Refusing ‘failure’
A patient’s hope for the future of women’s health and fertility

In 2008, Goldnar Miamee went to her OB/GYN and said, “I know this may sound funny, but I feel like a menopausal woman.” With a laugh, her doctor said “Oh, you’re too young for that.” She thought nothing of it at the time. But a few years later, after trying to get pregnant without success, she was diagnosed with primary ovarian failure.

“I was not ready to accept that as a diagnosis, so I found out about the NIH study,” Miamee said. “Coming here was a life changing experience. I finally was able to accept my condition, which is actually primary ovarian insufficiency.”

Primary ovarian insufficiency (POI) is a condition in which women younger than 40 have ovaries that stop releasing eggs, or release them only intermittently, and stop producing normal amounts of the hormones estrogen, progesterone and testosterone, or produce them only intermittently.

Miamee is a part of the Eunice Kennedy Shriver National Institute of Child Health and Human Development natural history study Ovarian Follicle Function in Women with Spontaneous Primary Ovarian Insufficiency. The study aims to learn more and improve treatments for young women with POI and clarify the differences from menopause.

During the study, Miamee and many participants came to realize that POI is not just about fertility.

“Not only did I lose my chance of having children, but I also was living with hot flashes and mood swings, depression and possible bone loss,” she said. As part of the study, she was prescribed hormone replacement therapy to increase their levels. “I didn’t take them for the first six months because I thought I don’t need it. I finally decided to take the hormone replacement therapy and found them to help tremendously. POI was really affecting my life before; but then was under control.”

While recruitment ended in 2011, the natural history study continues to take...
Why do adolescents participate in medical research?

Teens feel they are contributing to society when they participate in medical research even if there are no direct benefits to them, according to a study led by Clinical Center staff.

Chief of the Bioethics Department, Christine Grady, and staff member Dave Wendler led the study, Parental Permission and Adolescent Assent and Decision Making in Clinical Research, from 2008 to 2010 in collaboration with Lori Wiener and Sima Zadeh of the National Cancer Institute pediatric oncology branch, and Drs. Ben Wilfond and Doug Diekema and staff at Seattle Children’s Hospital.

In analyzing the data, they’ve come to some interesting conclusions.

“There are many teens participating in medical research,” Grady said. A lot of changes occur during adolescence which means diseases and possible treatments might affect teens differently than other age groups. “We need teens to participate in research to understand how to provide better medical care for them.”

Federal regulations governing the protection of human subjects in medical research require adolescents provide assent and parents or legal guardians provide permission for most research. The federal regulations don’t provide specific guidelines for what the consent or permission process should look like, Grady said.

“Enrolling in a medical research trial is a significant decision. We want to gain a better understanding of what teens understand about the research and how much they were involved in the decision-making,” Grady said. “To make the experience as ethical as possible and to protect them, we need to understand it from their perspective.”

Grady and team conducted structured interviews with 147 teens, ages 13-17, and Seattle Children’s Hospital staff interviewed 30 teens. All had been enrolled in a clinical study in the previous six months.

Teens answered about 100 questions and a parent or guardian was also interviewed about the teen’s experience during enrollment.

“This was a remarkably well-balanced cohort,” Grady said. Teens were 51 percent female, 49 percent male with about 20 percent at each age. About 20 percent were healthy volunteers, and the rest ranged from moderately ill to severely ill.

“We could not have interviewed this many teens without the help of the Clinical Center’s doctors, nurses and other staff who referred so many patients to us,” Grady said.

Survey questions ranged from overall satisfaction with the enrollment process to specific elements of how the decision was made to volunteer.

A high percentage of teens felt supported throughout the decision-making process, and normally the teen and parent made the decision to enroll together. Despite emerging independence, in this situation, teens generally want parents’ input and advice.

Recommendations from the findings of this study include: provide teens with detailed information about what to expect at each step of the research and tailor the assent process to them, where possible.

Grady said they have also recommended teens be given the option of signing an assent form as teens reported this gives them a sense of power and control in the process.

The survey addressed the ethics of involving teens in medical research that did not benefit them. “What we learned from the surveyed teens was they did not feel exploited by such studies,” Grady said. “They understood they were making a valuable contribution to help other people, and they were willing to do that.”

The researchers found teens and parents overwhelmingly reported they would be willing for the teen to complete a non-invasive procedure such as an extra blood draw or chest x-ray and more than half would also be willing to do a skin biopsy even if it was not going to benefit them but was for the research.

Parents said the offer of money would make no difference in their decision about these procedures. Healthy teens were more likely than teens with serious illnesses to report money would make them more likely to agree to extra tests.

About 25 percent reported they felt pressure to enroll from parents and friends in some cases from medical staff and researchers too.

“We went into it thinking that younger teens and those with more severe illnesses would have notable differences from older teens and healthy volunteers in feeling pressure to participate in research or satisfaction with the process. This was not the case,” Grady said.

Articles have been published in the Pediatrics Official Journal of the American Academy of Pediatrics (http://tinyurl.com/k26bvsx) and the Journal of Adolescent Health (http://tinyurl.com/m6snwgv).
new scientific approaches to learning more about POI. Miamee, along with 500 other women, ranging from age 18 to mid-30s, now have the opportunity to have genetic testing done on the samples of blood they provided.

Dr. Lawrence Nelson, principal investigator of study, and his team are working with researchers at Washington University in St. Louis through a collaborative agreement on conducting whole exome sequencing on the women's samples.

“If we can find genetic causes of this then we can eventually develop tests that are predictive of who’s going to get it,” Nelson said. “Women could have the genetic testing done and determine if they are likely to develop POI and either change their plans to get pregnant earlier, or adopt or [say] my career’s really important to me so now I know let’s focus on that.”

But as the NIH team was preparing the protocol, they came across an ethical dilemma.

“We’re doing research; we’re looking at POI; this is the main reason for doing it, but what happens if we find a gene that’s related to breast cancer in our research? What do we do about that?” Nelson said.

Miamee, who was consulted in the writing process of the new consent form for the genetic testing, said, “I would definitely want to know, but I do see that there are women who didn’t want to know. To me, that’s one of the positive sides of this whole study.”

After extensive conversations with leading genetic experts, they decided that the academic researchers would notify NIH, who would then consult with patients, if they come across one of 57 genes specific to a disease or condition other than POI, such as familial hypercholesterolemia or malignant hyperthermia susceptibility.

A genetic counselor and support team will be made available to those with an abnormal gene that has been clinically validated, which is expected to occur in only one in 100 women. There are also known ‘next steps’ for patients to follow for each of the 57 genes, so they can take action to stay healthy.

“Even if [NIH] never finds the result, I’m OK with the fact that people are spending the time and initiative to even try,” Miamee said. “There were other diseases where people participated in a study and maybe in their lifetime they never got answers, but at some point, I’m confident they will, maybe past my time, but I’m sure something good will come out of it.”

The long-term goal is to transfer a fully-integrated patient care and research program to the community where it would be self-sustaining by people supportive of women with POI. Miamee has already taken the first step to reach out to the community by creating a group called Positive Optimistic and Involved for POI. “I just wanted to use my good experience and knowledge to help,” she said.

### Upcoming Events

**NIH Medical Research Scholars Program scientific presentations**
May 12-13, 2014; 8:30 a.m. - 5:30 p.m.

**Lipsett Amphitheater**
Forty five students will present their medical research.

**Contemporary Clinical Medicine Great Teachers Lecture; Antiplatelet therapy: from serendipity, to random screening, to rational molecular design**
May 14, 2014; noon - 1 p.m.

**Lipsett Amphitheater**
Presented by Barry S. Coller, MD, Rockefeller University Hospital.

**Office of Research on Women’s Health Scientific Forum; Sex differences in neuroscience: past, present, and future perspectives**
May 14, 2014; 2 p.m. - 4 p.m.

**Lipsett Amphitheater**
Presented by Story Landis, PhD, NINDS, Vicky Holets Whittemore, PhD, NINDS, Cheryl Bushnell, MD, Wake Forest Baptist Stroke Center, Margaret McCarthy, PhD, University of Maryland School of Medicine.

**NIH Director’s Wednesday Afternoon Lecture Series; Interplay between genes and environment in insulin resistance and metabolic syndrome; the unique role of the gut microbiome**
May 21, 2014; 3 p.m. - 4 p.m.

**Masur Auditorium**
Presented by Ron Kahn, MD, Harvard Medical School.

**NIH Director’s Wednesday Afternoon Lecture Series; ABC transporters: structures, functions, and reaction mechanisms**
May 28, 2014; noon - 1 p.m.

**Lipsett Amphitheater**
Presented by Kaspar Locher, PhD, ETH Zürich.