Mimicking Pregnancy To Reduce Breast Cancer Risk

By Rabiya Tuma

Women who have a full-term pregnancy before their mid-20s substantially reduce their lifetime risk of breast cancer, compared with women who either have children later in life or do not have children, according to many epidemiological studies. Women who breastfeed their babies further reduce that risk.

Now breast cancer researchers are asking whether those observations can be transformed into a feasible breast cancer prevention strategy. Some investigators contend that the goal should be at the forefront of breast cancer research, whereas others express concern that pregnancy is too complex to mimic. Despite the challenges, several research groups are trying to tackle the question, and a few are even starting to test their hypotheses in women at high risk for breast cancer.

Scientists once believed that a woman’s age at her first full-term pregnancy is the most important factor, in terms of pregnancy’s role in breast cancer risk. But recent studies have shown that it plays less of a role than the number of births and duration of breast-feeding, said Valeria Beral, M.D., director of the cancer epidemiology unit at the University of Oxford, during her presentation at the San Antonio Breast Cancer Symposium in December.

The role of multiple pregnancies became clear in 2002 when the Collaborative Group on Hormonal Factors in Breast Cancer, an international research group based at the University of Oxford, published a pooled analysis of 47 studies that included approximately 50,000 breast cancer patients and 96,000 healthy women. The team, of which Beral is a member, reported that when they held the age at first birth constant, each birth was associated with a 7% lower relative risk of breast cancer and each 12 months of breast-feeding was associated with a 4.3% lower risk.

One can see the association of lower risk and early, multiple pregnancies by comparing the rate of breast cancer in developed and developing countries. The incidence of breast cancer in the United States and Europe is 6.3% among women up to age 70 years. By contrast, the rate is 1.2% in rural Africa and Asia. Although diet and environment may account for some of that difference, the Collaborative Group estimates that the incidence in developed countries could theoretically drop to 2.7% if women adopted the same reproductive patterns as women in developing countries have.

Beral is careful to emphasize that no one is advocating that women have more children. Rather, she argues that with such an enormous benefit to be gained, at least in theory, scientists should be trying to find ways to mimic the effects of pregnancy. In her view, though, the approach is desperately understudied. “It is almost as if the data is forgotten and people want some other answer,” Beral said. “It is as if people are saying, ‘Okay, we know that, but what next?’ rather than saying, ‘This is it. This is the big part. Everything else is small in comparison.’ If we want to prevent breast cancer, you have to go to the big picture.”

**Huge Challenge**

Beral concedes that the task is not simple. Only full-term pregnancies appear to be associated with lower risk, suggesting that some hormonal shift late in pregnancy is key. But the critical hormone(s) is unclear. Nor is it clear why a woman has to be relatively young, say, under 25 years, for the association to hold. Further complicating the scenario is that a woman’s short-term risk of breast cancer actually increases for several years after pregnancy, regardless of her age, and the protective quality of childbirth shows up only about 10 years later and then persists for the rest of her life. This unexplained paradox is one example of the questions that remain understudied.

With these complications, it’s no surprise that some breast cancer experts have concluded that the limited time and money available for research is better spent elsewhere. “I think the idea that someone would figure out exactly what the common denominator is during these changing nine months of pregnancy and that it could be developed into a targeted treatment would be a huge challenge,” said Edith Perez, M.D., professor of medicine at the Mayo Clinic in Jacksonville, Fla. “Pregnancy is not one change—it is not like having a broken toe—so many things happen. So it is not a low-hanging fruit.”

“I want to continue putting my effort to understand the individual changes in breast cancer so we can develop better treatments and prevention strategies,” Perez added.

Further complicating the effort is that any prevention strategy based on these observations may well have to focus on young women. “If you were talking about introducing a new therapy like this to patients who were 60 years of age and had a very high risk of getting a cancer, that is one thing,” said C. Kent Osborne, M.D., director of the Dan L. Duncan Cancer Center at Baylor College of Medicine in Houston. “But now you are talking about using something in younger women, most of whom will never get breast cancer in their lives. That is where the challenge comes in.”

Osborne also pointed out that even if one identified a plausible prevention strategy,
testing it would be a major undertaking. Proving its efficacy would require monitoring women for several decades: a cumbersome and expensive proposition. Such an expenditure seems unlikely, because Americans seem reluctant to use chemopreventive strategies already available or even to change their lifestyle habits to lower cancer risk.

Looking for the Mimic

Despite the considerable hurdles, several research groups are trying to find a way to mimic the changes of pregnancy in order to prevent breast cancer. Scientists have demonstrated that exposing female rats and mice to pregnancy levels of estrogen and progesterone for their normal gestation time of 3 weeks reduces their susceptibility to breast cancer in a variety of chemically induced and genetically induced breast cancer models. As with natural pregnancy in humans and rodents, the lower risk lasts for most of the animal’s lifetime.

Translating those results to humans gets a little tricky. “The problem is that in rodents the hormones don’t go up that much, whereas in humans they go up astronomically,” said Malcolm Pike, Ph.D., a professor at the University of Southern California Keck School of Medicine in Los Angeles, who has been interested in the issue for decades. Such high doses could cause serious side effects, including blood clots.

Pike and others, though, think that a way around the excessively high hormone doses may exist. In the 1990s, Jose Russo, M.D., professor and director of the breast cancer research laboratory at Fox Chase Cancer Center in Philadelphia, and colleagues showed that treating virgin rats for 3 weeks with human chorionic gonadotropin (hCG), a hormone produced in pregnancy, also protected the animals from chemically induced breast cancer. And like a full-term pregnancy, the protection that hCG treatment conferred was long lasting. Moreover, hCG treatment reduced tumor growth in animals that were exposed to carcinogens prior to hormone treatment.

Human studies hint that the strategy might be worth testing. Knowing that hCG has been used for fertility treatments (an approved indication) and for weight-loss treatments (an off-label use not supported by evidence), researchers at Keck asked women about prior hCG use in a case-control study of nearly 1,500 women. They found a trend for increased use of hCG in the control group compared with the breast cancer group, though the difference was not statistically significant. Nonetheless, the researchers argue that this finding warrants further study. More recently, Russo and colleagues reported that short-term hCG treatment reduced tumor cell proliferation from 18% in biopsy specimens to 4% in post-treatment surgical specimens in 20 postmenopausal women with breast cancer in a double-blind, placebo-controlled study. The change in proliferation was statistically significant.

On the basis of those data, Pike’s and Russo’s groups are each conducting prospectively designed studies in women to test the effect of short-term hCG use. In Russo’s study, which is currently enrolling participants, women with BRCA1 mutations will receive three weekly injections of recombinant hCG for 90 days. To evaluate the effect of the treatment, the researchers will compare breast biopsy samples taken at the beginning of the study, at the completion of treatment, and 6 months after completion of treatment. They will look for changes in gene expression, cell proliferation, and tissue structure. Pike’s team plans to use a similar approach, though their study is not yet open for enrollment.

To evaluate the effect of hCG treatment, however, scientists need to know what changes occur during a natural pregnancy and then identify patterns associated with pregnancy-induced protection. With that in mind, Russo’s team is using microarrays to assess gene expression patterns in breast biopsy specimens from two independent cohorts of women. Each cohort includes 40 women who have given birth and 20 women who have not. The final data from the new cohorts are not yet available.

Russo is not the only one looking for such differences. In 2006 the Avon Foundation announced an $8 million initiative to study pregnancy and breast cancer prevention. Many studies that the initiative funded, including Russo’s, look for biomarkers that define the protected state in women who have given birth. “We don’t know if understanding what is going on during pregnancy will lead us to a prevention strategy, but it is worth pursuing because of the huge potential impact,” said Marc Hurlbert, Ph.D., scientific director for the foundation, noting that some women younger than 25 years at the time of their first birth can have as much as a 40% lifetime risk reduction.

Like Pike and Russo, Dan Medina, Ph.D., professor in the department of molecular and cellular biology at Baylor, is optimistic that research with a more targeted approach can find a preventive strategy. His group is trying to understand the long-term effects of pregnancy on a woman’s genome or epigenome. If scientists can identify the relevant changes that occur in response to the hormone exposure and that affect protection, they might be able to find agents that induce those genomic changes without hormone exposure.

Thus far, his group and other research groups, most of which the Avon Foundation funds, are finding differences in proteomic, genomic, and epigenetic patterns in breast tissue from women who have had children and women who have not. “What has not been done yet is a meta-analysis of all the different studies,” Medina said. “For any individual group to get enough samples is difficult, but with six or seven groups, you start to get enough.”

Groups working on translating the basic observation into a prevention strategy do not think that one will emerge quickly, but they are convinced the possible gains are worth a long-term effort. “I think it is a very feasible preventive approach,” Medina said, “and long lasting.”