low birth weight in women with anemia during the first 20 weeks. Such a study should also compare the differences in the umbilical cord parameters in women who develop anemia at different gestational stages.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Data availability

All data generated or analyzed during this study are included in this article, and additional details or raw data are available from the corresponding author upon reasonable request.

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