

UDC 611.013.68:615.387



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CURRENT STATUS AND PERSPECTIVES OF CRYOSTORAGE AND CLINICAL APPLICATION OF THE UMBILICAL CORD BLOOD IN UKRAINE AND IN THE WORLD

ABSTRACT

The article summarizes current trends in the use of umbilical cord blood components in medical practice and describes the origin, types and tendencies of cord blood banks development in Ukraine and abroad. Presented results of the opinion poll of residents of different regions of Ukraine on the subject «stem cells» / «cell therapy» demonstrate a high awareness and interest of various sociological categories of the population on modern medical technologies using stem cells as well as positive attitude of pregnant women and obstetricians towards cord blood banking. The importance of creating a public cord blood bank in Ukraine is substantiated.

KEYWORDS: umbilical cord blood, stem cells, cord blood banks, the opinion poll

Umbilical cord blood is a part of fetus blood that remains after birth in the vessels of the umbilical cord and placenta, that for a long time were regarded as medical waste and discarded [14, 15]. The first attempts of clinical application of umbilical cord blood refer to the 30's years of the twentieth century and were aimed at the compensation of blood loss; however, due to the small volume (50-150 ml) umbilical cord blood did not get wide use in transfusion medicine [4].

In 1982, the American scientist H. Broksmeyer made a revolutionary announcement that cord blood is a source of hematopoietic stem cells and may be considered as an alternative to bone marrow transplant for the treatment of malignant and genetic diseases of hematopoiesis [12]. In 1988, in Paris, Prof. Eliane Gluckman performed the world's first transplant of cord blood hematopoietic stem cells of a sibling to treat the child with Fanconi anemia [15]. The success of this operation attracted huge attention of the medical community to the umbilical cord blood, led to the emergence of cord blood banking and played an important role in the development of biotech industry in general [12, 16]. It should be noted that the first recipient of cord blood transplant as up-to-date is completely healthy and lives full life [1, 2].

As of 2015, more than 35,000 transplants of hematopoietic cord blood stem cells for the treatment of cancer and other diseases in children and adults were performed worldwide [11]. In 2006 and then again in 2010, the European Group for Blood and Marrow Transplantation announced cord blood equivalent to bone marrow [1]. Experience of transplants of hematopoietic stem cells derived from the umbilical cord blood

revealed a number of its advantages compared to other adult sources of hematopoietic stem cells (bone marrow and peripheral blood), namely:

- Lower risk of the «graft-versus-host» disease even in case of incomplete immunological compatibility [1, 4, 12-15];
- Higher proliferative potential, that is important for regenerative therapy [13];
- Lower risk of infection for the recipient, in particular cytomegalovirus infection [2];
- The immediate availability of a transplant due to the large number of births in the world (about 130 million / year) [13, 14];
- Noninvasiveness of procedures of cord blood collection [1, 4, 12-15];
- Ethics [1, 13, 15].

The disadvantages of cord blood transplants include longer period of engraftment and insufficient number of cells in the graft to restore hematopoiesis after myeloablative therapy in adults [1, 15]. However, modern biotechnologies enable to overcome these limitations, implementation of methods of transplantation of two umbilical cord blood samples into clinical practice make possible wide application of this material in recipients weighing more than 50 kg [1, 11]. Thus, according to EUROCORD, transplantation of two umbilical cord blood samples was found to be more effective compared to one sample transplant although this method is more expensive [1, 11]. Due to application of two samples, the number of cord blood transplants performed in adults to date overexceeds this index in children [1, 11]. If from 1988 to 2014, 53 % of cord blood

transplants were performed in children and 43 % in adults, from 2008, the number of such operations in adults annually overexceeds its number in children [1, 2]. But at the same time, according to some experts, a double cord blood transplantation is characterized by a higher probability of the «graft-versus-host» disease [1]. In some hematological centers intrafemoral transplantation of umbilical cord blood is being practiced in order to reduce «cell losses» [1, 11]. Also today ex vivo expansion of hematopoietic stem cells of umbilical cord blood is widely used as well as methods of facilitation of graft engraftment including the use of a population of mesenchymal stem cells, pretransplantation genetic and pharmacological manipulations with cells, including the use of dipeptidylpeptidase inhibitors and moderate hyperthermia for modifications of the expression of CXCR4 [1].

It should be noted that if in the early 90's of the 20th century related transplants prevailed among cord blood transplantations, from the year 2000 number of unrelated transplants is annually increasing, that as of 2014 made about 90 % of the total number of cord blood transplants, performed from 1988 [1, 2]. During the last decade a significant increase of the number of cord blood transplants to patients older than 50 years was detected [1, 2]. Interestingly, in 2012 a slight decrease in the number of cord blood transplants performed in Europe and the US was observed, but also marked increase in the transplantation activity using cord blood was revealed in Japan (1000 transplants/year), Korea, France, Mexico, United Kingdom of Great Britain and Northern Ireland [2].

Discovery of unique populations of mesenchymal stem cells in umbilical cord blood in addition to hematopoietic stem cells, expanded horizons for its clinical application far beyond oncology [12-14]. The results of preclinical and clinical studies showed promising regenerative therapies using cord blood stem cells in the treatment of diseases of cardiovascular system, liver, nervous system, musculoskeletal disorders, etc. [1, 12-14]. The US Food and Drug Administration (FDA) approved a number of clinical trials for the evaluation of the safety and efficacy of cord blood stem cells in the treatment of acquired hearing loss, autism spectrum disorders, cerebral palsy, juvenile diabetes, sports injuries, lung cancer, Parkinson's disease, rheumatoid arthritis, liver fibrosis [7].

The umbilical cord blood was also shown to be an ideal source for obtaining induced pluripotent stem cells, for the discovery of which Shinya Yamanaka and John Gurdon were awarded the Nobel Prize in 2012 [1].

The endothelial progenitor cells isolated from umbilical cord blood are considered promising for the purpose of neovasculogenesis in vitro and in vivo to treat ischemic diseases [19]. In 2011, the Institute of Cell Therapy (Kyiv, Ukraine) received the State patent # 56808 on the method of treatment of vascular diseases using stem cells [2].

An important place among modern immunobiologic drugs belongs to cord blood derived T-lymphocytes and approaches to use them in specific immunotherapy of cancer and treatment of a number of viral and autoimmune diseases, and posttransplant complications are under investigations [1, 11].

Within recent years the attention of many researchers is increasingly attracted by the value of cord blood plasma as a source of many growth factors that may exert a regenerative effect, and it also serves as a substrate for the production of artificial tears [1]. Based on cord blood platelets, woundhealing gel was developed, that was shown to have a number of advantages compared to the same drug, obtained from platelets of adult donors [1].

The development of therapies using cord blood components contributed to the emergence and world expansion of cord blood banking as a separate biomedical industry [12, 13, 16]. The first cord blood bank was established in 1991 at the New York Blood Center in the US [12]. Soon, such biobanks emerged in France (Paris), Italy (Milan), Germany (Dusseldorf) [12]. Today cord blood banks are functioning in almost all countries of the world and have become an integral component of health care institutions. Cord blood banking refers to industries with the fastest development [2, 16]. If in 2005, only 23 cord blood banks were actively

operating in the world, in 2013 their number exceeds 480, that is, only during a seven-year period 21-fold increase in the number of companies involved in the biotechnology industry occurred [2].

There are public and private (family, autologous) kinds of cord blood banks [2, 12, 13]. Public cord blood banks are mainly created at transplant centers and operate due to public funding or funds of charitable organizations [12, 13]. Public cord blood banking is based on unselfish donation of umbilical cord blood by women after childbirth [12, 18]. Information on samples of umbilical cord blood stored in public banks is enrolled in the International Register of Hematopoietic Stem Cells Donors and the sample is delivered to the relevant transplant center in the country or abroad when a transplant of a particular phenotype is required [2, 12, 13]. It was calculated that about 20 % of all cord blood samples harvested in the United States, are exported abroad [2].

Private cord blood banks enable willing parents, due to the contract, to preserve cord blood at childbirth for the family needs in case of a disease treated with stem cells [18]. Autologous cord blood banking is considered a kind of biological insurance, and storage of cord blood is the most popular service in the industry of banking of human tissues and cells [2]. In some countries, the government programs provide free cord blood storage to families if the treatment with hematopoietic stem cells is indicated to one of the members [1]. And today one more hybrid form of cord blood banking emerged in the world, when public biobanks also provide a service of the personal storage of stem cells [12, 18].

Currently more than 3 million samples are preserved in cord blood banks worldwide, 650,000 of which in public banks and 2.5 million – in a family type biobanks [16]. Growth of cord blood banking industry makes about 10 % per year [2].

Up-to-date cord blood banking holds an important place in the network of hematopoietic stem cells donors, as despite more than 22 million donors registered in the World Register of Hematopoietic Stem Cells, sometimes this is impossible to provide all patients with compatible transplants in a short period of time, especially to ethnic minorities [12]. Thus, it was estimated that between 2006 and 2010, 45 % of unrelated hematopoietic stem cells transplants to representatives of ethnic minorities were performed using cord blood [1].

Due to high medical and biological value of cord blood, banking of this biological material in the developed world is supported by a number of public and social programs. In particular, in the USA family expenses for cord blood storage can be excluded from the annual taxes [2]. Also some US states adopted laws that oblige medical personnel to inform pregnant women about cord blood storage opportunities [2]. As the umbilical cord blood is considered to be absolutely ethical as a source of stem cells, cord blood banking is developed both in traditional catholic countries (Spain, Italy, Poland, etc.), and the countries of the Muslim world [12, 13, 16]. Although, in some countries, particularly in China, only activities of public banks are allowed [2]. Also, in most countries a number of national and international regulations governing the activities of biobanks were adopted as well as pursuant accreditation committees were established and relevant licensing conditions approved [2, 8, 10].

CORD BLOOD BANKING IN UKRAINE

Ukraine is one of a few world countries, where since the early period of 20th century, technologies of cryopreservation of cells and tissues were actively developing, and to date national scientists made a significant progress in cryobiology and cryomedicine [4]. The first prototype of a modern cord blood bank was established in Ukraine in 1984 at the Kharkiv city blood transfusion station [3, 4]. It was the first European experience of banking of cord blood, but its main value what considered for hemotransfusions [3, 4]. The bank was functioning for 5 years and preserved samples were transferred to the Kharkiv Institute of Cryobiology and Cryomedicine of the National Academy of Sciences of Ukraine [4].

New stage of cord blood banking in Ukraine began in 2004 when the first Ukrainian cryobank of cord blood stem cells and other human cells and tissues was established at the Institute of Cell Therapy [2, 3].

 Fig. 1. Questionnaire of sociological survey of the residents of Ukraine on the subject of cell therapy in 2010 and 2015.

QUESTIONS WITH OPTIONS OF ANSWERS

Have you ever heard terms «stem cell» and «cell therapy»?

- Yes, and this is bad
- Yes, and this is good
- Yes, and this is doubtful
- It seems, I have heard something
- No, I haven't heard anything
- I don't wish to talk on this subject

Do you know that umbilical cord blood of a newborn is rich in stem cells and it may be collected and preserved in blood bank?

- Yes
- No, I hear that for the first time

Would you preserve the umbilical cord blood at birth of your baby, knowing that it may be used in the treatment of more than 50 diseases?

- Yes, undoubtedly
- I am not sure, depends on price
- I am not sure, depends on which diseases
- No
- I don't know what to answer

It should be noted that the development of cord blood banking in Ukraine was something different from international practice, since abroad the first cord blood banks were public and launched at hematologic clinics [4, 6]. In Ukraine, due to a number of socio-economic factors the only form of cord blood banking that emerged in the country was that of a family type and its development was favored by characteristic for Slavs, and Ukrainians in particular, deep family traditions, dedication in attitude to the children and the high cancer awareness after the Chernobyl disaster in 1986 [3, 4, 6]. However, due to the not high standard of living in the country and low insurance culture of the Ukrainian population, in Ukraine up-to-date cord blood is stored in about 0.1-0.2 % of births, mostly in the capital and big cities [2, 4, 6].

Actually in Ukraine 3 biobanks offer future parents services of cord blood cryostorage and totally they have stored about 20,000 samples. One biobank of the umbilical cord blood and other human tissues and cells (Institute of Cell Therapy) is accredited according to ISO 9001: 2008 [2]. In addition to storage of umbilical cord blood, service of preservation of the placenta and umbilical cord tissue is also available in Ukraine [5]. Thus, the Institute of Cell Therapy cryobank implemented as methods of isolation and cultivation of stem cells from the placenta and produce unique placental extracts and tissue preparations for the use in medicine and cosmetology [5].

Law of Ukraine «On Licensing of the Certain Types of Activities» (Article 9, Part 3, paragraph 22), provided that such type of activity as: «The activities of banks of umbilical cord blood, other human tissues and cells» should be licensed. The decree of the Cabinet of Ministers of Ukraine of 27.07.2011, # 798 defined the State Service of Ukraine on Fighting with HIV-infection/AIDS and Other Socially Dangerous Diseases as the licensing body of the «Activities of the Bank of Umbilical Cord Blood, Other Human Tissues and Cells». The Decree of the Ministry of Health of 10.04.2012, # 251, approved «Licensing Terms for the Activity of Banks of Umbilical Cord Blood, Other Human Tissues and Cells» [2].

In Ukraine, because of the absence of the public cord blood banking, hematopoietic and mesenchymal stem cells are mainly used in regenerative medicine in clinical trials [2-4]. In 2008, the Institute of Cell Therapy was the first medical institution in Ukraine that received a permission of the Coordination Center of Transplantation of Organs, Tissues and Cells of Ministry of Health of Ukraine to conduct clinical trials using stem cells [2, 3]. In 2012, the Ministry of Health of Ukraine officially approved meth-

 Fig. 2. Questionnaire of sociological survey of the pregnant women of different regions of Ukraine on the subject of cell therapy

QUESTIONS WITH OPTIONS OF ANSWERS

Have you ever heard terms «stem cell» and «cell therapy»

- Yes, and this is bad
- Yes, and this is good
- Yes, and this is doubtful
- It seems, I have heard something
- No, I haven't heard anything
- I don't wish to talk on this subject

Do you know that umbilical cord blood of a newborn is rich in stem cells and it may be collected and preserved in blood bank?

- Yes
- No, I hear that for the first time

Are you going to preserve the umbilical cord blood at birth of your baby, knowing that it may be used in the treatment of more than 50 diseases?

- Yes, undoubtedly
- No, this is too expensive
- No, I do not believe in cell therapy
- No, I do not trust blood banks
- No, I do not trust anybody

 Fig. 3. Questionnaire of sociological survey of the obstetricians-gynecologists of the different regions of Ukraine on the subject of cell therapy.

QUESTIONS WITH OPTIONS OF ANSWERS

Your attitude to stem cell therapy

- This is the future
- I do not believe in it
- I know too little about it
- This is business
- This is quackery

Would you like to know more about advances of cell therapy?

- Yes, of course
- I am not interested in it

Do you know that umbilical cord blood is a rich source of stem cells which are used in the treatment of more than 50 serious diseases?

- Yes, I am quite well acquainted with this subject
- I have heard something about it
- I am not interested in it

Do you recommend your patients to store cord blood at childbirth?

- No, let them decide independently
- I will discourage from this decision
- Yes, if a family can afford this
- Yes, of course

ods of treatment of pancreatic necrosis, critical lower limbs ischemia, burns and frostbites using cord blood stem cells, developed by the V. K. Gusak State Institute of Urgent and Recovery Surgery of the Academy of Medical Sciences of Ukraine and Institute of Cell Therapy [2]. Currently the Institute of Cell Therapy continues clinical trials on evaluation of the effectiveness of treatment of cardiomyopathies, type 2 diabetes, viral hepatitis and liver cirrhosis using stem cells [2]. Scientific Practical Center of Pediatric Cardiology and Cardiac Surgery of the Ministry of Health of Ukraine developed and introduced into clinical practice a unique technique of application of autologous cord blood components during heart operations in infants [17].

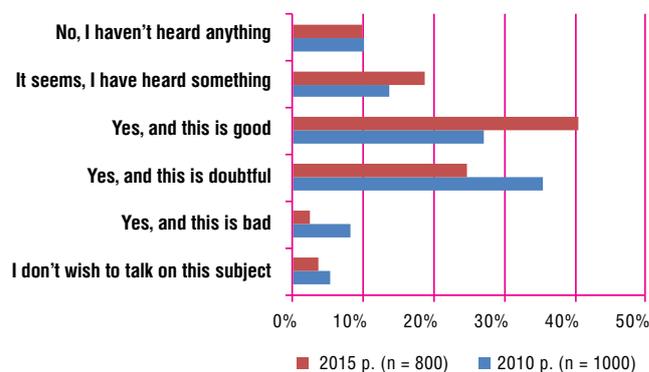
To analyze social factors that may affect the development of cord blood banking in Ukraine, opinion and attitude of health workers to biotechnologies and innovative therapies and prediction of the further development of this industry we conducted a sociological survey of the population of Ukraine, the results of which were compared with similar studies published in 2006 and 2010 [4, 9]. We interviewed direct unfiltered flow of people passing by in Kyiv, Dnipropetrovsk, Lviv and Odessa what allowed to take into account also regional peculiarities of the mentality of residents of Ukraine. In general, 800 adults of various sociological categories were interviewed (Fig. 1). Statistical sampling error (with probability 0.95 and without design effect) does not exceed 3.46 % for values close to 50 %. In addition to this we conducted an anonymous interviewing of pregnant women (Fig. 2, n = 760) and obstetricians-gynecologists (Fig. 3, n = 132) in Kyiv, Dnipropetrovsk, Lviv and Odessa regions, including regional centers. Sampling error (with probability 0.95 and without design effect) for values close to 50 %, does not exceed 3.55 % and 8.53 % respectively.

Results of the survey of 2015 as well as of a similar poll conducted in 2010 (n = 1000, sampling error for values close to 50 %, does not exceed 3.1 %), showed that about 90 % of the respondents aged 19 to 65 years are familiar with the terms «stem cell» and «cell therapy» (Fig. 4, 5). It is worth noting that this index is about 20 % higher compared to the results of a similar survey carried out in 2006, which revealed that these terms were unknown to approximately every third respondent [7]. Also, according to the data of 2015, the number of people with a positive attitude to cell therapy increased for 13.5 % compared with the results obtained in 2010 (Fig. 4). This may result from the active coverage of the achievements of cell medicine in media during recent years, including announcements on official approval of the methods of cell therapy developed by Ukrainian scientists by the Ministry of Health of Ukraine in 2012 and the Nobel Prize of 2012, which was awarded for the discovery of induced pluripotent stem cells. In 2015, we also noted a 10 % decrease of the number of respondents who considered cell therapy to be something questionable compared to the data of 2010 (Fig. 4). Both in 2010 and 2015, more than half of respondents said that they know that cord blood is a source of stem cells (Fig. 4), actually this index is 10 % higher than it was found in 2006 [9]. However, if in 2010 every second respondent confirmed readiness to preserve cord blood at birth of their child as a biological insurance, as of 2015 only 30 % of respondents choose this option (Fig. 4). Also in 2015, the number of respondents whose decision about cord blood storage will depend on the price of the service increased almost for 30 % compared to the survey of 2010 (Fig. 6).

The results of our survey showed that 97 % of pregnant women heard about stem cells and 80 % of interviewed future mothers know that cord blood is a rich source of them (Fig. 7, 8). About 50 % of interviewed pregnant women expressed a positive attitude to cell therapy. At the same time, only 1.3 % of respondents from this sociological category are going to sign a contract with one of the biobanks to store the cord blood at childbirth (Fig. 9). According to the survey, the cost of services of cord blood cryostorage is too high for 87.1 % of interviewed pregnant women, another 5.7 % respondents said that they do not trust banks of umbilical cord blood. The results of the survey of 2015 are comparable with the data of similar studies conducted in 2010. According to the poll conducted in the city of Kyiv (n = 200), the number of pregnant women with a positive attitude to cell therapy in 2015 increased twofold in comparison with the data of 2010, and the number of respondents, having doubts on the value of stem cells decreased for 30 % (Fig. 10). Statistical sampling error (with probability 0.95 and without design effect) does not exceed 6.93 % for values close to 50 %.

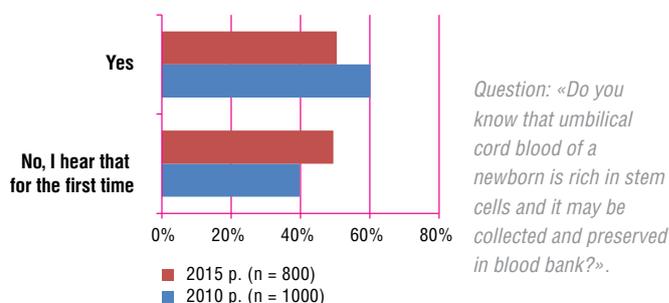
Since the better part of medical information pregnant women receive from the personnel of obstetric clinics we asked obstetricians-gynecologists from different regions of Ukraine to fill anonymously a provided questionnaire (Fig. 3). As the survey showed, almost 75 % of obstetricians know that cord blood is a rich source of stem cells (Fig. 11), more than 50 % of them are positive about cell therapy (Fig. 12), and about 15 % of interviewed doctors consider that they do not have enough

Fig. 4. Results of survey of unfiltered flow of passers-by in 2010 and 2015.



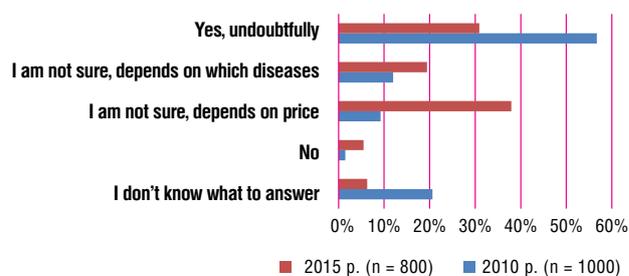
Question: «Have you ever heard terms «stem cell» and «cell therapy»?»

Fig. 5. Results of survey of unfiltered flow of passers-by in 2010 and 2015 (n = 1000).



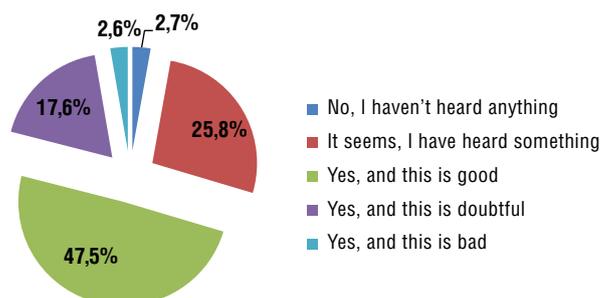
Question: «Do you know that umbilical cord blood of a newborn is rich in stem cells and it may be collected and preserved in blood bank?».

Fig. 6. Results of survey of unfiltered flow of passers-by, 2010 and 2015.



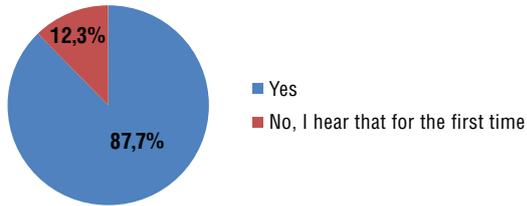
Question: «Would you preserve the umbilical cord blood at birth of your baby, knowing that it may be used in the treatment of more than 50 diseases?»

Fig. 7. Results of survey of pregnant women on the theme of cell therapy, 2015 (n = 760).



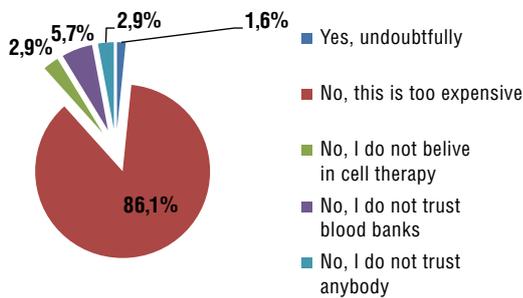
Question: «Have you ever heard terms «stem cell» and «cell therapy»?»

Fig. 8. Results of survey of pregnant women on the theme of cell therapy, 2015 (n = 760).



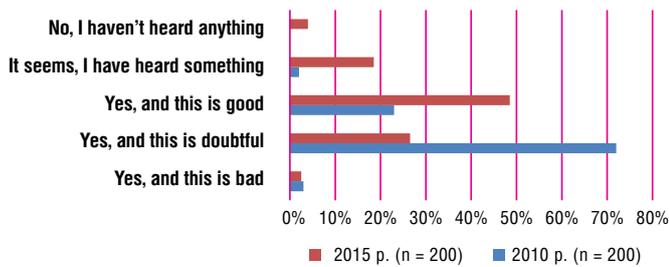
Question: "Do you know that umbilical cord blood of a newborn is rich in stem cells and it may be collected and preserved in blood bank?"

Fig. 9. Results of survey of pregnant women on the theme of cell therapy, 2015 (n = 760).



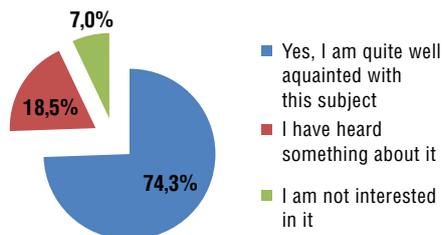
Question: «Are you going to preserve the umbilical cord blood at birth of your baby, knowing that it may be used in the treatment of more than 50 diseases?»

Fig. 10. Results of survey of pregnant women, Kyiv, 2010 and 2015.



Question: «Have you ever heard terms «stem cell» and «cell therapy?»»

Fig. 11. Results of survey of obstetricians-gynecologists on the theme of cell therapy, 2015 (n = 132).

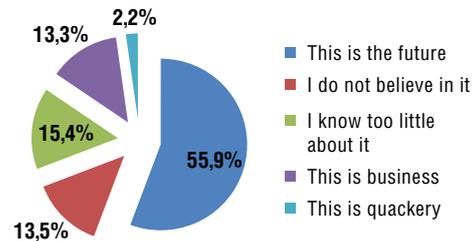


Question: «Do you know that umbilical cord blood is a rich source of stem cells which are used in the treatment of more than 50 serious diseases?»

knowledge on this theme to make conclusions. Every 10th obstetrician treats umbilical cord blood banking as a commercial project (Fig. 12) and 84.2 % of doctors confirmed a desire to learn more about stem cells (Fig. 13). Only 8.4 % obstetricians recommend cord blood storage to their patients, however, according to survey results both of 2010 and 2015 none of the surveyed doctors discourages pregnant women from a decision to store umbilical cord blood (Fig. 14). Another 20 % of obstetricians and gynecologists, as shown by a study, recommend cord blood storage if a family can financial afford this service.

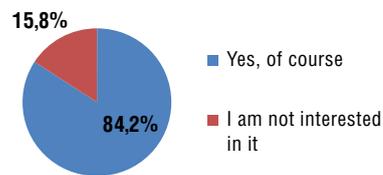
Thus, the results of the survey demonstrated high awareness and interest of Ukraine's population of various sociological categories on modern medical technologies using stem cells, positive attitude of pregnant women and health professionals to cord blood banking, that together with the availability of highly competitive technologies of cryopreservation of biological material developed by national scientists, may be considered as favorable conditions for the establishment of a public cord blood bank in Ukraine. As the number of hematopoietic stem cells transplants being performed in Ukraine is far behind other European countries, non-relative transplants in Ukraine are not yet performed and patients are forced to seek donor bone marrow transplant abroad, organization of a public cord blood bank may become an important step in the development of national hematological transplantology. Due to high, compared to other European countries, number of births in the country, peculiarities of HLA-phenotype and high migration activity of the population of modern Ukraine, international integration of the national cord blood bank would definitely be important also for the global registry of hematopoietic stem cells.

Fig. 12. Results of survey of obstetricians-gynecologists on the theme of cell therapy, 2015 (n = 132).



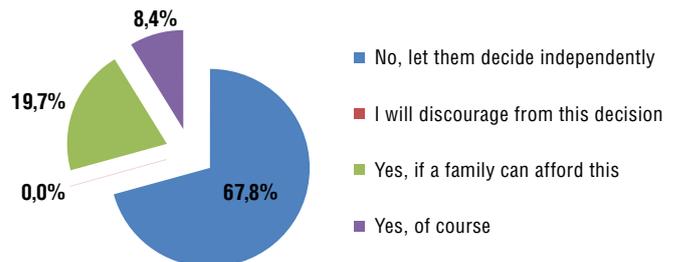
Question: "Your attitude to stem cell therapy?"

Fig. 13. Results of survey of obstetricians-gynecologists on the theme of cell therapy, 2015 (n = 132).



Question: «Would you like to know more about advances of cell therapy?»

Fig. 14. Results of survey of obstetricians-gynecologists on the theme of cell therapy, 2015 (n = 132).



Question: «Do you recommend your patients to store cord blood at childbirth?»

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The authors indicate no potential conflicts of interest.

Received: November 1, 2015

Accepted: November 28, 2015