Giants in Obstetrics and Gynecology Series: a profile of Linda C. Giudice, MD, PhD, MSc

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Linda C. Giudice, MD, PhD, MSc, is Distinguished Professor, Chair Emerita, and the Robert B. Jaffe, MD, Endowed Professor in the Reproductive Sciences at the University of California, San Francisco (UCSF). Dr Giudice has conducted pioneering research in endocrinology of the endometrium, and she has made major contributions to our understanding of the biology of the menstrual cycle, thus laying the foundation for the implementation of precision medicine in reproductive disorders involving the endometrium.

With a strong background in chemical engineering and biochemistry, Dr Giudice is a physician-scientist whose unique perspective has enabled her to make important contributions to translational science in reproduction. She discovered a protease that specifically cleaves insulin-like growth factor-binding protein (IGFBP)-3, the major IGFBP in the circulation. In addition, she characterized the transcriptome of the human endometrium and identified gene expression profiles for the proliferative early, mid-, and late secretory phases of the menstrual cycle. Her studies of the endometrial transcriptome in women with endometriosis uncovered classifiers for the diagnosis and staging of the disorder, representing an alternative to surgical diagnosis and staging. Moreover, Dr Giudice was a major contributor to the concept of a role for progesterone resistance in the endometrium and, in particular, the endometrial stromal fibroblast of women with endometriosis and polycystic ovary syndrome.

In addition to many fundamental and translational discoveries, Dr Giudice has been instrumental in establishing reproductive environmental health as an important field globally, bringing it to the attention of clinicians, researchers, and the public. She has been a teacher and mentor to many early-career physician-scientists, helping propel translational research in the field of obstetrics and gynecology.

Dr Giudice has held many key leadership positions, and currently, she is the president of the International Federation of Fertility Societies and Chair of the International Federation of Gynecology and Obstetrics Committee on Reproductive and Developmental Environmental Health. She is an elected member of the US National Academy of Medicine and the US National Academy of Inventors.

She is the former president of the American Society for Reproductive Medicine, the Society for Gynecologic Investigation, the Society for Reproductive Endocrinology and Infertility, and the World Endometriosis Society. Dr Giudice was on the UCSF Steering Committee on Women’s Precision Medicine and the March of Dimes Scientific Advisory Council.

In recognition of her discoveries and scientific contributions, Dr Linda Giudice is recognized as a “Giant in Obstetrics and Gynecology” in this issue of the American Journal of Obstetrics and Gynecology (AJOG).

Early Life: A Family Focused on Education
Linda was born in Brooklyn, New York, into a close-knit Italian family. Her father, born in Sicily, emigrated to the United States with his parents at the age of two, and her mother’s parents emigrated from Italy before Linda was born. The family had a strong focus on the value of the children’s education, and Linda’s generation was the first to attend college. In elementary school, Linda was accelerated twice, skipping fifth grade and completing grades seven through nine in two years. The family moved from Brooklyn to Norfolk, Virginia, because Linda’s father was in the military, and she finished high school there.

Linda’s interests were broad: she recalled how much she loved not only math and science but also poetry, history, music, languages, and other subjects. She told me that math inspired her to understand how things worked, which developed into a love of chemistry and physics in high school. These interests led her to pursue an undergraduate degree in engineering.

College and the Journey From Physics to Biology
“’I was fascinated by nuclear physics and thought that nuclear engineering was for me,” Linda said. However, she soon learned that she preferred chemistry to physics and graduated from Columbia University with a Bachelor of Science degree in Chemical Engineering, enriched with a strong
foundation in organic, analytical, inorganic, and physical chemistry.

The next academic step took Linda in a more biologic direction, and she progressed with a Master of Science degree in biomedical engineering at Washington University, St. Louis. Pursuing a more fundamental understanding of biology, Linda then attended the University of California, Los Angeles, for her PhD, where she worked with Dr John Pierce, a protein chemist, on the structure and function of gonadotropins. Linda recalls it as a “thrill”—she was able to use biochemical and spectroscopic techniques to elucidate the structure, function, and binding properties of the gonadotropin hormones and thyroid-stimulating hormone (TSH). In addition, she gained essential knowledge of reproductive biology, molecular biology, and genetics.

Linda returned to New York to participate in her first postdoctoral position at Rockefeller University where she worked with Dr Günter Blobel, before he was awarded the Nobel Prize in Physiology or Medicine in 1999, “for the discovery that proteins have intrinsic signals that govern their transport and localization in the cell.” Linda’s focus was on RNA and protein processing, including translational modification of proteins. “It was a very exciting time at Rockefeller,” she said. “There was a strong emphasis on cell biology, and a lot of independence given to graduate students and postdocs. I had a really fantastic group of postdoctoral colleagues. We had fun in New York City, understanding and discovering cell biology.”

**Medicine: the “aha” Moment**

Linda’s work at Rockefeller assumed a basic science focus and was not as translational in nature as her doctoral studies. She undertook a second postdoctoral position in the Clinical Endocrinology Branch in the Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD) at the National Institutes of Health (NIH) where she worked on the thyroid axis—in particular, the processing of TSH and the neurophysin and oxytocin precursors. During her time at the NIH, Linda had an epiphany. Her mentors there were internists and endocrinologists who opened the world of translational medicine to her. A colleague invited her to attend rounds with the clinical fellows, a group that included Dr Bruce Weintraub, a prominent endocrinologist, and the late Dr Saul Rosen, who became deputy director of the NIH Clinical Center.

“Translational medicine—hearing the dialogue, seeing the trust that patients had in the physicians, and knowing that some of the things happening with the patients were being investigated in the laboratory with an ability to help patients through clinical care and research was the ‘aha’ moment for me—the moment I realized translational science and translational medicine were exciting,” she said. Linda’s husband, Dr Athanasios “Sakis” Theologis, a plant biologist, was supportive when she told him she was thinking of applying to medical school. Linda chose Stanford University, adding another line to her zigzag across the country.

**The Path to Obstetrics and Gynecology**

Early on, Linda’s focus was on the biology of the pituitary gland and the regulation of the menstrual cycle. She carried this interest with her throughout the agonistic training she received in her postdoctoral training and medical education. Linda’s internship in internal medicine included one rotation in labor and delivery and one rotation in the outpatient gynecology clinic, which cemented her path for the future. Her interest in reproduction and reproductive medicine was enriched by the context in which she was working: around the same time, in the early 1980s, the first baby conceived through in vitro fertilization (IVF) was born in the United States. During her medical training, Linda’s mentorship with the late Dr Kent Ueland, then Chair of Obstetrics and Gynecology at Stanford, and several other obstetricians there, including Dr Jagdip “Jags” Powar, impacted her career path. She learned laparoscopic surgery from Dr Emmet Lamb at Stanford, and she finished the last two years of her residency under the training of Dr James Warren at Washington University. Furthermore, Linda returned to Stanford as a Reproductive Endocrinology and Infertility Fellow under the leadership of Dr Lamb, and after completing her training, she was appointed to the Stanford faculty as Assistant Professor.

**The Discovery of Insulin Growth Factor-Binding Protein Proteases**

At the time, Stanford had a strong group of investigators in pediatric endocrinology, focused on growth disorders in children, who were studying growth hormone and insulin-like growth factors (IGFs). Linda attended the group’s laboratory meetings, and an interest emerged in IGF and IGFBPs, mainly because IGFBP-1 is a major protein in the human decidua.

Linda’s team discovered that the serum of pregnant women contains a protease that cleaves IGFBP-3 and increases the availability of IGF-I and IGF-II. This important observation represented the discovery of a new member of the family and a new mechanism for regulation of IGF action. The story behind this discovery is interesting: the biotech company Genentech had just cloned the cDNA for IGFBP-3 and then had expressed it. Linda and her colleague, Dr Ron Rosenfeld, a pediatric endocrinologist, obtained the protein, and through a lot of effort, they went on to discover an IGFBP-3 protease. A group in Paris had a similar observation,

and both groups presented their preliminary findings at the annual meeting of the Endocrine Society. Together, they had to decide whether to compete for publication or publish simultaneously for greater impact. “We thought the message about the importance of the proteases and what they do to increase the bioavailability of the IGFs would have more impact if there were back-to-back papers from two independent groups who found the same thing at the same time,” Linda told me. The two groups agreed, and their papers were both accepted and published in the Journal of Clinical Endocrinology & Metabolism.” This discovery, and the subsequent finding that IGFBP-4 protease is of trophoblast...
origin, opened new lines of investigation into the mechanisms responsible for IGF action. The biologic properties of these growth factors are relevant not only for reproduction but also for oncological conditions.

Transcriptomic Studies of the Endometrium During the Menstrual Cycle

As a physician, Linda was engaged in clinical work, IVF in particular. She told me about the striking changes shown during the menstrual cycle that are visible with ultrasound and how these changes reflect the serum concentrations of estradiol and progesterone and the histology of the endometrium. One of Linda’s major contributions was the characterization of the endometrial transcriptome to understand endometrial biology (Figure 1).

In the early 1990s, Dr Ron Davis, a pioneering geneticist at the Stanford Genome Technology Center, and several colleagues had a hand in establishing Affymetrix, a biotechnology research and development company that produced DNA microarrays. Linda was one of the first faculty at Stanford to use this technology and to apply functional genomics tools to understand reproduction. Her team was one of the first groups to use microarray technology to identify differentially regulated genes during the menstrual cycle (Figure 2). For example, she found that immune-related genes were among the most differentially expressed during the mid- vs early secretory phase of the menstrual cycle. The most highly regulated gene was the cytokine CXCL-14 (also known as a breast- and kidney-expressed chemokine, BRAK)—the main function of which is to recruit monocytes and other cells during the implantation window. Another cytokine was leukemia inhibitory factor (LIF), which has been implicated in endometrial receptivity in mice and humans. Some patients with low concentrations of LIF in the midsecretory phase have been reported to experience infertility and recurrent spontaneous abortion. Other factors identified included toll-like receptors, antimicrobial peptides, and interleukin-15. In addition, the findings led to the identification of candidate genes for regulation by progesterone. Another important paper, entitled “Discovery of new inducible genes in in vitro decidualized human endometrial stromal cells using microarray technology,” emerged from her work.

Linda and her team leveraged the information derived from the study of the endometrial transcriptome to gain insight into the biology of endometriosis, which led to the identification of a proinflammatory phenotype in the endometrium of women with disease and of classifiers to stage endometriosis, based on information derived from an endometrial sample instead of that obtained from surgical diagnosis or staging. In addition, this information identified potential targets to mitigate the adverse events of endometriosis. In collaboration with Dr Karen Smith-McCune, a physician-scientist at UCSF, they found that the endometrial...
transcriptome of women who used either an oral contraceptive or the levonorgestrel intrauterine device revealed proinflammatory markers, raising issues about the safety of these agents in HIV transmission.

The Methylome of the Human Endometrium During the Menstrual Cycle
Linda and her team characterized the epigenomic changes in the endometrium during the menstrual cycle—the rationale for these studies was that the endometrium undergoes major changes in response to cyclic variations in circulating estrogen and progesterone and that cellular and molecular changes mediated by steroid nuclear receptors and transcription factors can alter epigenetic marks in the genome. By characterizing the endometrial methylome during the menstrual cycle, her team was able to show that changes occurred during different phases of the cycle and that there was a correlation between the transcriptome and the DNA methylome (there was an association between DNA methylation and gene expression in several loci, which is important in endometrial biology). These observations were recapitulated when endometrial stromal fibroblasts were treated in vitro with estradiol and progesterone.

Progestosterone as the Master Regulator of the Endometrial Stromal Fibroblast
Linda’s studies on the transcriptome and methylome of the endometrium helped define the molecular and cellular events that occur during the menstrual cycle (Figure 3). These observations converged with her long-standing interest in the regulation of endometrial cell biology. The endometrial stromal fibroblast incubated with progesterone becomes decidualized and is often referred to as the decidualized endometrial stromal fibroblast. This cell is thought to be key for leukocyte recruitment to the endometrium during the secretory phase and in decidualization and angiogenesis. Decidual cells are central to the formation of an adequate maternal-fetal interface and, therefore, are considered key for the establishment of pregnancy. Linda has had an interest in the role of progesterone in the regulation of endometrial function and has contributed substantially to developing the concept of progesterone resistance. Monitoring progesterone function is not straightforward, as there is no easy bioassay available for use in clinical practice. Linda and her team put fibroblasts in culture and challenged them with progesterone before carrying out transcriptomic analyses of signaling pathways to understand the normal progesterone response.

The Endometrium of Women with Endometriosis
Endometriosis affects 6% to 10% of women in the general population and 35% to 50% of those with pelvic pain and/or infertility. In 1927, Sampson published a key paper in AJOG proposing that endometriosis of the peritoneal cavity presented as a result of retrograde menstruation and implantation of the endometrium outside of the uterine cavity. Emergent from that theory was a puzzling question: What is the difference between the endometrium in women with or without endometriosis? Linda’s team pursued studying the global gene expression of the endometrium and found that the transcriptome revealed molecular dysregulation of genes participating in the proliferative-to-secretory transition. Importantly, they found changes consistent with an attenuated progesterone response, and these changes were observed not only in messenger RNA but also in the DNA methylome. The increased frequency of infertility may be related to the existence of a proinflammatory phenotype in the endometrium of women with endometriosis. Indeed, endometrial stromal cells from women with endometriosis do not fully express progesterone-induced decidualization markers.
in vitro.21–23 These findings not only are important for endometriosis but also raise the possibility that some complications of pregnancy have origins in defective decidualization: there are encouraging data suggesting that this may be the case in preeclampsia, as women with severe preeclampsia have a different transcriptome compared to those with normal pregnancy outcome.24–26

Endocrine Disruptors and Reproductive Health: A Second “aha” Moment

Several years ago, a patient reached out to Linda to ask if she thought her upbringing in New York, where the local river was heavily polluted with polychlorinated biphenyls, which are endocrine disruptors, could have affected her fertility. Linda recalled the conversation: “I said, ‘I have no idea,’ but I thought we should look into it.” A review of the literature showed evidence of the effect of environmental chemicals in animals, but there was little on the effects on reproductive health in humans.27–30 Linda’s team and the patient secured funding to hold a conference with reproductive endocrinologists, patient advocates for fertility, and several local political staff from the offices of Anna Eshoo and Nancy Pelosi. The 45-strong group discussed what was known about the effects of the environment on reproduction and fertility.31 “When I became Chair at UCSF, I established the Program for Reproductive Health and the Environment (PRHE),” Linda recalled, with an eye to move the field forward. A second conference was held at UCSF to discuss the environment and reproduction.31 “After that, it sort of snowballed,” Linda said. In 2010, a textbook on the topic was published by Cambridge University Press.32

From Stanford University to the University of California at San Francisco

After more than 25 years at Stanford University, except for two brief moves in the early years, Linda moved to UCSF in 2005, explaining that it was attractive given the institution’s great breadth and depth of research in clinical medicine through the Center for Reproductive Sciences, founded by Dr Robert Jaffe. Linda served as Chair of the Department of Obstetrics and Gynecology and Reproductive Sciences at UCSF for 11 years. In addition to establishing the PRHE at UCSF, she recruited Dr Tracey Woodruff to lead PRHE, which today is a leader in reproductive environmental health research and education. She also recruited Dr Marco Conti to lead the Center for Reproductive Sciences, which has been home to an NIH Center for Research, Training and Innovation in Reproduction and Infertility for the past decade. The Department, under her tenure, was ranked number one in NIH funding and continues to have a strong foundation in basic, translational, and clinical research. Linda recruited many clinical and clinical research faculty and supported, with Kaiser Permanente, the Undergraduate Research Intern Program for UC Berkeley students underrepresented in medicine to experience research and clinical shadowing at UCSF. This eight-week summer program was pioneered and co-led by UCSF faculty member Dr Patricia Robertson and Dr Juan Guerra of Kaiser Permanente, and it has enabled over 60 students to go on to careers in medicine and science. In addition, in 2015, Dr Giudice stewarded the move of the UCSF Department of Obstetrics, Gynecology and Reproductive Sciences from its headquarters at the Parnassus Campus for over 50 years to its new home at the new Mission Bay Campus, comprising the Betty Irene Moore Women’s Hospital, the Bakar Cancer Hospital, the Benioff Children’s Hospital, and a major complex for basic research in multiple disciplines.

Life at Home

Outside of research, Linda enjoys watching classic films and reading, biographies in particular, and long hikes in the hills in Northern California. She has taken great pleasure in reading the biographies of Eleanor Roosevelt, James Clerk Maxwell, and every member of the Tudor family.

Current affairs is often a topic of conversation for Linda and her husband, Sakis, who she met in graduate school and who is an Emeritus Adjunct Professor at UC Berkeley and an elected member of the National Academy of Science. As a plant molecular biologist, Sakis studied the plant growth factor auxin (a plant hormone produced in the stem tip that promotes elongation) and was part of the Arabidopsis Genomics Consortium, which first sequenced the whole genome of the plant (Arabidopsis, a genus in the family Brassicaceae that produces small flowering plants, eg cabbage and mustard, is a model organism used in the study of plant biology). In addition, he discovered many of the genes involved in fruit ripening and how to stop the process to preserve the fruit. Sakis’s team succeeded in delaying the ripening of tomatoes so that they could be transported across the country. Furthermore, he contributed to the elucidation of mechanisms responsible for fruit ripening and has a patent on ethylene, the main fruit-ripening hormone.33–35

Linda and Sakis have two sons. Their first-born, Alexander (Alekos), arrived when Linda was a third-year resident in Obstetrics and Gynecology, and their second, Aris, was born while she was a first-year Assistant Professor. Alekos and his wife now have two children, and at the time of our conversation, Aris and his wife had just delivered their first child. “It’s a new chapter of life for us and a very beautiful one at that,” Linda reflected.

A Legacy in Translational Research

Linda’s many leadership roles over the years, not only at Stanford and UCSF but also at the leading professional societies, reflect her prominent position in the field of endocrinology. She has published more than 350 peer-reviewed articles, and she has earned a long list of awards, including the Fredrick Naftolin Award for Mentorship from the Society of Reproductive Investigation, the Distinguished Researcher Award from the American Society for Reproductive Medicine,
and the 2008 Women in Science Award from the American Medical Women’s Association.

Professional recognition of her seminal contributions has resulted in numerous distinguished lectureships, including the NIH Director’s Inaugural Lecturer, the NICHD Sadler Lecturer, and the Royal Reproductive Biology Society Founders Oration and Medal. She is an elected honorary member (ad eundem) of the Royal College of Obstetricians and Gynecologists and holds honorary professorships from Aarhus University and the University of Florence. Linda has been continuously funded by the NIH and NICHD since 1990 for her research in reproductive science, and she also was the principal investigator of several K awards for mentoring the next generation in reproductive science and medicine.

Having mentored nearly 250 undergraduate and postgraduate students and faculty colleagues, Linda told me, “For me, the most important thing, scientifically, is the trainees whom I have had the privilege of mentoring over the years. They have been integral to the scientific process, and their careers, success, and happiness are of the highest importance to me.”

Linda has succeeded in bridging basic and clinical research in a way that will benefit women’s health for decades to come, as we enter the age of precision medicine. Her unshakable integrity, exceptional skill, and commitment to her work have established Linda as an authority and a leader.

For her pioneering work in translational endocrinology, the AJOG recognizes Dr Linda Giudice as a “Giant in Obstetrics and Gynecology.”

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REFERENCES