

BIOGRAPHICAL SKETCH

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NAME: Conrad, Kirk P.

eRA COMMONS USER NAME (credential, e.g., agency login): KIRK_CONRAD

POSITION TITLE: Professor, University of Florida College of Medicine

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Bowdoin College, Brunswick, ME	BA	1977	Biochemistry
Dartmouth Medical School, Hanover, NH	MD	1980	Medicine
University of Colorado Health Sciences Center, Denver, CO	Medical Intern	1980-1981	Medicine
Dartmouth Medical School, Hanover, NH	Postdoctoral Fellow (Heinz Valtin MD)	1981-1984	Renal Physiology
Case Western Reserve University, Cleveland, OH	Visiting Instructor/ Postdoctoral Fellow (Michael Dunn MD)	1985-1987	Renal/Cell Physiology

A. Personal Statement I have longstanding research interest in several areas of Reproductive & Perinatal Biology including: mechanisms underlying maternal renal and systemic vasodilation, and increased arterial compliance during normal pregnancy with emphasis on the ovarian hormone relaxin and underlying vascular molecular mechanisms **(1,2)**; maternal cardiovascular and renal adaptations to pregnancy in women conceiving by Assisted Reproductive Technologies (ART), as well as the perinatal outcomes of ART **(3,4)**; the potential role of dysregulated decidualization in the etiology of preeclampsia and other placental syndromes **(5, 6)**. I have combined preclinical and clinical research successfully throughout my career to translate our findings in animal models, tissues and cells to humans or vice versa. The main disease focus of my pregnancy research is preeclampsia—a hypertensive syndrome peculiar to human pregnancy. The concept of endometrial antecedents of preeclampsia arose from our work on the transcriptomics of chorionic villous samples obtained from women who developed preeclampsia with severe features. In this study, overwhelming molecular signatures of dysregulated decidualization both before pregnancy in the late secretory phase and after implantation emerged from transcriptomics of the CVS specimens when analyzed in the context of transcriptomics of normal endometrial maturation available in databases in the public domain using bioinformatics approaches. Over the past several years we have been establishing collaborations. and acquiring feasibility and preliminary data to support the current grant proposal, which is designed to investigate the health of the late secretory endometrium of women who experienced severe preeclampsia, the idea being that the antecedents of the disease may be dysregulated endometrial maturation before pregnancy.

(1) Pertinent Review: Sladek S.M., Magness R.R. and **Conrad K.P.** Nitric oxide and pregnancy. Am. J. Physiol. 272 (Regulatory Integrative Comp. Physiol. 41): R441-R463, 1997. (*358). PMID: 9124465.

(2) Pertinent Review: Conrad K.P. 2010 Ernest H. Starling Lectureship. Maternal vasodilation in pregnancy: the emerging role of relaxin. Am J Physiol. 301: R267-275, 2011(*72). PMID: 21613576.

(3) Conrad K.P. and Baker V.L. Corpus luteal contribution to maternal pregnancy physiology and outcomes in assisted reproductive technologies. Am. J. Physiol. Regulatory Integrative Comp. Physiol. 304:R69-72, 2013 (**Perspectives**). (*12). PMID: 23100030.

(4) von Versen-Höyneck F, Schaub AM, Chi YY, Chiu KH, Liu J, Lingis M, Williams RS, Rhoton-Vlasak A, Nichols WW, Fleischmann RR, Zhang W, Winn VD, Segal MS, **Conrad KP**, Baker VL. Increased preeclampsia risk and

reduced aortic compliance with in vitro fertilization cycles in the absence of a corpus luteum. **Hypertension**, in press.

(5) Rabaglino MB, Post Uiterweer ED, Jeyabalan A, Hogge WA, and **Conrad KP**. A bioinformatics approach reveals evidence for impaired endometrial maturation before and during early pregnancy in women who developed preeclampsia. **Hypertension** 65:421-429, 2015. (*20). PMID: 25421975.

(6) **Conrad KP**, Rabaglino MR, Post Uiterweer ED. Emerging role for dysregulated decidualization in the genesis of preeclampsia. **Placenta** 60:119-129, 2017 (*Invited Review*).

B. Positions and Honors

Positions and Employment

1984-1990	Assistant Professor, Department of Physiology, Dartmouth Med Sch, Hanover, NH
1990-1992	Assistant Professor, Departments of Physiology and of Ob/Gyn, University of New Mexico School of Medicine, Albuquerque, NM
1992-1994	Associate Professor, Departments of Physiology and of Ob/Gyn, University of New Mexico School of Medicine, Albuquerque, NM
1994-1999	Associate Professor, Department of Ob/Gyn and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA
1996-2006	Tenure Status, Department of Ob/Gyn and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA
1996-1999	Associate Professor (Secondary Appointment), Department of Cell Biology and Physiology, University of Pittsburgh School of Medicine, Pittsburgh, PA
2000-2006	Professor (Primary Appointment) Department of Ob/Gyn and Reproductive Sciences, and Professor (Secondary Appointment) Department of Cell Biology and Physiology, University of Pittsburgh School of Medicine, Pittsburgh, PA
2000-2003	Member, NIH Human Embryology and Development Study Section-1
2004	Sabbatical Leave, Honorary Fellow Department of Zoology, University of Melbourne, Parkville, Victoria, Australia, Jan-July.
2006-	Professor (with Tenure) Department of Physiology and Functional Genomics, University of Florida College of Medicine, Gainesville, FL
2007-	Professor (secondary appointment) Department of Ob/Gyn, University of Florida COM
2007-2010	Council Member, Society for Gynecological Investigation
2010-2014	Secretary Treasurer, Society for Gynecological Investigation
2014-2017	Grant Awards Committee, Society for Reproductive Investigation
2016-	J. Robert and Mary Cade Professor of Physiology

Honors and Awards

1976	James Bowdon Honor Society
1977	Magna Cum Laude
1979	Alpha Omega Alpha Honor Society
1980	Good Physicians Award (Dartmouth Medical School)
1985-1990	Physician Scientist Award, K11 HD00662
1988-1993	8th Mallinckrodt Scholar Award
1990	Outstanding Teacher Award in the Basic Sciences
1991-1994	Flinn Newly Independent Investigator Award (American Heart Association)
1993	Basic Medical Sciences Teaching Award presented by UNM Sch. of Medicine Graduates
1995-1999	Research Career Development Award, KO4 HD01098
2010	Ernest H. Starling Distinguished Lectureship of the American Physiological Society Water & Electrolyte Homeostasis Section
2010	Senior Faculty Research Award for the University of Florida Chapter of Sigma Xi
2010	Sir William Liley Lectureship, Perinatal Research Society
2012	Dutch Heart Foundation Lecture
2013, -14, -16	Exemplary Teacher Award University of Florida College of Medicine
2018-2021	University of Florida Term Professorship

C. Contributions to Science (*Examples guided in part by some of the more highly cited works in Web of Science. H-Index 46.)

1. Early career work focused on validating the chronically instrumented gravid rat as a model for human renal (and systemic) maternal adaptations to pregnancy, which are epitomized by massive vasodilation **(1)**. After demonstrating that the conscious gravid rat manifests circulatory changes during pregnancy similar to women, this animal model was used to address the major hypothesis at the time that vasodilatory prostaglandins were responsible. After 3 years of work, the hypothesis was unsupported **(2)**. These negative results set the stage to investigate a new and exciting vasodilatory substance in this context, endothelium-derived relaxin factor or nitric oxide (NO). Indeed, the metabolic production of the major second messenger of NO, cGMP, was markedly enhanced during rat gestation **(3)**. A major change in phosphoinositide metabolism was also discovered in the vasculature of gravid rats **(4)**.

(1) Conrad K.P. Renal hemodynamics during pregnancy in chronically catheterized, conscious rats. Kidney Int. 26:24-29,1984 (*116). PMID: 6332938.

(2) Conrad K.P. and Colpoys M.C. Evidence against the hypothesis that prostaglandins are the vasodepressor agents of pregnancy. Serial studies in conscious rats. J. Clin. Invest. 77: 236-245, 1986 (*145). PMID: 3944253.

(3) Conrad K.P. and Vernier K.A. Plasma level, urinary excretion and metabolic production of cGMP during gestation in rats. Am. J. Physiol. 257: R847-R853, 1989 (*139). PMID: 2552845.

(4) Conrad K.P., Barrera SA, Friedman PA and Schmidt VM. Evidence for attenuation of myo-inositol uptake, phosphoinositide turnover and inositol phosphate production in aortic vasculature of rats during pregnancy. J. Clin. Invest. 87:1700-1709, 1991 (*29). PMID:1850759.

2. Subsequently, increased NO production was discovered in rat gestation **(1)**. A functional role for NO in the gestational renal vasodilation and hyperfiltration was then demonstrated in the conscious rat **(2)**, and endothelial ET_B receptor signaling was shown to mediate the increased NO **(3)**. Interestingly, although strong evidence for increased cGMP production was also obtained in human pregnancy, whether NO biosynthesis also increased was unclear **(4)**. However, it seems likely that circulating and urinary products of NO metabolism may not necessarily accurately reflect local production by arterioles, the latter determining blood flow.

(1) Conrad K.P., Joffe G.M., Kruszyna H., Kruszyna R., Rochelle L.G., Smith R.P., Chavez J.E. and Mosher M.D. Identification of increased nitric oxide biosynthesis during pregnancy in rats. FASEB J. 7:566-571,1993 (*383). PMID: 7682524.

(2) Danielson L.A. and **Conrad K.P.** Acute blockade of nitric oxide synthase inhibits renal vasodilation and hyperfiltration during pregnancy in conscious rats. J. Clin. Invest. 96:482-490,1995 (*123). PMID: 7542284

(3) Conrad K.P., Gandley R.E., Ogawa T., Nakanishi S. and Danielson L.A. Endothelin mediates renal vasodilation and hyperfiltration during pregnancy in chronically instrumented conscious rats. Am. J. Physiol. 276: F767-F776, 1999 (*66). PMID: 7542284

(4) Conrad K.P., Kerchner L.J. and Mosher M.D. Plasma and 24-hour urinary NO_x and cGMP in normal pregnancy and preeclampsia in women on a reduced-NO_x diet. Am. J. Physiol. 277: F48-F57, 1999 (*77). PMID:10409297.

3. Next, the potential reproductive hormones that mediate the dramatic maternal circulatory changes of pregnancy including the increase in global arterial compliance were investigated in the gravid rat model. Based mainly on the coincidence in the pattern of change of both circulating relaxin and the systemic and renal hemodynamic adaptations during human pregnancy, we mainly focused on this ovarian hormone. To make a long story short, administration of relaxin to conscious, nonpregnant rats recapitulated the circulatory (and osmoregulatory) changes of pregnancy **(1)**; moreover, immunoneutralization or elimination of circulating relaxin in midterm pregnant rats inhibited the circulatory (and osmoregulatory) changes of pregnancy **(2)**. Based on studies in conscious rats and isolated renal arteries from rats and mice, as well as subcutaneous arteries from humans, the long-term (hours to days) vasodilatory responses to relaxin are mediated by arterial-derived VEGF/PIGF, MMP-2 or -9, endothelial ET_B receptor activation and NO **(3, 4)**.

(1) Danielson L.A. Sherwood O.D. and **Conrad K.P.** Relaxin is a potent renal vasodilator in conscious rats. J. Clin. Invest. 103:525-533,1999 (*185). PMID: 10021461.

- (2) Novak J., Danielson L.A., Kerchner L.A., Sherwood O.D., Ramirez R.J., Moalli P.A. and **Conrad K.P.** Relaxin is essential for renal vasodilation during pregnancy in conscious rats. J. Clin. Invest. 107:1469-1475, 2001 (*137). PMID: 11390429.
- (3) Jeyabalan A., Novak J., Danielson L.A., Kerchner L.J., Opett S.L. and **Conrad K.P.** Essential role for vascular gelatinase activity in relaxin-induced renal vasodilation, hyperfiltration, and reduced myogenic reactivity of small arteries. Circ. Res. 93:1249-1257, 2003 (*98). PMID: 14593002.
- (4) McGuane J.T., Danielson L.A., Debrah J.E., Rubin J.P., Novak J. and **Conrad K.P.** Angiogenic growth factors are new players in the sustained relaxin vasodilatory pathway in rodents and humans. Hypertension 57:1151-60, 2011 (*50). PMID: 21536992.

4. Though more limited, evidence from our group and other investigators shows that the impact of relaxin on the renal and systemic circulations in humans is comparable to the rat model (**ref. 2 in Personal Statement**), thus setting the stage for investigation of the hormone in heart failure (**1, 2**), preeclampsia (**3**) and our current Program Project Grant HD065647 titled "Corpus luteal contributions to maternal circulatory physiology and outcomes in assisted reproductive technologies." Although the results from the Phase II and IIIA trials were encouraging, unfortunately the phase IIIB trial for acute heart failure recently failed. The data have not yet been published. Importantly, the circulatory effects of relaxin are sex independent, most likely due to the existence of a local, arterial-derived relaxin-ligand receptor system (**4**).

- (1) 2004 U.S. Patent Application Serial No. 10/819,039 for Use of Relaxin to Treat Diseases Related to Vasoconstriction. **Primary Inventor: Conrad KP.**
- (2) 2005 U.S. Patent Application No. 11/084,670 Use of Relaxin to Increase Arterial Compliance. **Co-Inventors: Conrad KP and Shroff SG.**
- (3) **Conrad KP.** G-protein coupled receptors as potential drug candidates in preeclampsia: targeting the relaxin-insulin-like family peptide receptor 1 for treatment and prevention. Human Reproduction Update 22:647-664, 2016 (**Invited review**) (*9). PMID: 27385360
- (4) Novak J., Parry L.J., Matthews J., Kerchner L.J., Indovina K., Hanley-Yanez K., Doty K.D., Debrah D.O., Shroff S.G. and **Conrad K.P.** Evidence for local relaxin ligand-receptor expression and function in arteries. FASEB J. 20: 2352-62, 2006 (*67). PMID: 17077312.

5. Research was expanded to include the human placenta.

In our early studies, we discovered the expression of endothelial nitric oxide synthase (1993), erythropoietin (1993) and its receptor (1996), and hypoxia inducible transcription factor (2000) in the human placenta, as well as investigated the potential contribution of inflammatory cytokines in the pathogenesis of preeclampsia (1997). After studying delivered placentas from women with preeclampsia, however, I realized that molecular signatures were likely to reflect as much or more consequence than cause of the disease. For example, we investigated Hypoxia Inducible transcription factors (HIF α) in the human placenta during normal development (**1**), in preeclampsia and normotensive IUGR. HIF α and downstream genes were clearly increased in the former (**2**), but not in the latter (**3**). Based on these studies of delivered placentas, however, it was not possible to ascertain whether inappropriately elevated HIF α in the first trimester may have contributed to the etiology of preeclampsia, which is widely believed to begin in early gestation. Therefore, we collected early placentas (chorionic villous samples of ~11.5 gestational weeks) in women who experienced a normal pregnancy or severe preeclampsia 6 months later, and subjected the samples to DNA microarray analysis. To our surprise, rather than reflecting HIF α activation, a major molecular signature of impaired (pre-)decidualization emerged including deficient NK cell number and/or function (**4**) and **ref. 4 in Personal Statement**.

- (1) Rajakumar A.R. and **Conrad K.P.** Expression, ontogeny and regulation of hypoxia inducible transcription factors in the human placenta. Biol. Reprod. 63:559-569, 2000 (*112). PMID: 10906065.
- (2) Rajakumar A., Brandon H.M., Daftary A., Ness R. and **Conrad K.P.** Evidence for the functional activity of hypoxia inducible transcription factors overexpressed in preeclamptic placentae. Placenta 25:763-9, 2004 (*115). PMID: 15451190.
- (3) Rajakumar A., Jeyabalan A., Markovic N., Ness R., Gilmore C. and **Conrad K.P.** Placental HIF-1 α , HIF-2 α , membrane and soluble VEGF receptor-1 proteins are not increased in normotensive pregnancies complicated by late onset intrauterine growth restriction. Am. J. Physiol. 293: R766-74, 2007 (*33). PMID: 17507435.

- (4) Founds S.A., Conley Y.P., Lyons-Weiler J.F., Jeyabalan A., Hogge W.A. and **Conrad K.P.** Altered global gene expression in first trimester placentas of women destined to develop preeclampsia. Placenta 30: 15-24, 2009 (*145). PMID: 19027158.

Click for a full list of publications in:

<https://www.ncbi.nlm.nih.gov/sites/myncbi/1TUh93Yilukr/bibliography/43109883/public/?sort=date&direction=ascending>

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

- **5P01HD065647** 09/27/2011-02/28/2019 (mid-project extension and NCE)

NIH/NICHD

Corpus Luteal Contribution to Maternal Pregnancy Physiology and Outcomes in ART

Role: PD/PI

The Program Project will investigate the corpus luteal contribution to maternal pregnancy physiology and outcomes in ART using fundamental, clinical, and epidemiological approaches. Its successful completion will provide novel and groundbreaking insights into the maternal physiology of ART and spontaneously conceived pregnancies, as well as the adverse pregnancy outcomes of ART. We expect that it will also facilitate the translation of this newly gained knowledge to improving clinical practice.

- **USAMRMC PR140949** 04/01/15-01/19/19 (NCE)

Discovery Award Proposal

Role: PI

Potential Therapeutic Use of Relaxin in Healing Cranial Bone Defects

The purpose of this project is to test whether the many salutary actions of relaxin to improve blood flow will accelerate bone fracture healing in a preclinical mouse model.

- **UF COM Matching Bridge Funds** 07/01/14-open

Endometrial Antecedents of Preeclampsia

Role: PD/PI

These bridge funds were allocated after R21 HD076278-01A1 titled "Endometrial Antecedents of Preeclampsia" received a 12%, but was not funded. These bridge funds supported feasibility/preliminary data for the RO1 submission.

- **UF COM Matching Bridge Funds** 01/01/17-open

Long-term Consequences of Assisted Reproduction on the Physiology and Health of Offspring

Role: PD/PI

Bridge funds were allocated after R03 HD092814 titled "Long-Term Consequences of Assisted Reproductive Technologies (ART) on the Physiology and Health of Offspring: A Pilot-Feasibility Study" was withdrawn by CSR, because NICHD would not pick it up, and other relevant Institutes do not honor the RO3 mechanism. Subsequently, NICHD reversed its position, and the RO3 will be reviewed October 2018.

Recently Completed Research Support

- **CRLX030AUSNC06T** 05/15/2014-01/31/2017

Novartis Pharmaceuticals Corp

Role: PI

Unveiling Novel Signaling mechanisms of Serelaxin in Vasculature

The purpose of this project is to elucidate: the cellular localization of the relaxin receptor, RXFP1, in the vascular wall that is relevant to "sustained" arterial vasodilation by Serelaxin; the cellular basis for attenuation of angiotensin II contraction by Serelaxin; the mechanism underlying the unexpected preserved vasodilation of Serelaxin in the setting of endothelial dysfunction or denudation.