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Three obstetric factors should be considered in umbilical cord blood donor selection

Tri akušerska faktora koja bi trebalo uzeti u obzir prilikom procesa selekcije donora umbilikalne krvi

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Abstract

Background/Aim. The umbilical cord blood (UCB) volume and hematopoietic stem cells count are used as indicators for hematopoietic potential of UBC units. These indicators are affected by a collection method and obstetric factors. It was established that birth weight and placental weight affect the volume and hematopoietic stem cells count in UCB units. The influence of other obstetric factors is less clear. The aim of this study was to investigate the impact of obstetric factors on hematopoietic potential of UCB units. **Methods.** The study involved 103 consecutive UCB units collected during 2013. Relationship of UCB volume, total nucleated cells, $CD34^+$ cells and Colony Forming Unit-Granulocyte Monocyte count with maternal and neonatal characteristics was retrospectively analyzed. **Results.** It was shown that birth weight, placental weight and umbilical cord length ≥ 31 cm significantly increased the volume of collected samples, total nucleated cells, $CD34^+$ cells and Colony Forming Unit-Granulocyte Monocyte count. Gestational age between 38−40 weeks increased significantly all umbilical factors (volume, total nucleated cells, $CD34^+$ cells, and Colony Forming Unit-Granulocyte Monocyte count). Gender did not have an influence on quality of UCB units except on total nucleated cells and $CD34^+$ cells count. Other obstetric factors did not affect significantly the quality of UCB units. **Conclusion.** Our study confirmed that birth weight, placenta weight, length of the umbilical cord and gestational age independently influenced the UCB unit volume, and absolute count of nuclear cells and hematopoietic stem cells. Due to a positive correlation between birth weight and placental weight, only birth weight, umbilical cord length and gestational age should be standard parameters in procedure of donor selection.

Key words:
fetal blood; hematopoiesis; stem cells; obstetrics; granulocyte-macrophage progenitor cells.

Apstrakt

Uvod/ Cilj. Zapremina umbilikalne krvi i broj matičih ćelija hematopoeze koriste se kao pokazatelji hematopoetskog potencijala jedinice umbilikalne krvi. Na ove pokazatelje utiču metode prikupljanja i akušerski faktori. Ustanovljeno je da porođajna masa i masa placente utiču na volumen i broj matičih ćelija hematopoeze u jedinici umbilikalne krvi. Uticaj drugih akušerskih faktora je manje jasan. Cilj ovog rada bio je da se istraži uticaj akušerskih faktora na hematopoetski potencijal jedinice umbilikalne krvi. **Metode.** Istraživanje je uključilo 103 uzastopnih jedinica umbilikalne krvi koje su sakupljene tokom 2013. godine. Retrospektivno su analizirani odnos volumena umbilikalne krvi, broja nuklearnih ćelija, $CD34^+$ ćelija i broja opredeljenih progenitorskih ćelija za granulocite i monocite sa karakteristikama neonatusa i majke. **Rezultati.** Pokazano je da veća porođajna masa, masa placente i dužina pupčane vrpce ≥ 31 cm značajno povećavaju volumen sakupljenih uzoraka, broj nuklearnih ćelija, $CD34^+$ ćelija i opredeljenih progenitorskih ćelija za granulocite i monocite. Gestaciona starost između 38–40 nedelje značajno povećava volumen, broj nuklearnih ćelija, $CD34^+$ ćelija i opredeljenih progenitorskih ćelija za granulocite i monocite. Pol ne utiče na kvalitet jedinice umbilikalne krvi, osim na broj nuklearnih ćelija i $CD34^+$ ćelija. Drugi akušerski faktori ne utiču značajno na kvalitet jedinica umbilikalne krvi. **Zaključak.** Naše istraživanje potvrđuje da porođajna masa, masa placente, dužina pupčane vrpce i gestaciona starost nezavisno utiču na volumen umbilikalne krvi, apsolutni broj nuklearnih ćelija i broj matičih ćelija hematopoeze. Zbog pozitivne korelacije između porođajne mase i mase placente, samo porođajna masa, dužina pupčane vrpce i gestaciona starost trebalo bi da budu standardni parametri u proceduri selekcije donora.

Ključne reči:
krv fetusa; hematopoeza; matične ćelije; porodiljstvo; granulociti-makrofagi progenitorske ćelije.

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Introduction

Traditional sources of hematopoietic stem cells (HSCs) are bone marrow (BM) and peripheral blood (PB). Umbilical cord blood (UCB) has been a known source of hematopoietic progenitor cells since 1988 [1]. The major disadvantages of UCB units are that they contain a limited number of HSCs and that additional cells cannot be obtained after the time of original collection. In addition, compared to BM and PB transplantations, the delayed hematopoietic reconstitution, higher risk of graft failure and increased transplantation-related mortality have been reported [2]. Clinical studies have shown that a cell dose of more than 2.0×10^7 total nucleated cells (TNCs)/kg recipient body weight and at least 1.7×10^5 $CD34^+$ cells/kg are the most significant predictors of the outcome [3]. It is also confirmed that regardless UCB collection, the average number of TNC per mL of UCB is equivalent [4]. This leads to the conclusion that an increased UCB unit volume provides increased TNC number and thus has a greater hematopoietic potential [5].

The volume of UCB unit is correlated with both a method used for UCB collection and obstetric factors [6]. Several authors have investigated the influence of obstetric factors on unit volume and HSCs count [7–10]. Based on contemporary study results, it was unambiguously established that birth weight (BW) and placental weight (PW) affect the volume as well as HSCs count in UCB samples, while the influence of other obstetric factors is less clear.

The aim of this study was to investigate the impact of obstetric factors on the hematopoietic potential of UCB units.

Methods

Umbilical cord blood collection

UCB units were collected from January 2013 to May 2013 with the institutional Ethics Committee approval. The selection criteria for UCB collection were: a signed informed consent for UCB collection and further usage in the experimental study, uncomplicated pregnancy and full-term vaginal delivery [gestational age (GA) 40 ± 2 weeks], the absence of neonatal asphyxia (Apgar score ≥ 8) and BW more than 2,500 grams. Pregnancies with more than one fetus were excluded. A total of 103 deliveries fulfilled the inclusion criteria. The infants were delivered according to normal obstetrical practices and UCB was collected while the placenta was still *in utero*. The original transfusion set (Syringe/Flush/Syringe) and original active method was used for the UCB sampling [6]. The UCB volume was determined as the actual net volume of UCB collected (i.e., not including the anticoagulant volume). UCB units were kept at 4°C and a further analysis was performed during the next 24 hours. The evaluation of the UCB unit quality was performed by measuring TNC, $CD34^+$ cells and Colony Forming Unit-Granulocyte Monocyte (CFU-GM) cells counts.

Cell quantifications

Nuclear cells and mononuclear cells (MNCs) count was determined by the flow cytometry Technicon H–3 (Technicon Corp, Tarrytown, NY, USA). TNC count was calculated by the multiplication with the UCB volume. A total MNC number was determined in the samples of collected UCB and cell suspension after the separation using Ficoll–Isopaque (density: 1.077 g/mL) as a density gradient (Pharmacia, Uppsala, Sweden) by centrifugation at 400 *g* for 35–40 min. The interface layer was collected and washed two times in phosphate-buffered saline (PBS) for 10 min. The MNCs concentration in 1 mL of the cell suspension was determined using the Spencer's chamber.

Total $CD34^+$ cell count was determined using the flow cytometer EPICS XL–MCL (Coulter, Krefeld, Germany). MNCs were incubated with mouse antihuman anti–CD34 monoclonal antibodies, and results were shown as a percentage of positive cells. The total $CD34^+$ cells number was calculated using the following formula: [(total MNCs number after Ficoll–separation/100) × $CD34^+$ cells count (in %)] [11].

Clonogenic assays were performed using the commercially available methylcellulose medium, Methocult GF H4434 (Stemcell Technologies, Vancouver, Canada). MNCs were added to the mentioned medium in the final concentration of 20,000 cells *per* mL. One mL of cells in methylcellulose medium was plated in duplicate into 35 mm diameter Petri dishes and incubated at 37°C and 5% CO_2 for 14 days. The colonies were counted on 14th day of incubation using an inverted microscope at 50× magnification. CFU–GM colonies were defined as the groups of 50 and more cells, while the clusters are defined as the groups of less than 50 cells.

Statistical analysis

All statistical analyses were performed using SPSS for Windows (version 16.0) package (SPSS Inc, Chicago, IL, USA). The groups were compared using the Student *t*-test or Mann-Whitney *U* test, when appropriate. The relation between variables was analyzed using the Pearson's correlation and the multiple regression analysis. The level of significance was set at $p < 0.05$.

Results

Characteristics of UCB units

A total of 103 deliveries were analyzed in our study. The maternal, infant, placental, obstetric and cord characteristics are shown in Table 1. The mean UCB unit volume was 91.63 mL (range, 52–147 mL). The mean TNCs count was 11.35×10^8 (range, 6.2–42.82×10^8). The mean total $CD34^+$ cells count was 3.02×10^6 (range, 1.16–9.52×10^6) and the mean total CFU-GM count was 87.28×10^4 (range, 40.6–283.31×10^4).

The mean maternal age was 29.61 years, with a range from 19 to 41 years and the average GA was 39.13 weeks (range, 38–42 weeks). The mean BW was 3,347.24 g (range from 2540 g to 4870 g) and the mean PW was 723.71 g (range from 247 g to 1,220 g).

Table 1

Obstetric and umbilical cord blood (UCB) characteristics (n = 103)

Parameters	n (%)	Mean ± SD	Median	Min.	Max.
UCB volume (mL)	103	91.63 ± 24.54	89.6	52	147
TNCs ($\times 10^8$)	103	11.35 ± 5.27	10.37	6.2	42.82
$CD34^+$ cells ($\times 10^6$)	103	3.02 ± 2.81	2.94	1.16	9.52
CFU-GM ($\times 10^4$)	103	87.28 ± 28.92	82.39	40.6	283.31
Maternal age (years)	103	29.61 ± 5.24	28	19	41
GA (weeks)	103	39.13 ± 1.42	39	38	42
BW (g)	103	3347.24 ± 429.37	3324	2540	4870
PW (g)	103	723.71 ± 112.06	705	247	1220
Cord length (> 30 cm)	62 (60.19)				
Cord length (≤ 30 cm)	41 (39.81)				
Birth order (1)	59 (57.28)				
Birth order (> 1)	44 (42.72)				
Infants' gender					
male	53 (51.45)				
female	50 (48.54)				

TNCs – total nucleated cells; ‡CFU-GM – Colony Forming Unit-Granulocyte Monocyte; GA – gestational age; BW – birth weight; PW – placental weight; SD – standard deviation.

Table 2

Influence of obstetric factors on the UCB unit quality

Parameters		Volume (mL)		TNCs ($\times 10^8$)		$CD\ 34^+$ cells ($\times 10^8$)		CFU-GM ($\times 10^4$)	
	n	mean ± SD	r	mean ± SD	r	mean ± SD	r	mean ± SD	r
Gender									
male	53	98.9 ± 20.1		14.1 ± 6.6		4.0 ± 2.0		14.1 ± 6.6	
female	50	92.8 ± 26.3		14.4 ± 9.8		4.0 ± 2.7		14.4 ± 9.8	
GA (weeks)									
≤ 40	79	99.6 ± 24.3		15.2 ± 8.7		4.3 ± 2.5		15.2 ± 8.7	
≥ 41	24	84.2 ± 17.7†		10.8 ± 5.2*		2.9 ± 1.6*		10.8 ± 5.2*	
Cord length (cm)									
≤ 30	42	75.3 ± 13.9		8.9 ± 1.6		2.2 ± 0.9		8.9 ± 1.6	
≥ 31	61	110.2 ± 18†		17.9 ± 9.0†		5.2 ± 2.2†		17.9 ± 9.0†	
Birth order									
1st	59	96.2 ± 22.3		13.7 ± 7.2		3.9 ± 2.2		13.7 ± 7.2	
more	44	95.6 ± 25.9		14.9 ± 9.6		4.1 ± 2.5		14.9 ± 9.6	
BW			0.959†		0.868†		0.919†		0.932†
PW			0.901†		0.851†		0.889†		0.894†

*** – $p < 0.05$; †– $p < 0.01$; TNCs – total nucleated cells; CFU-GM – Colony Forming Unit-Granulocyte Monocyte; r – correlation coefficient; GA – gestational age; BW – birth weight; PW – placental weight; SD – standard deviation.**

Totally, 60.19% of the cords were longer than 30 cm and 39.81% were shorter than 30 cm. The number of previous live births (birth order) was classified into two groups: the first group included maternal first live birth and the second group included one and more than one previous live births. In 57.28% of the cases, it was the maternal first live birth and 50.48 % of births were male.

The impact of obstetric factors on the UCB unit quality

By using the bivariate analysis, it was shown that the greater BW and PW the larger was the UCB volume, and the higher were TNCs, $CD34^+$ cells, and CFU-GM counts ($p < 0.01$ and $p < 0.01$, respectively) (Table 2). Additionally, the multiple regression analysis showed that there was a positive correlation between BW and blood volume, TNCs, $CD34^+$ cells and CFU-GM counts ($p < 0.01$) (Tables 3–6). PW was also positively correlated with the volume of UCB, TNCs, $CD34^+$ cells and CFU-GM counts ($p < 0.05$) (Tables 3–6).

The cord length also impacted the quality of units as shown by the bivariate analysis. Cords greater than or equal to 31 centimeters had a larger volume of UCB units and a greater number of TNCs, $CD34^+$ positive cells and CFU GM cells ($p < 0.01$) (Table 2). Additionally, the multiple regres-

sion analysis showed that there was a positive correlation between the cord length and blood volume, but no correlation between the cord length and other factors (TNCs, $CD34^+$cells, CFU-GM counts) ($p > 0.05$) (Tables 3–6).

The bivariate analysis showed that GA had significant influence on the UCB volume and number of TNCs, $CD34^+$ positive cells and CFU-GM (Table 2). In children younger than 40 weeks, significantly larger the UCB volume and increased TNCs, $CD34^+$ positive cells and CFU-GM counts were found ($p < 0.01$ and $p < 0.05$, respectively) (Table 2). Additionally, the multiple regression analysis showed that there was a significant negative correlation between GA and TNCs, $CD34^+$cells and CFU-GM counts ($p < 0.05$) (Tables 3–6).

The gender did not influence any umbilical parameters (volume, TNCs, $CD34^+$ cells and CFF-GM counts) on the bivariate regression analysis ($p > 0.05$) (Table 2). In addition, when we used the multiple regression analysis, we observed a significant correlation between the gender and TNCs ($p < 0.05$) (Table 4) and the gender and $CD34^+$ cells ($p < 0.05$) (Table 5). On the other hand, there was no correlation between the gender and other umbilical factors (UBC volume and CFU-GM count) ($p > 0.05$), (Tables 3 and 6).

When we analyzed the birth order, we did not observe any correlation between the birth order and umbilical factors (UCB volume, TNCs, $CD34^+$ cells and CFU-GM cells) ($p > 0.05$), (Tables 2–6).

Table 3

Multivariate analysis of the UCB volume influence on other obstetric factors

Parameters	Unstandardized coefficients		Standardized coefficients	*t*	*p*	95% Confidence interval for B	
	B	Std. error	Beta†			lower bound	upper bound
(Constant)	-34.850	6.811		-5.117	< 0.001	-48.370	-21.330
Gender	1.885	1.435	0.040	1.314	0.192	-0.962	4.733
Birth weight	0.034	0.004	.747	9.281	< 0.001	0.027	0.041
Placental weight	0.016	0.008	.140	1.998	0.049	< 0.001	0.032
Gestational age	-4.330	1.598	-.077	-2.710	0.008	-7.502	-1.159
Cord length	4.987	2.050	0.104	2.432	0.017	0.917	9.057
Birth order	-2.099	1.269	-0.044	-1.653	0.102	-4.619	0.421

UCB – umbilical cord blood; B – regression coefficient; Beta – standardized regression coefficient.

Table 4

Multivariate analysis of total nucleated cell influence on other obstetric factors

Parameters	Unstandardized coefficients		Standardized coefficients	*t*	*p*	95% Confidence interval for B	
	B	Std. error	Beta			lower bound	upper bound
(Constant)	-29.332	4.104		-7.147	<0.001	-37.477	-21.186
Gender	2.128	0.864	0.129	2.462	0.016	.412	3.844
Birth weight	0.01	0.002	0.636	4.575	<0.001	0.006	0.015
Placental weight	0.012	0.005	0.311	2.579	0.011	0.003	0.022
Gestational age	-2.170	0.963	-0.111	-2.254	0.026	-4.081	-.259
Cord length	-1.509	1.235	-0.090	-1.222	0.225	-3.961	0.943
Birth order	1.105	0.765	0.066	1.445	0.152	-.413	2.623

B – regression coefficient; Beta – standardized regression coefficient.

Table 5

Multivariate analysis of CD^+ 34 cells influence on other obstertic factors

Parameters	Unstandardized coefficients		Standardized coefficients	*t*	*p*	95% Confidence interval for B	
	B	Std. error	Beta			lower bound	upper bound
(Constant)	-8.758	0.914		-9.581	<0.001	-10.573	-6.944
Gender	0.715	0.193	0.153	3.714	<0.001	0.333	1.097
Birth weight	0.028	0	0.625	5.706	<0.001	0.002	.004
Placental weight	0.032	0.001	0.282	2.967	0.004	0.001	0.005
Gestational age	-0.549	0.214	-0.100	-2.562	0.012	-0.975	-0.124
Cord length	0.212	0.275	0.045	0.770	0.443	-0.334	0.758
Birth order	0.025	0.170	0.005	0.147	0.884	-0.313	0.363

B – regression coefficient; Beta – standardized regression coefficient.

Table 6
Multivariate analysis of Colony Forming Unit-Granulocyte Monocyte influence on other obstetric factors

Parameters	Unstandardized coefficients		Standardized coefficients	*t*	*p*	95% Confidence interval for B	
	B	Std. error	Beta			lower Bound	upper bound
(Constant)	-243.956	23.356		-10.445	<0.001	-290.317	-197.595
Gender	9.089	4.919	0.073	1.848	0.068	-0.676	18.854
Birth weight	0.09	0.013	0.755	7.216	<0.001	0.066	0.116
Placental weight	0.067	0.028	0.219	2.411	0.018	0.012	0.123
Gestational age	-12.042	5.478	-0.082	-2.198	0.030	-22.917	-1.168
Cord length	-5.999	7.031	-0.047	-0.853	0.396	-19.955	7.958
Birth order	4.902	4.353	0.039	1.126	0.263	-3.739	13.542

B – regression coefficient; Beta – standardized regression coefficient.

Discussion

The number of HSCs is the most significant factor for transplantation success and overall prognosis. The possibility of finding of an increased number of these cells in samples taken from UCB led to an intensive research in this area. Several strategies have been developed for increasing cell number and overcoming the main obstacle in using UCB as the source of HSCs in the allogeneic transplantation. The most practical strategy is to improve a collection method and evaluate an influence of obstetric factors on the UCB sample quality.

With regard to obstetric factors, several studies have demonstrated that BW and PW correlate with both the HSCs number and UCB sample volume [12–16], likely due to the relationship between BW and circulatory volume in the fetal and neonatal period. Neonates with BW > 3,500 g had UCB units with greater CD34+ cells and CFU count [16] and also greater UCB volume and TNCs count [17]. Some authors showed a positive correlation between PW, BW and UCB volume, CD34+ cells and CFU count, and also a positive correlation was found between TNCs count and BW, but the statistically significant correlation between TNCs and PW was not found [18]. BW and PW were found to correlate significantly with the UCB volume. One gram of BW increase increases the UCB volume by 0.015 mL. Similarly, each gram increase in PW would contribute to a 0.013 mL increase in the UCB volume [19]. Our research confirmed that larger BW and PW result in a larger volume of collected UCB units as well as an increase in the absolute number of TNCs, $CD34^+$ cells and CFU-GM. In fact, all neonates with BW more than 3,300 g had PW more than 700 g (mean values of male and female neonates in our population – data not shown). Using these results, we suggest that in the process of donor selection measuring, BW is sufficient without the need for assessing PW. We recommend to collect UCB after a fetal delivery and before a placental delivery occurs. It would accelerate the procedure of UCB collection.

Our study also showed that the umbilical cord length had a significant impact on the UCB unit quality. This finding is consistent with the previous research [20] that the umbilical cord length has a positive correlation with the UCB volume. Umbilical cord lengths of more than 30 cm are associated with a greater UCB unit volume and the number of relevant cells. Our results are in agreement with those of other authors and reflect that a significant amount of UCB (about ¼) resides in the umbilical cord [9]. Therefore, our recommendation is to clamp umbilical cord as close to a neonate as possible with respect to the standard obstetric procedure.

Some data suggest that GA is correlated with the UCB sample volume, and that pregnancy duration (more than 40 gestational weeks compared to 38–40 gestational weeks) significantly decreases the sample volume. This can be explained by the relative placental insufficiency [13]. Also, some authors showed that neonates with younger GA have better quality of UCB (greater CFU count and/or CD34+ cells) [21, 22]. These relationships are probably due to mobilizing signals produced by placental tissue during the fetal development. On the other hand, other authors have concluded that older GA positively correlates with the UCB volume and TNCs count [23]. Some authors showed that there is not a positive correlation between GA and UCB unit quality (volume, CD34+ cells, CFU, TNCs count) [18]. Our results confirmed a significantly larger UCB volume and an increased number of TNCs, $CD34^+$ positive cells and CFU-GM cells in babies born at less than 40 weeks of gestation.

Gender of neonates and its influence on the UCB unit quality is still being clarified. In our study, UCB of male neonates had greater CD34+ cell count, which could be explained by the fact that the mean BW of male neonates was statistically significantly larger than the mean BW of female neonates [21, 23]. On the other hand, some authors did not find a difference between the male and female UCB unit quality [24], while other showed that UCB unit taken from a female neonate had a greater CD34+cell count [21]. Our study did not show any influence of gender on the UCB unit quality.

Some studies have concluded that UCB samples taken from first-time deliveries have an increased volume and HSCs count, because first-time newborns have larger BW on average [15]. Our study did not show any influence of the birth order of pregnancy on the UCB unit quality, which is consistent with earlier findings [25].

Conclusion

Our study showed that BW, PW, length of the umbilical cord and GA independently influence the UCB unit volume,

absolute count of nuclear cells, as well as HSCs, but only BW, umbilical cord length and GA should be standard parameters in procedure of donor selection, due to a positive correlation between BW and PW. Therefore, UCB should be collected after a fetal delivery and before placental delivery occurs and the umbilical cord should be clamped as close to a neonate as possible. This would lead to a shorter time needed for foundation of a public UCB bank and improve the quality of UCB units.

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