KNOWLEDGE AND ATTITUDE OF PREGNANT WOMEN TOWARDS CORD BLOOD BANKING IN HOSPITAL KUALA LUMPUR

By

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DISCLAIMER

I hereby declare that this dissertation records the result of the study performed by me and that it is of my own composition.

Further, I have acknowledged all sources used and have cited these in the reference section.

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LIST OF ABBREVIATION

ACOG	American College of Obstetricians and Gynecologists
CB	Cord Blood
CBB	Cord Blood Banking
CD	Cluster of differentiation
FDA	Food and Drug Administration
GVHD	Graft versus host disease
HCP	Healthcare professional
HKL	Hospital Kuala Lumpur
HLA	Human leukocyte antigen
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplantation
ICC	Intraclass correlation coefficient
I-CVI	Item-level content validity index
IRT	Item response theory
MSC	Mesenchymal stem cell
NBC	National Blood Centre

NSCCC	National Stem Cell Coordinating Centre
PBSC	Peripheral blood stem cell
UCB	Umbilical cord blood
UCBT	Umbilical cord blood transplantation
USM	Universiti Sains Malaysia
WHO	World Health Organisation

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ABSTRAK

Latar Belakang: Darah tali pusat (UCB) adalah sumber sel hematopoietik yang berharga, tidak memerlukan prosidur pengambilan yang invasif dan mudah diperolehi. Ia telah digunakan sebagai alternatif untuk pemindahan sumsum tulang sejak beberapa dekad yang lalu. Darah tali pusat digunakan sebagai salah satu pilihan terapi untuk penyakit-penyakit yang melibatkan sel darah, sistem pertahanan dan sistem metabolik. Untuk tujuan ini, didapati peningkatan jumlah bank darah tali pusat di seluruh dunia. Lantaran itu, kajian ini bertujuan untuk menilai pengetahuan dan sikap wanita hamil terhadap perbankan darah tali pusat di Kuala Lumpur, Malaysia.

Kaedah/Model: Kajian keratan rentas dijalankan di kalangan 322 wanita hamil yang menghadiri klinik antenatal di Hospital Kuala Lumpur dari November 2019 hingga Mac 2020. Data dikumpul menggunakan borang soal selidik yang diisi sendiri oleh responden. Borang soal selidik ini mengandungi 34 soalan yang terdiri daripada maklumat sosiodemografi, soalan pengetahuan dan soalan penentu sikap. Beberapa langkah telah diambil bagi merekabentuk dan mengesahkan borang soal selidik. Data dianalisis menggunakan SPSS versi 26.0.

Keputusan: Hanya 11.5% peserta mempunyai pengetahuan asas mengenai perbankan darah tali pusat. Hanya 18% daripada peserta mengetahui penggunaan utama darah tali pusat dan lebih daripada 90% tidak tahu tentang proses dan penyimpanan darah tali pusat. Kira-kira 80% daripada mereka yang disoal selidik tidak mengetahui konsep pusat darah tali pusat awam. Hanya 23% peserta mempunyai sikap positif terhadap perbankan darah

tali pusat. Kiraan statistik mendapati terdapat signifikan korelasi antara skor pengetahuan dan sikap (p<0.001).

Kesimpulan: Kajian ini menunjukkan kurangnya tahap pengetahuan dan terdapat sikap negatif di kalangan wanita hamil terhadap perbankan darah tali pusat. Oleh itu, strategi yang komprehensif harus diformulasi untuk menambahbaik proses penyampaikan maklumat yang tepat kepada ibu mengandung supaya mereka dapat membuat pertimbangan yang sewajarnya dalam penyimpanan darah tali pusat. Kakitangan kesihatan harus memainkan peranan penting dalam memberikan maklumat yang jelas, tepat dan berdasarkan bukti saintifik yang sedia ada kepada ibu hamil mengenai perbankan darah tali pusat.

***Kata Kunci**: Darah tali pusat, perbankan darah tali pusat, pengetahuan, sikap, wanita hamil*

ABSTRACT

Knowledge and Attitude of Pregnant Women Towards Cord Blood Banking in Hospital Kuala Lumpur

Introduction: Umbilical cord blood (UCB) is a valuable, non-invasive and easily accessible hematopoietic stem cells source used as an alternative for bone marrow transplantation over the past few decades. UCB is accepted as a therapeutic option for numerous haematological, immune system and metabolic disorders. This has resulted in the rising number of umbilical cord blood banks worldwide. This study aimed to assess pregnant women's knowledge and attitude towards cord blood banking (CBB) in Kuala Lumpur, Malaysia.

Methods: A cross-sectional study was conducted among 322 pregnant women attending antenatal clinic in Hospital Kuala Lumpur from November 2019 to March 2020. Data were collected using the self-administered questionnaire of 34 questions consisting of sociodemographics, knowledge measure and attitude determinant. A series of steps were taken to develop and validate the questionnaires. The data were analysed using SPSS version 26.0.

Result: Only 11.5% of the participants had fundamental knowledge about CBB. Only 18% knew the primary use of UCB, and more than 90% didn't know about cord blood collection process and storage. Approximately 80% of those surveyed didn't know the concept of public CBB. Only 23% of participants had a positive attitude towards CBB. A

statistically significant relationship was found between knowledge score and attitude (p<0.001).

Conclusion: This study demonstrates a significant lack of knowledge and a negative attitude among pregnant women. Therefore, comprehensive strategies should be formulated to disseminate accurate information by the respective government agencies. Besides, healthcare professionals should play a vital role in providing transparent, evidence-based and regulated information to expectant mothers about CBB.

Keywords: umbilical cord blood, cord blood banking, knowledge, attitude, pregnant women

CHAPTER ONE

INTRODUCTION

1.1 Overview

This chapter contains an introduction to umbilical cord blood, cord blood banking, and knowledge level on cord blood banking, especially among pregnant women in various countries. This chapter also includes research justifications and research questions.

1.2 Background of study

Cord blood is a major area of interest within the field of regenerative medicine. Umbilical cord blood (UCB) is a rich source of hematopoietic stem cells (HSC) which is used as an alternative to bone marrow for hematopoietic stem cells transplantation (HSCT) for the last 30 years [1]. UCB is currently accepted as a therapeutic option for numerous haematological, immune, and metabolic disorders in pediatric and adult patients [2]. In response to the successful use of UCB for HSCT with the promising outcome, public and private cord blood banks have been developed globally. Public cord blood banks collect, process, and store donated UCB units for any suitable patient and the government funds them [3]. Meanwhile, the private cord blood banks collect directed cord blood donation for the family's exclusive use who banked it. In order to process and store the UCB unit, private banks charge the donating parents a fee [3].

There is a greater need for UCB units to be collected and kept in public banks for the general population, who may benefit from unrelated allogeneic HSCT. Experts recommend storing cord blood in private banks only when warranted by the presence of medical conditions requiring related umbilical cord blood transplantation (UCBT) [4]. Parents can opt to donate their newborn's cord blood to the public bank, store it in a private

bank for future use or discard it. Pregnant women ought to have enough understanding of UCB banking to make the right decision. This study aimed to assess pregnant women's knowledge and attitude towards cord blood banking (CBB) in Kuala Lumpur, Malaysia.

1.3 Literature review

Cord blood is found in the umbilical cord and the placental vasculature after the birth of a newborn. It contains a heterogeneous mixture of cells, including blood cells (erythrocytes, leucocytes, and platelets) and different populations of stem cells [5]. UCB is a rich source of both immature and mature HSC equivalent to that found in the bone marrow, and it is useful for HSCT [6]. This discovery had changed the world's perception of cord blood from once thought of as a biological waste to a potentially curative therapy for many diseases.

There have been progressively rapid developments in the field of UCB transplantation (UCBT) for the last 30 years. The first successful UCBT was performed on 6 October 1988 at Hospital Saint-Louis, in Paris, France in a 5-year old boy with Fanconi anaemia [7]. He received UCB from his human leukocyte antigens (HLA) identical sister. The UCB transplant recipient achieved complete haematological cure and he is a healthy adult now. Initially, successful related and unrelated UCBTs were performed primarily in pediatric patients [8]. Following promising results in pediatric cases, UCBT was extended to adult patients with haematological disorders who lacked the availability of HLA matched adult donor with the first unrelated cord blood transplant in adult was performed in 1996 [9]. Several studies have supported the use of UCB as a feasible alternative source of HSC in allogeneic HSCT in adults [10,11]. Since these initial transplants, approximately more than 40,000 UCBTs have been performed worldwide until the present time [12] and World Health Organization has reported that more than 2000 UCBT

are carried out annually [13]. Notably, one-third of all UCBTs worldwide were done in Japan [14]. Currently, the Food and Drug Administration (FDA) has approved UCB stem cells use only in HSCT to treat nearly 80 diseases [15]. The application of UCBT now has transitioned from non-malignant conditions to malignant diseases. UCBTs have been used to treat non-malignant conditions which include severe combined immune deficiency [16], hemoglobinopathies such as thalassemia [17,19] and sickle cell disease [18,19], Fanconi anaemia [7], Krabbe's disease [20], chronic granulomatous disease [21], and Hurler's syndrome [22]. Hematopoietic cell transplantations using UBC also have been performed in hematologic malignancies such as acute leukaemia, chronic leukaemia and lymphoma both in adult and paediatric populations [23-26].

Exciting novel applications of UCB for regenerative therapy are now being explored. Many studies have been published on the novel UCB cell-based therapy, particularly involving neurologic disorders, diabetes mellitus type 1 and cardiovascular diseases [27]. Mesenchymal stem cells (MSC) found in cord blood have recently been evaluated for the treatment of severe COVID-19 in clinical trials. [28]. However, this unconventional practice of UCBT is still limited to clinical trials and further assessment to demonstrate its safety profile and clinical benefits are required [27].

Comparative studies seem to show that outcome of UCBTs is comparable to that of bone marrow and peripheral HSCTs [29-32]. UCB provides several distinct advantages over the use of bone marrow or peripheral blood stem cells (PBSC). Advantages include easy non-invasive collection without risk to mother or newborn [33], less risk of viral contamination, rapid availability [34], decreased incidence and severity of graft-versus-host disease (GVHD) [35], expanded donor pool [36] and less stringent human leukocyte antigen (HLA) matching requirement which allow 1-2 HLA mismatches out of 6 [36]. That could be attributed greatly to the fact that UCB stem cells are immunogenically

naïve. Thus it is proposed as an alternative option particularly for patients of racial or ethnic minorities when HLA matched adult donor is not available or when the time to transplant is very critical [37]. However, the main disadvantages of UCB are delayed engraftment and graft failure caused by the limited number of haematopoietic progenitor cells in a single UCB unit for the reconstitution of the bone marrow particularly of an adult patient [38]. Poor immune cell reconstitution, in turn, has resulted in a significant risk of infection related morbidity and mortality to the recipient as well as increased cost [38]. In addition to ongoing numerous innovative clinical trials, a number of strategies have been adopted to mitigate poor bone marrow engraftment after UCBT. These strategies include expansion of cord blood donor pool, optimisation of collection and processing, selection of optimal transplantable UCB unit [39], use of double cord blood units [40], ex-vivo expansion [41-43] and co-infusion of UCB unit together with PBSC from third party haploidentical donor [44]. Another interesting approach to improve UCBT is augmenting the homing capacity of UCB stem cells via direct injection into patient's marrow [45], cell fucosylation [46], pretreatment with prostaglandin E2 [47] and inhibition of CD26 peptidase [48]. Cord blood-derived cytotoxic T-lymphocytes, after ex-vivo modification and expansion, has been administered to speed immune reconstitution to prevent common transplant related viral infection [49].

Utilising UCB for HSCT with the promising outcome and growing clinical trials for exciting novel therapies have contributed to the establishment of cord blood banks. It is also noteworthy that UCB units can be cryopreserved at -196ºC in liquid nitrogen for more than 20 years for future transplantation. As a result, cord blood banks have grown exponentially [50]. Two types of cord blood banking exist, namely public cord blood bank and private cord blood bank. Public banks collect, process, and store donated UCB units, and they are funded by the government. These units are made available to the

general public in need of HSCT around the world. Meanwhile, the private bank collects directed cord blood donation for the family's exclusive use who banked it. Private banks apply charges to process and store the UCB unit. American College of Obstetricians and Gynecologists (ACOG) recommends storing UCB in private banks only when warranted by the presence of medical conditions requiring related UCBT [51]. The rationale behind this recommendation is that the likelihood of a person using autologous UCB unit later in life was estimated to be very low and the presence of inherited genetic disorder may hinder autologous UCBT [52].

Presently, more than 800,000 UCB units are cryopreserved in public banks across 45 countries and on average, 4100 units are released annually for transplantation [53]. Whereas, approximately 4 million UCB units are being stored in private banks worldwide, but the number of units released for clinical use is much lower, only about 130 units per year [53]. Greater demand for UCB units in unrelated allogeneic transplants necessitates access to a large quantity of UCB units in public cord blood banks. To find good HLA matched UCB unit, public banks are required to have an optimal inventory depending on the population size and presence of ethnic minorities [54]. All cord blood banks must meet regulatory requirements outlined by national regulatory bodies. Accreditation from international bodies ensures that the quality of banked UCB units meets the international level.

In Southeast Asia, Malaysia, Singapore, Thailand, and Vietnam are implementing both public and private CBB. Public cord blood banks aren't available in other countries of this region. However, there are private cord blood banks in Indonesia, Brunei, Myanmar, and Philippines [55]. As a country that performs a large number of UCBTs in the Asia-Pacific region, Japan has six public cord blood banks with 11 287 cord blood units cryopreserved as of March 2017 and facilitates more than 1300 unrelated cord blood transplants annually

[56]. Singapore Cord Blood Bank, the internationally accredited Singapore's public cord blood bank, was established in 2005 for unrelated UCBT. The non-profit, South East Asia's biggest public cord blood bank has over 11,000 units in its inventory. It has successfully facilitated over 282 cord blood transplants in Singapore and 15 other countries worldwide as of 1 February 2021 [57]. Vietnam has three public and two private cord blood banks with less than 10 000 UCB units cryopreserved in all five banks. [58]. It was reported that 7.2% of UCBT (around 20 transplants) were performed at one of the country's major transplant centre until 2017 using CBU units taken from the hospital's public cord blood bank [59]. The first public cord blood bank in Thailand was established in 2002. The same year, it provided CBU to a boy with Wiskott-Aldrich syndrome, which was the first successful unrelated mismatched cord blood transplantation in Thailand [60]. To date, a number of related and unrelated UCBT transplants have been successfully performed.

In Malaysia, the first experience of umbilical cord blood transplantations began much earlier than the existence of cord blood banks in the country. Chan and Lin reported the first UCBT in Malaysia in a two-year-old boy with beta thalassemia major [61]. He was transplanted with the HLA matched UCB from his beta thalassemia carrier female sibling on 31 July 1997 with an excellent outcome. From 1997 until 2016, a total of 107 cord blood or cord blood and marrow co-transplantations were performed where 78 transplants involved unrelated cord blood units [62]. In Malaysia, the first Public Cord Blood Bank housed in National Blood Center (NBC) was established in 2002 following anticipated demand for HSCT and Hospital Kuala Lumpur is the major cord blood collection centre. As the country's largest public cord blood bank, it has cryopreserved nearly 7500 transplantable UCB units to date. Several private companies are providing UCB banking service in Malaysia, which include StemLife Bhd, CryoCord Sdn. Bhd., and Cellsafe

International Sdn Bhd. All cord blood banks in Malaysia must adhere to the standards for cord blood collection, processing, testing, banking, selection, and release outlined by The National Standards for Cord Blood Banking and Transplantation, 2008 [63].

Many studies were conducted internationally to explore pregnant women's knowledge and attitude of CBB involving countries in North America [64], Europe [65-70], Middle East [71-74], Australia [75], Asia [76-79] and Africa [80-81]. However, there is very limited published literature on this issue in Southeast Asia countries [82]. The vast majority of previous studies have shown that CBB knowledge among pregnant women is inadequate and their attitude towards CBB varies from country to country.

1.4 Research justification

The evolving use of HSCT for various disease in the country has led to increased requests for allogeneic stem cells made to National Bone Marrow Registry and Cord Blood Bank in National Blood Center via National Stem Cell Coordinating Centre (NSCCC). On average, NBC receives 115 -120 UCB search requests annually. In 2017 however, there was a spike in UCB request where 146 requests were made due to the three consecutive cord blood transplants within six months. But to date, there were only 11 cord blood units issued from Cord Blood Bank since its establishment. Underutilisation of UCB hypothesised for several reasons: unavailability of HLA matched cord blood units, clinicians' factors, and limited facility. The possibility of finding an unrelated HLA matched UCB will be greater if a public UCBB has an inventory of 1 or 2 UCB units per 1000 population [3]. Unfortunately, in NBC, Cord Blood Bank has cryopreserved only around 25% of suggested optimal inventory due to low clinical conversion rate (rate of stored cord blood from collection) secondary to inadequate quantity or poor quality of stem cells obtained from the UCB. Exploring technical and clinical requirements in

collecting high-quality UCB units poses a significant challenge to the CBB field, which can be mitigated in part by increasing the number of cord blood collections.

However, recent evidence suggests that insufficient knowledge about UCB banking and UCBT in general causes expectant parents reluctant to donate UCB due to lack of motivation [65,74]. Hence, it is crucial to assess the knowledge level about CBB in our population and the quality of the information that people receive. The accuracy of information will significantly impact parents' decision to throw UCB as medical waste or store it in the bank. Unfortunately, up to date, there is no local study exploring pregnant women's knowledge and attitude towards CBB, even though several similar studies have been done in other countries. As the largest contributor of cord blood units to the public collection centre in Malaysia with nearly 11,000 births per year, a study is needed to assess and analyse the knowledge and attitude of CBB among pregnant women in Women and Children Hospital, Hospital Kuala Lumpur (renamed as Tunku Azizah Hospital). It is believed that information obtained from this study would contribute to the expansion of the national cord blood collection program in the future.

1.5 Research questions

1. What is the level of knowledge among pregnant women in Kuala Lumpur regarding CBB?
2. What is the attitude of pregnant women towards CBB in Kuala Lumpur?
3. What are the sociodemographic factors associated with pregnant women's knowledge and attitude towards CBB in Kuala Lumpur?

CHAPTER TWO

OBJECTIVES

2.1 General objective

To assess the overall knowledge and attitude towards cord blood banking (CBB) among pregnant women in Kuala Lumpur, Malaysia.

2.2 Specific objectives

i. To determine the knowledge and attitude towards CBB among pregnant women in Kuala Lumpur, Malaysia.

ii. To determine the association between knowledge and attitude towards CBB among pregnant women in Kuala Lumpur, Malaysia.

iii. To determine the association between sociodemographic factors and knowledge and attitude towards CBB among pregnant women in Kuala Lumpur, Malaysia.

2.3 Alternative hypothesis

There is a significant association between knowledge about CBB and attitude towards CBB among pregnant women.

There is a significant association between sociodemographic factors and knowledge about CBB among pregnant women.

There is a significant association between sociodemographic factors and attitude towards CBB among pregnant women.

2.4 Null Hypothesis

There is no significant association between knowledge about CBB and attitude towards CBB among pregnant women.

There is no significant association between sociodemographic factors and knowledge about CBB among pregnant women.

There is no significant association between sociodemographic factors and attitude towards CBB among pregnant women.

CHAPTER THREE

METHODOLOGY

3.1 Study background

This study aimed to assess the knowledge and attitude of pregnant women towards cord blood banking. It was conducted in Hospital Kuala Lumpur, which is the largest cord blood collection centre in Malaysia. This study was conducted in two phases: Phase I and Phase II. Phase I involved the process of developing and validating the questionnaire. A sequence of steps involved in designing and validating the research questionnaires. A total of 121 participants were included in questionnaire validation. Data collected was analysed using SPSS to obtain Cronbach's alpha for reliability test and R software to assess the psychometric properties of the knowledge items. Subsequently, the questionnaire was modified based on validation and reliability results. In Phase II, the validated questionnaires were distributed to 325 pregnant women who met the subject criteria for data collection. Data obtained was analysed using SPSS.

3.2 Phase I

3.2.1 Questionnaire Development

Several steps were taken to develop the research questionnaire. An extensive literature review regarding knowledge and attitude towards CBB among expectant mothers was done to recognise relevant items used in previous questionnaires. Educational tools and brochures provided by the Ministry of Health Malaysia on CBB were also analysed. Some items in the questionnaire were adapted and modified from previous studies' validated questionnaires [64, 68, 73, 76]. Permissions to adapt the questionnaires were obtained from the authors. Other newly developed items were incorporated into the questionnaire

to address the objectives of our study adequately. The questionnaire was constructed in Malay language. Throughout questionnaire development, several meetings and a group discussion with the supervisors were held. After the initial pool of questionnaire items were written, qualified experts consist of Obstetrician and Gynecologist, Family Medicine Specialist, Haematopathologist, Transfusion Medicine Specialist, and Pediatrician in a formal group discussion reviewed the items to ensure that the questions are accurate and free of item construction problems and grammatically errors. Some items that had been found unnecessary were excluded from the questionnaire. On the other hand, there were few items added after the discussion.

The questionnaire had a total of 34 questions and composed of three primary sections: (i) demographics (10 items), (ii) knowledge measure (18 items), and (iii) attitude determinant (6 items):

(i) The first section referred to the sample demographics, such as age, race, gravidity, number of children, gestational age, education level, occupation, household income, and source of knowledge regarding CBB. The literature identified these variables as having possible predictive value for cord blood banking knowledge and attitude among pregnant women.

(ii) The second section to assess the knowledge on CBB consisted of 18 close-ended questions using three scale answer 'True, False, Don't know'. This section included questions about the definition of cord blood, cord blood collection and storage and its uses.

(iii) The third section consisted of six closed-ended questions which determine the attitude towards CBB, from the willingness to store UCB to the bank model preference.

3.2.2 Questionnaire Validation

The questionnaire was validated through a series of steps as listed below:

A. **Content validity.** Content validity was carried out to verify if the newly developed questionnaire had targeted the study aim. In this step, five experts consist of a Transfusion Medicine Specialist, a Family Medicine Specialist, a Clinical Hematologist, an Obstetrics & Gynecology Specialist and a Pediatrician evaluated the content of the newly developed questionnaire to assess how clear and relevant the items were concerning the construct of interest. Criteria used by the experts for retention or deletion of items were relevance, clarity, simplicity, and ambiguity. Experts indicated their decision (to remove, keep, or modify) for each item and provided comments for the altered items. Items which were consistently judged to be removed were eliminated and an amendment was made to the modified items. The content validity index for items (I-CVI); scale-level content validity index, universal agreement calculation (S-CVI/UA); scale-level content validity index, averaging calculation method (S-CVI/Ave) were computed to indicate the content validity [83-85]. Item-level Content Validity Index (I-CVI) for relevancy was calculated for each item. Items with I-CVI score of ≥ 0.8 were considered appropriate.

B. **Face validity**. In this step, a random face to face interview with 30 pregnant women at Obstetrics and Gynecology Clinic, Hospital Kuala Lumpur were documented to ensure that respondents interpret each item in the way it was intended. The respondents were requested to give their feedback on the readability, simplicity and understandability of each item. They are encouraged to provide any suggestions or opinions. All the suggestions and opinions were noted

and reviewed with experts. At the end of the content validity and face validity process, the revised questionnaire was then used in the pilot study to assess the items' psychometric quality.

C. Pilot study (Validation study). In this stage, a pilot study was conducted to validate the newly developed questionnaire before use in the actual study.

Pilot study design:

A cross-sectional design approach was used to conduct the pilot study.

Pilot study area and duration:

The pilot study was conducted at antenatal care clinic in Obstetrics and Gynecology Department of Hospital Kuala Lumpur (HKL) from April 2019 until May 2019.

Pilot study population:

This pilot study's target population was the pregnant women attending antenatal care clinic of Obstetrics and Gynecology Department, Hospital Kuala Lumpur during the pilot study period.

Pilot study subject criteria:

Inclusion criteria

Malaysian citizen

Age ≥ 18 years old

Pregnant women at any gestational age

Able to read, write and understand Malay language

Exclusion criteria

Participant who did not provide informed study consent

Unable to comprehend in Malay or English languages

Illiterate

Health care staff

Pilot study sample size:

The sample size for the validation study was calculated based on the estimation for the reliability (internal consistency) since there is no definitive estimation of sample size for the Item Response Theory (IRT) analysis to assess the psychometric properties of the knowledge items. However, a previous study has recommended a sample size between 100 to 500 for the IRT analysis [86]. To get a minimum expected Cronbach's alpha of 0.8 with 95% CI, the study will need 136 respondents for 18 items. However, only 121 participants were recruited due to time constrain. For the test-retest analysis, a minimum sample size of 46 was adequate to detect an intraclass correlation value of 0.80. However, only 30 respondents completed the second questionnaire.

Pilot study sampling method and subject recruitment:

Recruitment of participants for the pilot study was done at the waiting area in front of the antenatal clinic, Department of Obstetrics & Gynecology, Hospital Kuala Lumpur within the stated time interval. The respondents were recruited through a convenience sampling method. The researchers invited participants who meet the subject criteria to join the pilot study.

Pilot study data collection method:

A written summary of the study's information was provided to the interested women and they were allowed to ask questions. The researcher explained every subject about the study aim, the process involved, and their rights in this study. Written consent for study participation was obtained. The consent form and

questionnaire were in Malay language for all respondents. The researcher or research assistant distributed the self-administered questionnaire to the participants to be filled up by themselves. The questionnaire needed approximately 15 to 20 minutes to be completed. Participants were allowed to ask the researcher or research assistant if there was any unclear question. A small token of appreciation was given to the consented participants after they had completed the questionnaire. To ensure anonymity and confidentiality of the participants, the completed questionnaire and consent form were collected separately. The individual right to withdraw from the survey at any moment was ensured. Subsequently, the completed questionnaire was submitted and checked by the investigator. If any missing data occur, the respondent was approached back to complete the questionnaires.

Pilot study statistical analysis:

Data was coded for entry using SPSS statistical software version 24.0 (IBM Corporation, New York, USA). Descriptive statistics were used to summarise maternal characteristics. The data was then analysed to assess the questionnaire's psychometric properties based on all 18 items in the knowledge domain. Items in the attitude domain were not evaluated for psychometric properties since only one item from this domain was used to measure the attitude.

Two-parameter logistic item response theory (2-PL IRT) analysis using R package *ltm* was performed for the knowledge section as it consisted of unidimensional items with dichotomous responses [87]. Difficulty index in the range of -3 to +3 and discrimination index in the range of 0.35 to 2.5 were considered acceptable [88]. Item fit was assessed by chi-square goodness-of-fit per item and assumption

of unidimensionality was checked by modified parallel analysis [88-89]. The IRT analysis was performed using R software version 4.0.2 in R Studio environment. For internal consistency reliability, a Cronbach's alpha coefficient > 0.7 was considered acceptable [90]. For reliability of each individual item, items with a corrected-item total correlation value of 0.3 were acceptable. The intra-class correlation coefficient (ICC) was used to evaluate the level of test-retest reliability in this study. An ICC value between 0.4 to 0.75 was considered acceptable and an ICC value of ≥ 0.75 was deemed excellent.

3.2.3 Finalisation of questionnaire

After the validation process, the questionnaire was revised and amended based on validation and reliability results before administrating to pregnant women in Women and Children Hospital, Hospital Kuala Lumpur for the actual study. Results of validation study are available in Chapter 5.

3.3 Phase II

3.3.1 Study design

A cross-sectional design approach was used to conduct this research.

3.3.2 Study area

Antenatal care clinic in Obstetrics and Gynaecology Department of Women and Children Hospital, Hospital Kuala Lumpur

3.3.3 Study duration

Data collection for the actual study was done from November 2019 till March 2020.

3.3.4 Study population

Reference population: Pregnant women residing in Kuala Lumpur

Source population: Pregnant women attending Women and Children Hospital, Hospital Kuala Lumpur

Target population: Pregnant women attending antenatal clinic of Obstetrics and Gynaecology Department of Women and Children Hospital, Hospital Kuala Lumpur during the study period

3.3.5 Subject criteria

3.3.5.1 Inclusion criteria

Malaysian citizen

Age ≥ 18 years old

Pregnant women at any gestational age

Able to read, write and understand Malay language

3.3.5.2 Exclusion criteria

Participant who did not provide informed study consent

Illiterate

Participant who had participated in pilot study

Healthcare staff

3.3.6 Sample size

The sample size calculation was done in accordance with objectives. The calculation was done using Power and Sample Size Calculations Software version 3.1.2.

For the first specific objective, the sample size calculated using single proportion estimation formula with a confidence interval of 95%, precision estimate of 5%, p (expected prevalence) of 26.5% for knowledge and 15% for attitude which gave the sample size of 295 and 195 respectively [76].

To the best of author's knowledge, the information needed to calculate the sample size for the second specific objective, which is to determine the association between knowledge and attitude, was not available from the previous study.

Sample size calculated for the third specific objective, to determine the associated sociodemographic factors of knowledge score, was based on education level, with an alpha of 0.05, power 0.8, P_0:0.33, P_1: 0.09 and M:1, which produced sample size of 44 [76]. The sample size estimation for associated sociodemographic factors of attitude is also based on education level, with alpha 0.05, power 0.8, P_0:0.89, P_1: 0.8 and M:1, and resulted in a sample size of 253 [81].

The biggest sample size was calculated for the first specific objective, which was 295. Therefore, the sample size required in this study was 325 subjects with 10% subject dropout included.

3.3.7 Sampling method and subject recruitment

A total of 325 participants were selected through systematic sampling among pregnant women attending the antenatal care clinic of Women and Children Hospital, Hospital Kuala Lumpur. Every third registered woman was recruited. Pregnant women who full fill the subject criteria were invited to join the study.

3.3.8 Research tool

This study's research tool was a self-administered structured and validated questionnaire developed in the Malay language. It is available in Appendix 1.

3.3.9 Data collection method

A written summary of the study's information was provided to the interested women and they were allowed to ask questions. The researcher explained every subject about the study aim, the process involved, and their rights in this study. Written consent for study participation was obtained. The consent form and questionnaire were in the Malay language for all respondents. The researcher or research assistant distributed the self-administered questionnaire to the participants to be filled up by themselves. The questionnaire needed approximately 15 to 20 minutes to be completed. Participants were allowed to ask the researcher or research assistant if there was any unclear question. A small token of appreciation was given to the consented participants after they had completed the questionnaire. To ensure anonymity and confidentiality of the participants, the completed questionnaire and consent form were collected separately. The individual right to withdraw from the survey at any moment was ensured. Subsequently, the completed questionnaire was submitted and checked by the investigator. If any missing data occur, the respondent was approached back to complete the questionnaires.

3.3.10 Statistical analysis

This study used a scoring scheme for knowledge section. A correct response was assigned one point, while an incorrect or unsure response was assigned zero point. The total score ranges from 0–18, with a higher score indicates better knowledge about CBB. A participant whose answer was correct for six core items in the knowledge domain (items 11, 12, 15, 19, 21b and 22) was considered to have fundamental knowledge about CBB.

For attitude section, the response was categorised as positive attitude if the participant answered the question 'Are you willing to store umbilical cord blood?' as 'Yes' or as negative attitude if the answer was 'No' or 'Unsure.'

Data were coded for entry and analysis using SPSS version 26.0 for Windows (SPSS, Chicago, IL, USA). All study variables were analysed using descriptive statistics and presented as mean ± SD for continuous variables and frequency (percentages) for categorical variables. Simple logistic regression was used to evaluate the correlation of the knowledge score with attitude. Associations between sociodemographic characteristics of pregnant women and their knowledge score were analysed using simple and multiple linear regression analyses. Meanwhile, to determine the associations between sociodemographic factors and their attitude towards cord blood banking, simple and multiple logistic regression analyses were used. Variables with p-value <0.25 in univariable analysis were selected for multivariable analysis. Statistical significance was defined as a p-value less than 0·05 (p <0·05).

3.3.11 List of variables

Independent variables: Age, race, gravidity, number of children, gestational age, education level, occupation, household income, awareness of CBB and source of information

Dependent variables: Knowledge of CBB and attitude towards CBB

3.3.12 Variables definitions

Fundamental knowledge:

Fundamental knowledge about CBB is the most basic and important understanding or information about CBB that a participant received through experience or study [91]. Since

knowledge level was measured using a questionnaire in this study, a participant whose answer was correct for six core items in the knowledge domain (items 11, 12, 15, 19, 21b and 22) was considered to have fundamental knowledge about CBB.

Positive attitude:

"A positive attitude is a state of mind that envisions and expects favourable results. A positive attitude is also defined as a willingness to try doing new things" [92]. Therefore, in this study, a positive attitude is the willingness to store umbilical cord blood in the cord blood banks.

3.3.13 Ethical issue

Ethical review board approval

Ethical approval from Human Research Ethics Committee Universiti Sains Malaysia (study protocol code: USM/JEPeM/18110728) and Medical Research and Ethics Committee of the Ministry of Health (reference no: NMRR-18-3100-44622) were obtained before conducting this study.

Subject vulnerability

The study participants were pregnant women attending the antenatal clinic of Women and Children Hospital, Hospital Kuala Lumpur during the study period. Subjects of both the pilot study and actual study were required to provide informed consent before participating in the study. They were granted complete freedom to participate without impacting the management and care of their medical condition.

Declaration of conflict of interest

There is no conflict of interest in this study.

Consent and confidentiality

Every subject was provided with the participant information sheet and required to sign an informed consent. This study's privacy and confidentiality will not be compromised as no identifiable personal data was taken and recorded from the participants. Subject demographic data were protected by assigning each participant to each designated code to make it anonymous and were entered into SPSS software. Data was presented as group data and will not identify the subject individually. This study results, raw or analysed, will not be revealed to any third party, except when required by law.

Security of sources documents and study data

The signed consent forms and completed questionnaires were deposited in a safe and secured cabinet in IPPT. In contrast, any electronic data generated during analysis was kept in a password protected and encrypted USB drive. The data will be kept protected for five years after the end of the research. It will be destroyed after the retention period.

Honorarium and incentives

Honorarium and incentives were given to participants and the research assistants involved in questionnaires distribution to participants.

3.3.14 Study flowchart