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Collection of umbilical cord blood and the risk of complications in postpartum women after natural labour in the context of the possibility of umbilical cord stem cells usage in clinical practice

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ABSTRACT

Objectives: Comparison of changes in peripheral blood venous morphology and the frequency of select complications in patients who underwent umbilical cord blood collection during the third stage of labour by in the utero method compared to patients who did not undergo this procedure. Presentation of current therapeutic possibilities of cord blood stem cells.

Material and methods: The study involved 248 patients who had a vaginal delivery and had umbilical cord blood taken by in utero method during the third stage of labour. The control group consisted of the first 400 patients who gave vaginal delivery starting in 2019. Each patient had a venous peripheral blood count taken before delivery and 18 hours after delivery. Changes in the results of laboratory tests and the occurrence of adverse outcomes, such as postpartum curettage, postpartum haemorrhage and manual removal of placenta, in the 3rd and 4th stage delivery periods, were analysed.

Results: In the blood donor group there were significantly lower haemoglobin (11.32 g/L vs 11.61 g/L, p = 0.004) and haematocrit (32.83% vs 33.82% p = 0.001) concentrations after delivery. Umbilical cord donors had a greater difference in haemoglobin (postpartum minus prepartum) (–1.4 g/L vs –0.9 g/L, p = 000), and haematocrit (–4.05% vs –2.5% , p = 0.000). The study group had a higher percentage of patients with postpartum anaemia (haemoglobin concentration < 10 g/L) (15.9% vs 10.64%, p = 0.05), but the result were borderline significant. The groups did not differ in terms of the percentage of postpartum curettage, PPH, manual removal of placenta, percentage of severe anaemia (Hb < 7 g/L) or transfusion requirement.

Conclusion: Collection of umbilical cord blood during the 3rd stage of labour using the in utero method is associated with a statistically significant increase of blood loss and a higher probability of postpartum anaemia. The observed changes are minor and may have little clinical significance in otherwise healthy patients.

Key words: cord blood; private banking; public banking; delayed cord clamping; stem cells; perinatal care

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INTRODUCTION

Umbilical cord blood banking became popular 30 years ago after the first allogeneic transplant of cord blood stem cells for the treatment of Fanconi anaemia [1]. The umbilical cord blood is an important source of allogeneic hematopoetic cells which can be used in the treatment of both cancer and non-cancerous diseases. Research is also being conducted concerning the use of allo- and autogenous stem cells derived from umbilical cord blood in regenerative medicine. Umbilical cord blood is collected during the third stage of vaginal delivery, or immediately after the cord clamping, in the case of a caesarean section. Most often, the procedure is performed "*in utero*," before the separation of the placenta. *In utero* collection increases the chance of collecting an appropriate volume of umbilical cord blood. This procedure is widely recognized as safe for the mother. However, there are few studies in literature assessing the impact of this procedure on maternal blood loss and the risk of adverse outcomes such as retained placenta, postpartum curettage and postpartum haemorrhage (PPH).

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Study Aims

This study aimed to compare changes in peripheral blood venous morphology and the frequency of select complications of third and fourth stage labour in patients whose umbilical cord blood was drawn *in utero* during the third stage of delivery with patients who did not undergo this procedure. The secondary aim was to present the current rationale for using stem cells from umbilical cord blood in the treatment of various diseases.

MATERIAL AND METHODS

This was a retrospective study of the medical records of all women who gave birth by vaginal delivery at the Department of Obstetrics and Gynaecology of the Provincial Combined Hospital in Kielce between November 1, 2016 and July 1, 2019 and had umbilical cord blood collected *in utero* for private or public banking (n = 248). The control group consisted of the first 400 patients who gave birth by vaginal delivery starting from January 1, 2019 and did not undergo cord blood sampling. All patients had the morphology of peripheral blood collected on one hour prior to delivery and 18 hours after delivery. The mean concentration of blood morphotic elements post-delivery and individual concentration differences for each patient were analysed. Adverse outcomes were the necessity of manual removal of placenta, postpartum curettage performed due to bleeding or incomplete placenta, or administration of tocomimetic drugs (carbetocin, methylergometin and misoprostol) due to postpartum bleeding. The incidence of postpartum anaemia, defined as haemoglobin (Hb) < 10 g/dL and severe postpartum anaemia defined as Hb < 7 g/dL was compared. Continuous variables were compared, the arithmetic mean as a measure of central tendency when the distribution is near normal, and the median, in the case of skewed distribution. The standard deviation and interquartile range were used as measures of spread. If assumptions of normal distribution and equal variance were met, then groups were compared using the Student's t-test. When there was a failure to meet the above-mentioned criteria, groups were compared using the Mann-Whitney U test. For qualitative variables, data were presented as a percentage of events in a given group. The groups were compared using the Pearson $\chi 2$ test, Yates correction was applied when low numbers were expected. Calculations were made using the Statistica 13.1 program (Stat Soft Poland). The number of patients in the control group was selected so that a 0.5 g/dL difference in the haemoglobin concentration between the groups could be detected at a test power of 90%. Current literature on the practical use of stem cells from umbilical cord blood in the treatment of various diseases is presented.

RESULTS

The study included 284 patients in the study group and 400 patients in the control group. The characteristics of the study and control groups are presented in Table 1. The groups did not differ in terms of parity, age, weight, length of the newborn, or haemoglobin concentration, haematocrit and platelet count before delivery. Patients from the study group had significantly lower haemoglobin concentration after delivery [mean difference (MD) = 0.28 g/dL] and lower haematocrit (MD = 0.99%), while platelet count did not differ significantly (Tab. 2). The difference between haemoglobin concentrations, hematocrits and platelet counts (postpartum value - prepartum value) was calculated for each patient individually. The value was then averaged and presented in the form of median and interquartile range due to a lack of normal distribution. The groups differed in terms of haemoglobin decrease (MD = 0.5 g/dL) (study group median –1.4 g/dL and control group median –0.9 g/dL, p = 0.000) and haematocrit (median = –4% vs –2.5%, respectively, p = 0.000). There were no observed differences in the platelet count reduction between the two cohorts of women. The occurrence of adverse effects during the third and fourth stage of labour was also analysed. The groups did not differ statistically in terms of post-partum curettage incidence (8.8% vs 10.5%, p = 0.74) or manual placenta removal (1.41%

Table 1. Demographic parameters of both groups

Parameters	Control group	Donor's group	p
Number of patients	400 (58.47%)	284 (41.52%)	total — 684
First delivery (percentage in group)	43.66% (n = 195)	56.34%(n=160)	p = 0.06
Age [years] (mean ± SD)	30.178 ± 4.83	30.79 ± 4.6	p = 0.29
Newborn weight [g] (mean ± SD)	3400.26 ± 410.9	3391.6 ± 368.5	p = 0.056
Newborn length [cm] (median, IQR)	54; 3	54; 3	p = 0.21
Hb before delivery [g/L] (mean ± SD)	12.52 ± 1.06	12.67 ± 0.95	p = 0.07
Hct before delivery [%] (mean ± SD)	36.5 ± 2.7	36.88 ± 2.50	p = 0.31
Plt before delivery [1000/mm^3] (median, IQR)	202 (68)	201 (68)	p = 0.79

Hb — haemoglobin concentration; Hct — haematocrit; PLT — platelets concentration; SD — standard deviation

Table 2. Outcome comparison

Parameters	Control group	Donor's group	p
Hb after delivery [g/dl] (mean+-SD)	11.61 ± 1.29	11.32 ± 1.32	p = 0.004
Hct after delivery [%] (mean ± SD)	33.82 ± 3.66	32.83 ± 3.97	p = 0.001
Plt after delivery [1000/mm^3] (median, IQR)	198 (67)	199 (62)	p = 0.90
diff Hb [g/dL] (median; IQR)	–0.90; 1.3	–1.40; 1.5	p < 0.001
diff Hct [%] (median; IQR)	–2.50; 4.1	–4.05; 4.6	p < 0.001
diff PLT (median; IQR)	–7; 31	–6.0; 27	p = 0.48
postapartum need for carbetocin administration	4%	3.52%	p = 0.74
postpartum need for methylergometrine administration	1.25%	0.35%	p = 0.21
postpartum need for misoprostol administration	5%	4.23%	p = 0.63
post-partum curettage	10.50%	8.80%	p = 0.46
manual removal of placenta	0.50%	1.41%	p = 0.20
Hb < 7 g/dL postpartum	0%	0%	not applicable
Hb < 10 g/dL postpartum	10.64%	15.90%	p = 0.05

Hb — haemoglobin concentration; Hct — haematocrit; PLT — platelets concentration; SD — standard deviation, IRQ – interquartile range; diff —difference

vs 0.5%, p = 0.2). The percentage of patients with postpartum anaemia (Hb < 10 g/dL) was compared, revealing that the percentage of patients with this diagnosis was over 5% higher in group with cord blood collection but difference had borderline statistical significance [15.9% vs 10.64%, p = 0.05, odds ratio (OR) = 1.63] (Tab. 2). In both groups, there were no patients with a post-delivery haemoglobin concentration below 7 g/dL and no patients who required a blood transfusion. The groups did not differ in terms of the percentage of patients receiving postpartum carbetocin, misoprostol and methylergomethin treatment (Tab. 2).

DISCUSSION

Cord blood unit (CBU) collection can potentially affect the third stage of delivery by prolonging duration and increasing the risk of blood loss in women. There are few reports in the literature discussing the occurrence of maternal risk associated with this procedure following vaginal delivery. One report showed an increase in the volume of blood lost among donors compared to the control group (321 ± 273 vs 255 ± 237 mL; p = 0.02), however, there was no increased risk of severe anaemia or need for blood transfusions in this group [2]. Our study did not assess the volume of blood lost by women giving birth but did assess the difference in haemoglobin concentration in peripheral venous blood before and after delivery. This comparison appears to be a more objective method than the inaccurate visual assessment of perinatal blood loss. The data we collected showed a greater loss in the study group as expressed by the difference in haemoglobin concentration before and after vaginal delivery (median difference in concentration in the two groups was 0.5 g/dL), and the percentage of postpartum anaemia not requiring blood transfusion was 5% larger in the donor group. Despite statistical significance or borderline statistical significance, the difference does not appear to be clinically significant in the otherwise healthy patient population. The results of our research may be the basis for designing a prospective randomized trial assessing the relative risk for cord blood donors. In our study, there were no differences in the percentage of retained placenta, however it is worth noting that this is a rare complication, therefore our statistical analysis has little power in detecting a difference (power = 25%). Therefore, the probability of not detecting a statistically significant difference, in the case of its actual existence, is as much as 75%. It is estimated that both groups would need to assess over 4.500 patients to detect a statistically significant difference between the groups, for this complication, with 90% power.

The idea of umbilical cord blood collection should be carefully considered. In addition to the potential impact on the course of the third and fourth stage of delivery and process of cord clamping, we should also consider relation between time of collection and quality of the collected material, as well as the long-term benefits of blood banking for the newborn, both in case of collection to private and public blood banks.

Blood sampling should take place after delayed cord clamping (DCC), which is recommended by WHO [3]. DCC (> 60 s) increases postnatal cord blood transfer to the baby. Studies have shown the benefits of this approach for full-term children, which include higher haemoglobin concentration (MD 1.49 g/dL, 95% CI –1.78 to –1.21) and lower risk of iron deficiency at 3–6 months [RR (relative risk) = 0.37, 95% CI 0.96–0.14] [4]. Some studies also indi-

cate a better psychomotor development of children aged four years old who had DCC after birth [5]. The benefits of this approach are especially apparent among premature babies, as delayed umbilical cord closure reduces hospital mortality by more than 30% (RR 0.68; 95% CI 0.52–0.90) [6]. Data in the literature regarding the risk of intraventricular haemorrhage, necrotizing enterocolitis and bronchopulmonary dysplasia, which remain contradictory [7, 8]. In the protocol, manufacturers of CBU collection sets suggest that it is not necessary to perform an early cord clamping during the CBU procedure. However, recent literature suggests that DCC may affect the quality and volume of CBU uptake. CBU quality is commonly assessed as the amount of total nuclear cells (TNCs) in the collected sample. A study by Ciubotariu et al. [9] showed that DCC > 60 s is associated with a small chance of obtaining a clinically useful CBU (TNC ≥ 1600×10^6). Of all CBUs collected 60–120 s after birth, only 2.6% met the criteria of clinical utility, and out of CBUs collected ≥ 120 s after birth, only 2.4%. DCC also affects the volume of CBUs collected — in the group of patients whose collection took place 60–120 seconds after childbirth, 38% of CBUs had a volume of less than 40 mL, and after 120 seconds, 46% of CBUs had a volume of less than 40 mL [8]. The volume of collected umbilical cord blood has a strong positive correlation with the CD34 + stem cell count in the sample ($r = 0.7618$, $p = 0.00$) [10]. Delayed collection reduces both the volume and the quality of the measured TNC of CBUs [11]. Given the above information, a potential conflict arises concerning DCC, the child's best interest and the medical staff's aspirations to collect as much CBU as possible. In the case of private collection, pressure to perform early cord clamping may be increased from parents who expect high quality material from the medical staff. In this research, we have not focused on the impact of DCC on the quality of CBUs, however there is an ongoing effort to focus on this subject.

Currently, around 800,000 CBUs are stored in public banks worldwide and around 4 million units in private banks [12]. Annually, the therapeutic use of cord blood is estimated at 3,300 units per year from public banks and 130 units from private banks. The chances of using each CBU for medical purposes are about 160 times greater for each unit donated to a public bank than for those donated to private banks [13]. In Poland, in 2018, 1188 hematopoietic cell transplants were performed and only in one case it was from CBU [14]. At the end of 2018, 3883 CBUs were deposited in public cord blood banks in Poland. At the same time, the Polish Organization and Coordination Centre for Transplantation "Poltransplant" has stated that public funds for banking CBU in the Central Register will not be increased due to increase transplants from haploidentical individuals [14]. It is difficult to estimate the number of units banked in private banks in Poland, but this number is certainly several times greater than CBUs stored in public banks. Worldwide, over 60% of CBU units issued from public banks are used to treat leukaemia [13], while most units issued from private banks (about 60%) are used in regenerative medicine [13]. Specifically, majority of the private bank CBUs (82%) are used to recover damage to the nervous system including hypoxemic ischemic encephalopathy, periventricular leukomalacia, cerebral palsy, apraxia, and traumatic brain injury [15]. Most units issued for regenerative purposes are used in clinical and experimental studies. Autogenous stem cell transplant is not the gold standard in any of the above-mentioned indications. A systematic review from 2019 [16], which collected controlled clinical studies from June 1, 2016 to April 1, 2018, investigated the use of stem cells in regenerative medicine. These authors identified four controlled studies treating cerebral palsy (CP), of which autogenic transplants were used in only one [17]. The study reported an improvement in motor function (GMFM-66) in children with CP one year after the use of allogeneic stem cell transplantation at a dose of ≥ 2×10^7/kg [17]. The authors of the review [16] found three additional studies assessing the usefulness of stem cell transplantation for children with type 1 diabetes, two of which included autogenous transplants. In the study, the authors did not report statistically significant differences in the main outcomes. A single study assessed the usefulness of using autologous CBU in the treatment of burns [18]. The authors of this study concluded that bone marrow and umbilical cord blood stem cells improve healing of burn injuries [18]. In total, out of 14 studies published in accordance with PRISMA standards over a two-year period, autogenic transplants were used in four studies and a moderate positive health effect was achieved in two of them. Limited scientific evidence indicating usefulness of CBU storage in private banks has been revealed in the guidelines and recommendations of major scientific societies. The American College of Obstetricians and Gynaecologists (ACOG), in 2019 indicated that routine cord blood donation to private banks is currently not supported by available scientific evidence [19]. The ACOG also strongly emphasizes the inability to use autologous CBU transplantation in the treatment of cancer due to the presence of genetic variants in transplanted cells. ACOG further points out that those who are most likely to achieve potential benefits from private banking of CBU are family members with a known disease where treatment with a hematopoietic cell transplant from a related donor is advised [19]. At the same time, ACOG accepts the societal benefit of public umbilical cord blood donation, while maintaining standards of perinatal care and DCC of neonate. The ACOG also recommends that healthcare professionals interested in private banking for financial reasons to disclose their conflict of interest to patients. The opinion of The Polish Society of Gynaecologists and Obstetricians was issued in

2010, positively reviewing umbilical cord blood collection, although not clearly indicating the type of donation (public or private) [20]. The current standards of perinatal care in Poland include an obligation to inform the patient about the possibility of depositing cord blood without distinguishing between types of banking (public or private) [21]. In the light of current medical knowledge, the position of The Polish Society of Gynaecologists and Obstetricians experts should be updated, and a patient who bears the costs associated with collecting and banking cord blood should be aware of the purposes for which cells can be used based on the method of banking (private vs public). Additionally, patients should be aware that most autologous CBUs are used in experimental therapy. In the public awareness, there is no differentiation between auto- and allogeneic stem cell transplants, and, in our opinion, private banking is misinterpreted not only by patients but also by doctors who with transplantation profesionally and consider it as remedy for childhood cancers. In the context of the scientifically proven benefits of DCC, the lack of strong research showing the benefits of private banking and the potential interference of collection with reducing the time to clamp the umbilical cord, the position of The Polish Society of Gynaecologists and Obstetricians should emphasize the priority of DCC in the third period of delivery.

CONCLUSIONS

Collection of umbilical cord blood using the "*in utero*" method after vaginal delivery is associated with a slight increased risk of blood loss in the third stage of delivery and a greater risk of postpartum anaemia. The observed changes are minor and likely have minimal clinical significance in otherwise healthy patients.

Currently, the possibilities of using umbilical cord blood stem cells in therapy are limited, resulting in a need to constantly update the recommendations regarding cord blood collection.

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Conflict of interest

None.

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