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Collection of a Lifetime: A Practical Approach to Developing a Longitudinal Collection of Women's Healthcare Biological Samples

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Abstract

Objective—The objective is to develop a biorepository of samples that represent all stages of a women's life. Importantly, our goal is to collect longitudinal physical specimens as well as the associated short and long-term clinical information.

Study Design—The Women's Health Tissue Repository was established to encompass four tissue banks: Well Women Tissue Bank, Reproductive Endocrinology & Infertility Tissue Bank, Maternal Fetal Tissue Bank, and the long-established Gynecologic Malignancies Tissue Bank. Based on their health status, women being seen in Women's Health at the University of Iowa are recruited to contribute samples and grant access to their electronic medical record to the biorepository. Samples are coded, processed, and stored for use by investigators.

Results—The Maternal Fetal Tissue Bank was the first expansion of our department's biobanking efforts. Approximately 75% of the women approached consent to participate in the Maternal Fetal Tissue Bank. Enrollment has steadily increased. Samples have been used for over 20 projects in the first 3 years and are critical to 7 funded grants and 3 patent applications.

Conclusion—Patient samples with corresponding clinical data are initially important to women's health research. Our model demonstrates that many research projects by faculty, fellows, and residents have benefited from the existence of the Women's Health Tissue Repository. While challenging to achieve, longitudinal sampling allows for the greatest opportunity to study normal

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Conflict of interest

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and pathological changes throughout all phases of a women's life, including pregnancy. This bank facilitates and accelerates the development of novel research, technologies, and possible therapeutic options in women's health. The establishment of more longitudinal biorepositories based on our model would enhance women's health research.

Keywords

biorepository; pregnancy; tissue bank

Introduction

Cell culture and animal studies have been important resources in advancing biomedical research. However, these systems are not perfect reproductions of human biological systems. As it is not always feasible or ethical to perform studies using humans, one of the most ideal means to perform translational research is to have a large repository of biological samples with corresponding demographic and clinical information.

Under ideal preservation conditions, these samples serve as indispensable resource for experimental research in numerous areas such as genetics and proteomics. Cancer biology has demonstrated the advantage of tumor banks. However, there are few banks designed to collect samples in order to answer questions about normal physiologic as well as pathologic processes that occur throughout the life of a woman and to address studies related to personalized medicine.

There are few biobanks in the United States dedicated to collecting samples longitudinally from participants throughout their pregnancies. The benefits to such collection are the ability to study changes that occur before the onset of clinical evidence of disease and to study how normal and disease processes change during gestation. However, such an effort is expensive and time consuming as it requires the participation of many women in order to have a substantial number of samples from women of different ages, race, BMI, socio-economic background, and family medical history who will develop pregnancy-related issues.

The department of Obstetrics & Gynecology at the University of Iowa Hospitals & Clinics (UIHC) began its biobanking initiative over 30 years ago with the collection of gynecologic tumor samples. This collection has been under the direction of the Gynecologic Oncology division and has led to numerous projects, grants, and publications. However, to more fully explore all of the stages of a woman's life, we expanded our tissue repository to include 3 additional banks: Reproductive Endocrinology & Infertility (REI), Maternal Fetal, and Well Women Bank. Additionally, we obtain male samples from the fathers through the Paternal Contributions to Children's Health (PATCH) biorepository. Each bank has its own Institutional Review Board (IRB) Approval and falls under the infrastructure of the umbrella "Women's Health Tissue Repository" (Figure 1). This infrastructure provides rigor in patient consent, sample handling and processing, and comprehensive coverage of clinical annotations of samples from electronic medical records. Centralization has proven useful in other large prospective collections, but also poses ethical, societal, and technological challenges [1–3]. For large centralized multi-institutional biobanks, ethical issues relate to ownership and distribution of samples as well as how personal data are published and de-

identified. Societal challenges include the development of regulatory frameworks for these multi-institutional or commercial biobanks. Ethical considerations relate to ownership, but also consider how samples may be used in the future and the clarity of long term storage and use in the consent process [4].

Logistically, having a centralized process within the department has supported standardized processes, but also allowed for focused recruitment of our patient population with an enhanced understanding of the clinical flow to patient visits, standard of care samples, and engagement of our faculty, staff, and learners in the collection and usage of samples. Thus, our model represents a hybrid of a large centralized biobank and a focused recruitment effort.

The first expansion of our tissue collection beyond the Gynecologic Oncology Bank began in March 2010 with the implementation of the Maternal Fetal Tissue Bank (MFTB). The REI and Well Woman Bank followed in 2011 and 2012, respectively. We now report on our successful efforts to expand into banking samples in the Maternal Fetal Tissue Bank and on the use of these samples. Expansion of this format of biobanking into other institutions would greatly enhance women's health research.

Materials and Methods

IRB approval (#200910784) was obtained to develop a biorepository of samples taken at the same time as clinically indicated samples of maternal blood, maternal urine, and amniotic fluid. Permission was also obtained to collect umbilical cord blood and placental tissues. This collection strategy eliminates the need for any study-specific procedures that are outside of routine clinical care. Further, we obtained permission for long term limited-access to the mother's and child(ren)'s medical records at UIHC. The mother provides consent for their child(ren) at the same time as they consent for themselves.

Ethical and regulatory considerations

Samples from patients that consent, but are later found to meet at least one of the exclusion criteria are discarded and not retained by the Tissue Repository Core. All participants are informed that they are free at any time in the future to withdraw their specimens from further scientific research. A patient's decision to participate in our tissue banking efforts has no effect on the clinical care that she or her child(ren) receives.

Patient Consent

One research assistant is primarily responsible for obtaining informed consent. The tissue banks have a partial Health Insurance Portability and Accountability Act (HIPAA) waiver that allows us to view patient scheduling information to identify patients that are eligible for participation. Before or after a clinic visit, patients are approached in the exam room and asked if they would like to hear about a research opportunity. The biorepository is described and all elements of the consent form are explained. After patients ask any questions, they are given the opportunity to enroll, decline, or to speak with a member of our research team at a future visit.

We are especially careful to inform patients that we may not know what projects or assays for which their samples will be used and that we may follow up their health indefinitely and that of their child (until age 18) through our electronic medical record. Patients are not contacted for follow-up. Patients have the choice to participate in a registry to participate in future studies.

The inclusion criteria for MFTB are: pregnant women who are at least 18 years old, English speaking, receiving care at the University of Iowa Hospitals & Clinics (UIHC), and able to provide informed consent are eligible to participate. **The exclusion criteria for MFTB are:** women who are less than 18 years of age, ward of the court, HIV positive, or are Hepatitis C positive. Children of women enrolled in MFTB who become wards of the court are also excluded.

Once the patient consents to the biorepository, the samples are acquired throughout pregnancy. Blood samples are taken at (any or all points):

1. 1st trimester (potentially at the initial OB visit, first trimester screening and/or any other medically necessary blood work being drawn);
2. 2nd trimester (potentially at the Glucose Tolerance Test, at Quad Screen and/or any other medically necessary blood work being drawn);
3. 3rd trimester (potentially at admission to Labor and Delivery and/or any other medically necessary blood work being drawn).

No extra venipunctures are performed for this biorepository. Extra blood (5–10ml) is drawn when blood is being drawn for other standard of care lab work.

If in excess, urine samples may be kept from any or all samples that are given in the Women's Health Outpatient Clinic, in Labor & Delivery, and in the Mother-Baby Unit.

If amniotic fluid is being withdrawn for a medically indicated reason, then an additional 1–10ml may be taken for this sample. No additional puncture is performed for this study. This sample is taken at the same time as the medically indicated sample and the volume is at the discretion of the medical provider.

Upon delivery, cord blood is collected from the placenta into Citrate Phosphate Dextrose Solution (Fenwal Technologies). After delivery of the baby, the cord is clamped and cut in the usual manner. All blood samples usually ordered by the medical provider on the cord blood will then be obtained. The excess blood (approximately 100–200ml) from the cord is collected by gravity at the bedside in the Labor and Delivery room.

If there is no medical indication to send the whole placenta for pathology, the placenta (in whole or part) is banked. If the placenta is sent for pathology, the placenta is returned to the bank for sample retrieval after pathology has processed the placenta (non-fixed) and retrieved its required specimens.

Sample collection, processing and storage

All samples are stored without any personal information. All participants are assigned a study ID number that is unique from their medical record number and any personal information. Samples are labelled with the study ID number, sample type, and date of collection. Blood is collected into ACD-A tubes (Becton Dickinson) and refrigerated until processed. For clinic visits, blood is drawn by phlebotomy at the same that clinically-indicated blood samples are being taken. Therefore, patients do not experience any extra venipunctures. For participants that are inpatient, blood is drawn at the time of IV insertion by nurses or at the time that other blood is being drawn. All samples are immediately put into a 4°C refrigerator. Excess urine is collected in clinic by tissue bank personnel; samples from inpatient areas are placed into the refrigerator by nurses and retrieved by tissue bank personnel.

Cord blood is collected at vaginal deliveries by health care providers. For cesarean deliveries, a nurse collects cord blood from the placenta immediately after removal; cord blood bags are then placed into the refrigerator by a nurse or environmental aid. Tissue bank personnel are paged immediately after deliveries and retrieve the placenta for immediate processing in lab for placentas that are not being sent for pathological analysis. If a placenta is being sent to pathology, the sample is taken fresh and unfixed by a member of the tissue bank to pathology. Pathology has agreed to process these tissue samples immediately and return the excess placenta to the study. After MFTB retrieves the study samples, we return any excess placenta tissue to pathology. Notations are made in the storage log for any sample that was out for an extended time prior to processing, such as placentas that went to pathology. Tissue bank personnel retrieve samples from the outpatient and inpatient areas 2–3 times per day. Samples are always brought back to lab on wet ice in covered ice buckets.

During processing, blood samples are separated into blood plasma and mononuclear cells. Plasma is aliquoted, snap frozen and stored at –80°C. The mononuclear cells are stored for viability in Roswell Park Memorial Institute medium (RPMI), 50% Fetal Bovine Serum (FBS), 10% dimethyl sulfoxide (DMSO), in liquid nitrogen. Maternal urine and amniotic fluid is aliquoted, snap frozen and stored at –80°C. Cord blood is processed into aliquots of serum, plasma, and cell pellets that are each snap frozen, and stored at –80°C. The remaining cord blood cells are separated by gradient centrifugation using Ficoll Plaque Plus (GE Healthcare). Mononuclear cells are stored for viability in 90% autologous serum and 10% DMSO and then maintained in liquid nitrogen. Placentae are dissected and samples are stored in liquid nitrogen and in *RNAlater* (Life Technologies) at –80°C.

Quality Assurance

Periodically, an aliquot of viable cells is thawed to check that cells remain viable and are not contaminated. This is done by a person independent of the person who processed and froze samples. For any derivative samples that are generated such as DNA, RNA, or protein, information is retained in our storage system regarding sample quality such as 260/280λ, RNA integrity number (RIN), or total protein concentration. Additionally, once an aliquot of a sample is given to an investigator, it does not come back to our main storage locations for samples. If we are given a previously used sample, it is stored in a separate storage location

with other used samples to prevent it from being mistaken as a new sample. This system prevents samples from being obtained by investigators after multiple-freeze thaw cycles.

Clinical Data Acquisition

The MFTB maintains a database to annotate samples with clinical information. In the first year of MFTB, data was manually extracted using standardized data extraction forms. This data has been used in the validation of an automated data extraction directly from the Electronic Health Record (EHR). The data extracted from the EHR is stored in a secure database program designed by the Institute of Clinical and Translational Science at the University of Iowa. The automated data extraction continues to be periodically validated by 2 of the authors (MKS and DAS).

Staff training and notification

The tissue bank is staffed by 2 full-time research assistants and at times is assisted by a part-time student worker. Both full-time staff are trained to consent patients and to process samples in order to provide cross-coverage. There are written protocols to follow for how each sample is processed. Additionally, the tissue bank has a clinical director that is a Maternal-Fetal Medicine specialists. The clinical director assists with training clinical staff and in overseeing data extraction. There is also the Principal Investigator and Director of the MFTB who oversees the daily operations of the tissue bank. The Principal Investigator of MFTB also oversees the Well Women, REI, and PATCH banks and the blood collection for the Gynecologic Oncology banks to ensure that samples between all banks are handled and processed in an identical manner. As necessary, the PI and clinical director will assist with sample processing or obtaining patient consent.

In addition to training for human subjects research, the research team receives training from the PI for proper consent and laboratory techniques. To train the clinical staff, the project was initially described to our department during a departmental meeting of all providers, including the house staff. At this time, staff received training in cord blood collection. Training sessions were also held with all shifts of Labor and Delivery nursing staff as well as with nursing and medical assistants in our outpatient clinic. Training sessions are repeated at least yearly during grand rounds and during an additional session with the OB/Gyn residents.

To advise the clinical personnel to collect specimens, enrollment in our biorepository is denoted in a non-permanent note that is placed within the electronic medical record. Recently, we have also been able to note involvement and instructions within the research module of the EHR.

Results

As of November 1, 2013, there are 1557 women enrolled of which 131 are still pregnant and 13 experienced either a spontaneous abortion or intrauterine fetal demise. Additionally, 1245 babies have been delivered at the University of Iowa Hospitals & Clinics and there are 131 consented women with pending deliveries. Therefore, 88.1% of women consented into the MFTB complete their prenatal care and delivery at UIHC. Thus, we have an exceptional

opportunity to collect longitudinal pregnancy samples from the women who consent to participate in MFTB. We have collected 2105 blood samples that have been divided into viable mononuclear cells and plasma and were then aliquoted and frozen. We have stored samples from 387 placentas and 892 umbilical cord bloods. Recruitment and sample collection is ongoing with approximately 35 women enrolled per month (Figure 2).

We have a 73% enrollment rate of women approached. Women who decline are not re-approached during their current pregnancy. The majority of our subjects are white (85%) which is representative of the Iowa population (Table 1) [5]. As shown in Table 2, the average maternal age at time of delivery is 29.5 years old. The average prepregnancy BMI is approximately 30. Overall, the women in MFTB are healthy: 21% of women were considered to be Group B Streptococcus (GBS) positive, 7.6% experienced preeclampsia, 8.75% had gestational onset diabetes mellitus and 13% experienced infertility issues prior to pregnancy (either male or female factor). The caesarean section rate among participants in MFTB was 30% (58.3% primary).

The majority of the pregnancies are singleton (94.2%). Of the 5.8% that are multiples, 95.8% are twin gestations (71.4% dichorionic-diamniotic). The average birthweight of all of the babies is 3201g and the gestational age at delivery is 38 2/7 weeks. The median APGAR score is 8 at 1min and 9 at 5min. The gender of the offspring was nearly equal (48% female) (Table 2).

This format for biobanking has proven productive for Women's Health Research. In 3 years, the biobank has been used for over 20 projects by faculty, fellows, and residents. There have been several new collaborations established between the Departments of Obstetrics & Gynecology and Internal Medicine, Pharmacology, and Pediatrics because of new research capabilities due to the MFTB. In addition, 3 patents and 7 grants have been awarded that have relied on the MFTB.

Comment

The goal of the Women's Health Tissue Repository (WHTR) is collect, bank, characterize, and distribute high quality human biological specimens related to the needs of investigators within our department and our collaborators. We have recently expanded our banking effort to include a Maternal Fetal Tissue Repository.

The samples obtained from these initial participants have enabled the development of new technologies including generating of patents to predict women at risk of various adverse pregnancy outcomes and the sequencing of the fetal genome from maternal plasma [6, 7]. The Women's Health Tissue Repository is a powerful research tool that has stimulated many projects and allows us to explore genetic, environmental, and health risk factors, as well as other variables in relation to the outcomes of pregnancy including short and long-term maternal health, length of gestation, and short and long-term child health outcomes.

We have found that faculty, staff, and residents are willing to assist in sample collection. Reminders and staff training increase our collection rate. We repeat our training at least yearly or more often as we notice an increase in missed samples. At training sessions, we

also seek input for how to better integrate the bank into the daily workflows of the clinic and inpatient areas, especially in labor and delivery.

While certainly our absolute numbers of samples and patient characteristics will change, we are able to learn the strengths and weaknesses from the first four years of our maternal fetal banking efforts. These lessons will inform our expansion efforts and are important for other institutions that seek to establish their own biorepositories. Because our overall patient population and health characteristics are reflective of Iowa and national incidence rates, we do not believe that there is a strong participation bias.

There are several strengths to our collection efforts. Our primary strength is our excellent fidelity of sample handling. This occurs because we collect an extra tube of blood solely for research use and all samples are processed using a standard operating protocol to ensure that all samples are handled in an identical fashion. While collecting leftover clinical samples would cost less in terms of phlebotomists and sample collection supplies, there would be significant differences in how samples were collected, handled, and time to final storage that would impair the ability to be confident in experimental results. Additionally, we have high resolution clinical information that correlates with all samples. This information makes these samples extremely valuable to translational research. To extend the usability of all samples, each sample is aliquoted prior to storage to prevent multiple freeze-thaw cycles and to allow multiple investigators access to the same samples. Further, we have stored samples such that they would be of maximal use in the future for many different experiments. For example, maternal and cord blood cells are stored to be viable when thawed. Thus, we are able to maximize the samples obtained at each collection and to have paired samples of plasma and cells. Placenta samples are kept in an RNA stabilization solution (RNA_{later} from Ambion, Life Technologies Carlsbad, CA) as well as in liquid nitrogen to allow them to be used for RNA, DNA, and protein extraction. Furthermore, having these samples linked to many elements in the EHR, will allow researchers to better answer very specific questions in women's health, such as studying as the effect of a specific medication on protein modification.

While we have tried to make our samples as flexible as possible, there will be experiments that will be incompatible with the manner in which they were collected. However, ACD-A tubes were chosen for maternal blood as we could extract both plasma and viable cells from the same sample. Because we collect a large volume of cord blood at delivery, we use bags designed to hold 250ml of cord blood sample. The cord blood bags also contain a citrate solution which is compatible for most experiments.

The main weakness of our biorepository is the lack of racial diversity in our participants. However, the profile of our patients is very reflective of those seen at UIHC and the population of Iowa. In the future, we may extend our efforts to other locations to expand the diversity of our participants. We will have to consider how the delay to sample processing time would affect the quality of the samples. Because of the protein degradation in samples and the logistics of patient consent, sample collection, and clinical data collection, we currently direct our efforts to biobanking specimens from patients treated at UIHC. As the

enrollment continues, our absolute numbers of diverse patients increases allowing a more ethnically and racially diverse set of patient samples to be utilized for assays.

Despite our homogenous racial population, our participants reflect overall statistics in obstetrics. The prevalence of GBS, preeclampsia, gestational diabetes, and infertility is similar to that reported globally [8–17]. Additionally, the rate of cesarean section in our participants was also similar to national trends [18]. Therefore, it is also highly unlikely that there is a strong selection bias in our participants despite our recruitment solely from a tertiary care center.

Our use of a local, yet centralized process has allowed us to overcome many of the logistical hurdles faced by national or even institutional biobanks. We have adapted our recruitment around the clinical workflows unique to the clinical divisions within our department. For example, our research assistants tailor their visit with patients at the preferred time for varying providers and divisions. This can be at the beginning or end of a clinic visit. Most importantly, because of our familiarity with clinical care specific to Obstetrics & Gynecology, research team members know which clinic visits are most likely to have standard of care labs drawn. This is a key aspect to providing proper reminders to ensure that lab requisitions are distributed and that samples are collected. Faculty, staff, and learner familiarity with the researchers and the results from studies utilizing the Women's Health Tissue Repository also assists in everyone understanding the importance of the bank to advancing research and being invested in sample collection. This investment has been key to the collection of samples such as cord blood and placenta at off hours. Additionally, awareness of the availability of samples has resulted in numerous residents, fellows, and faculty designing research projects to make use of the available material and clinical annotation. Not only does this expand research into women's health research, but it improves research efficiency and minimizes costs. A recent survey of biobank organizations found that 69% of respondents were concerned that the samples were being underutilized [19]. However, the Maternal Fetal Tissue Bank has been utilized in numerous projects to generate preliminary data for grant applications as well as to complete grant funded projects in the first three years. While there was an initial period of low usage while a sample base was built, the usage of the MFTB has increased steadily as our collection of samples from various patient, gestational age, and disease states has become more robust; this increased number of samples now allows appropriately powered studies to be performed.

There is a significant upfront investment required for successful biobanking. Many patients need to be consented before there can be large enough cohorts to be useful for study. Additionally, because we begin collecting samples very early in pregnancy, we do not know who will go on to develop pregnancy-related issues such as gestational diabetes, preeclampsia, or pre-term birth. However, the large numbers of healthy patients' samples that we have collected are actively being used to better define normal physiologic changes in pregnancy and serve as the control population for comparison. Our biorepository has already proven to be a very useful resource for research by residents and faculty; novel technologies are already being developed using these samples and research findings are being presented and published.

Tissue banking in Women's Health is vital to the future of translational research. Our current efforts to expand our biorepositories that collect samples from patients in the gynecology clinics and the reproductive endocrinology and infertility clinics will enhance our ability to perform translational research over all stages of a woman's lifetime. We believe that our model can be replicated at many other institutions and will advance women's health research.

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Figure 1. Schematic of Organizational Structure of the Women's Health Tissue Repository. Each individual repository has IRB approval and a unique consent form to best address the issues related to each patient population.

Figure 2.

Maternal Fetal Tissue Bank Enrollment continues to increase steadily. Blue diamonds note the number of pregnant women enrolled each month. Red squares represent the total number of pregnant women enrolled.

Table 1

Ethnic Distribution

Maternal Race	% of Subjects
White	85%
Asian	3.3%
African American	3%
Hispanic	3%
Multiracial	0.8%
Other	0.5%
Declined to List	4.2%

Table 2

Participant Characteristics

Characteristic	Average	Range
Maternal Age	29.75 years	18–44
Pre-pregnancy Body Mass Index	34.75 kg/m ²	17.02–58.09
1 min APGAR	8*	1–9
5 min APGAR	9*	1–9
Gestational Age at Delivery	38 5/7 weeks	24 6/7 – 42 2/7
Birth Weight	3201 grams	641 – 4786

* Median APGAR scores