On the Same Page

Continued Success in Clinical and Translational Research Programs: Part 1—Reproductive Physiology Program Project

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This past week, we learned of highly competitive scores on two major NIH grant applications involving clinical and translational research—one a Program Project Grant on reproductive physiology led by Kirk Conrad, MD, a professor of physiology and functional genomics and of obstetrics and gynecology, and the other a renewal of UF's Claude Pepper "Older Americans Independence Center," led by Marco Pahor, MD, director of the UF Institute on Aging.

At a time of congressional debate about cuts to the NIH budget (and even the prospect of a government shutdown), one can't speak with certainty about *any* NIH award until the check arrives. That said, we can celebrate the recognition given to our faculty by their peers in the review of these two projects, both of which scored in the top 2 percent.

This week's newsletter will focus on the PPG; the next issue will feature the Pepper Center.

In his PPG, Dr. Conrad has brought together UF faculty from a variety of departments and colleges, with collaborators from Stanford University, to study the role of early hormonal changes in pregnancy on pregnancy physiology and outcome. Interestingly, although the research hypotheses are based on findings obtained previously by the investigators from animal studies, this project will collect data from patients undergoing *in vitro* fertilization (IVF), a form of "assisted reproductive technology" (or ART). Thus, the title of the project: "Corpus Luteal Contribution to Maternal Pregnancy Physiology and Outcomes in ART." If fully funded, UF will receive a total of $7.7 million over the next five years to support this research.

First, let's go over some basic physiology regarding ovarian function and early pregnancy. In women with cyclic, predictable menstrual cycles, an egg matures in an ovarian "follicle," which releases its egg ("ovulation") at mid-cycle. After ovulation, the follicle that had released the egg turns into a "corpus luteum," which secretes progesterone that, in turn, thickens the lining of the uterus in preparation for implantation of an embryo. If there is no pregnancy, the progesterone is produced for about 14 days and then stops, resulting in a sloughing of the uterine lining (menstruation). In cycles resulting in pregnancy, the embryo begins to form a placenta that produces human chorionic gonadotropin (hCG), the hormone measured in pregnancy tests. hCG has the capacity to stimulate the corpus luteum to continue its secretion of progesterone; this is critical, because the lining of the uterus must continue to proliferate (and not slough) to nourish the developing embryo. After about 10 weeks, progesterone secretion by the corpus luteum wanes, and is supplanted by placental progesterone. However, the corpus luteum of pregnancy secretes other hormones as well, which continue throughout pregnancy. One such hormone is relaxin, which is the main focus of the Program Project.

Relaxin is a small protein hormone secreted by the corpus luteum, which circulates at low levels in the blood during the luteal phase of each menstrual cycle, and subsequently increases to high levels if pregnancy occurs. Peak serum concentrations are observed during

the first trimester that then decline to intermediate values for the remainder of the pregnancy. One of the most remarkable physiological adaptations transpiring during early pregnancy (and perhaps not coincidentally also during the luteal phase), which corresponds with the relaxin profile in the blood, is dilation of the maternal circulation, including exuberant increases in cardiac output, kidney blood flow and filtration. These physiological cardiovascular adaptations are believed to be critical to normal pregnancy and neonatal outcomes, because women who fail to show optimal changes in these parameters during early pregnancy are predisposed to abnormal outcomes such as preeclampsia (a hypertensive disease of pregnancy), intrauterine growth restriction or a combination of the two maladies.

Of particular importance to the Program Project Grant is that the investigators previously showed relaxin to be a potent vasodilator in rodents and humans, and to mediate the maternal circulatory adaptations discussed above during early pregnancy in rodents. In a pilot study, they further showed that infertile women who become pregnant using donor eggs, IVF and embryo transfer (see below), and who therefore lack a corpus luteum and circulating relaxin, show a markedly subdued gestational increase in kidney filtration, suggesting deficient increases in renal blood flow and cardiac output.

Thus, based on the convergence of the animal and epidemiologic studies performed by the investigators and others, the study authors advance the overarching hypothesis that abnormal circulating levels of relaxin (and possibly other corpus luteum hormones) in early pregnancy precludes the normal physiological cardiovascular adaptations to pregnancy that, in turn, predisposes to complications such as preeclampsia, fetal growth restriction and preterm delivery. If it is found that variations in corpus luteum production of relaxin (or of other yet-to-be identified hormone[s]) influences pregnancy outcome, then perhaps these hormone levels could be normalized in order to improve pregnancy outcome.

In their application, the investigators propose a new idea that maternal cardiovascular, renal, osmoregulatory and blood volume adaptations may be abnormal during pregnancy in many women conceiving by IVF. That is, in such women, pregnancy may begin in a state that is not physiological. In turn, this may be a contributing factor to adverse pregnancy outcomes after IVF. The three Projects and associated Cores of the proposed Program Project Grant, led by an interdisciplinary team, have been assembled by Dr. Conrad to address decisively this question for the first time using fundamental, clinical and epidemiological research thought-processes and methodologies.

Women who become pregnant through IVF will be asked to serve as research participants, along with control women who become pregnant "the old-fashioned way." Control women with singleton pregnancies will have one corpus luteum. However, because part of the IVF process involves stimulating the ovary to produce multiple follicles—which then results in multiple corpora lutea—relaxin levels will vary widely among such women who conceive through IVF. Finally, when donor eggs are used in IVF (for example, if the patient has premature ovarian failure), the pregnant woman will have no corpus luteum. (In such cases, early pregnancy is supported by administering progesterone.) This variation in corpus luteum status and number (none, one, many) is exploited in the research design.

The investigators believe that it is important for them to undertake the proposed investigation not only to pioneer the science in this never-before-studied niche, but also because if their

overarching hypothesis is correct, then clinicians may actually be able to do something about it. That is, in those IVF regimens in which the corpus luteum and circulating relaxin are absent (i.e., in cases where the egg comes from a donor), supplementation with relaxin (or perhaps with some other, as of yet, unidentified corpus luteum hormone) may be beneficial. Alternatively, in the case of ovarian stimulation and IVF, less ovarian stimulation might be recommended in order to reduce the number of corpora lutea, and thus reduce the circulating concentration of relaxin. Finally, in the event that maternal cardiovascular adaptations to pregnancy are normal in ART subjects, and there is no association found between corpus luteum status and adverse pregnancy outcomes, then these results should be reassuring to both physicians and their patients.

The investigators will address varying aspects of their central theme from different angles. In Project I, Dr. Conrad and collaborators will investigate, for the first time, maternal adaptations to IVF pregnancies, focusing on cardiovascular endpoints. In Project II, Mark S. Segal, MD, PhD, a professor of medicine and director of nephrology, and colleagues will study an additional novel and exciting maternal adaptation to pregnancy based on bone-marrow-derived endothelial cells and their relation to endothelial-dependent relaxation and maternal angiogenesis. Finally, in Project III, Valerie L. Baker, MD (Stanford University) and collaborators will investigate whether corpus luteum status correlates with obstetrical complications and adverse perinatal outcomes using databases from the Society of Assisted Reproductive Technology and Stanford's IVF program. These projects will be supported by three cores: administrative research management (P.I.: Dr. Conrad), data base coordination and biostatistics (P.I.: Keith Muller, PhD, a professor of health outcomes and policy), and analytic laboratory (P.I.: Maureen Keller-Wood, PhD, a professor and chair, department of pharmacodynamics).

Finally, it is important to underscore the fact that this PPG is exemplary of highly integrative and interdisciplinary research, insofar as it lies at the confluence of Reproductive Endocrinology and Infertility, Maternal Fetal Medicine, Cardiovascular and Renal Medicine, Epidemiology, and Biostatistics. Experts in all of these fields have been recruited into this Program Project Grant, and across the colleges of Medicine and Pharmacy. They hypothesize that there will be a correlation among corpus luteal number (or ovarian volume), plasma relaxin levels, maternal cardiovascular and renal adaptations, and pregnancy and neonatal outcomes. If the results of the study are supportive, then this may change clinical practice to include additional luteal support in the case of an absent corpus luteum (e.g., by administering relaxin), or in the case of multiple corpora lutea, to recommend less vigorous ovarian stimulation. Regardless of whether the hypothesis is found to be true, the maternal physiology of women who conceive by ART has never been investigated, and this research will fill this gap in fundamental knowledge.

Forward Together,

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