

BIOGRAPHICAL SKETCH

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NAME: **Brendan Carvalho**

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

POSITION TITLE: Chief of the Division of Obstetric Anesthesia, Associate Professor of Anesthesiology

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
University of the Witwatersrand, South Africa	MBBCh	12/94	Medicine
University of London, UK	MDCH	07/99	Clinical Hypnosis
Royal College of Anaesthetists, UK	FRCA	10/00	Anesthesiology
Plymouth University, UK	Diploma	08/01	Clinical Research
American Board of Anesthesiology, USA	Diplomat	10/14	Anesthesiology

A. Personal Statement

I have the training, expertise, and motivation necessary to successfully carry out the proposed research project. As Chief of the Obstetric Anesthesia division in the Department of Anesthesiology at Stanford University, I also have the necessary leadership and administrative skills as well as influence to make research projects realized. I have successfully administered and mentored research studies, and have collaborated with obstetricians, perinatologists, pharmacologists, epidemiologists and various medical specialties on a number of research projects. I have a broad experience in obstetric anesthesia, with specific expertise in pain management and peripartum pharmacology. As principal and co-investigator on several intramural, industry and NIH-funded grants, I have conducted a number of large-scale clinical and translational studies in pregnant patients. I have led the Obstetric Anesthesia division's research efforts for the past decade, producing numerous publications. Several of these studies have won awards including best research study and top trainee-mentored study at the Society of Obstetric Anesthesia and Perinatology (SOAP) annual scientific meetings. Several key research studies that I have published have led to important changes in the practice of obstetric anesthesia, and as a result have become a nationally and internationally recognized expert in the field. I have a proven track record of successfully completing proposed work as evidenced by my academic productivity and numerous research publications.

Key publications:

- a. Carvalho B, Clark JD, Qiao Y, Yeomans DC, Angst MS. The Effect of Continuous Wound Infiltration with Bupivacaine on the Local Release of Nociceptive and Inflammatory Mediators Following Cesarean Delivery *Anesth Analg* 2010;111(6):1452-9 (Cited in lead editorial)
- b. Carvalho B, Drover D, Atkinson L, Riley ET, Collins J. The ED50 and ED95 of Intrathecal Bupivacaine in Morbidly Obese Patients Undergoing Cesarean Delivery. *Anesthesiology* 2011;114(3):529-35 (Cited in lead editorial)
- c. Carvalho B, Zheng M, Aiono-Le Tagaloa L. Evaluation of Experimental Pain Tests to Predict Labor Pain and Epidural Analgesic Consumption *Br J Anaesthesia* 2013;110(4):600-6
- d. Carvalho B, Lemmens H, Ting V, Angst M. The Effects of Continuous Subcutaneous Instillation of Ketorolac and Hydromorphone on Wound Biochemistry in Surgical Wounds following Cesarean Delivery. *J Pain* 2013;14(1):48-56

B. Positions and Honors

Positions and Employment:

- 2001-2002 Obstetric Anesthesia Fellowship, Department of Anesthesia, Stanford University School of Medicine, Stanford, CA
- 2003-2010 Assistant Professor, Medical Center Line, Department of Anesthesia, Stanford University School of Medicine, Stanford, CA
- 2011- Associate Professor, Medical Center Line, Department of Anesthesia, Stanford University School of Medicine, Stanford, CA
- 2013 - Chief, Division of Obstetric Anesthesia, Department of Anesthesia, Stanford University School of Medicine

Other Experience and Professional Memberships:

- 2014-15 California Society of Anesthesiologists (CSA) Educational Programs Division Committee
- 2013-14 American Society of Anesthesiologists (ASA) Obstetric Anesthesia Educational Subcommittee
- 2014- SOAP 2nd VP (Executive board member position and future SOAP president)
- 2013 American Heart Association Cardiac Arrest in Pregnancy Scientific Statement Writing Group
- 2013- SOAP Bylaws Committee
- 2012-13 ASA Obstetric Anesthesia Educational Track Subcommittee
- 2012 - Journal of Anesthesiology and Clinical Science Editorial Board Member
- 2012- Departmental Faculty Senator, Stanford University School of Medicine
- 2012- CSA District 4 Delegate
- 2012 SOAP Taskforce Director (CPR Pregnancy Consensus Statement)
- 2011-12 California Society of Anesthesiologists District 4 Alternate Delegate
- 2011-13 Society for Obstetric Anesthesia and Perinatology (SOAP) Director-at large board member
- 2011- Sol Shnider Annual Meeting Planning Committee
- 2011- International Journal of Obstetric Anesthesia Editorial Board Member
- 2011- Open Journal of Anesthesiology Editorial Board Member
- 2011- Journal of Pain and Relief Editorial Board Member
- 2009-10 ASA Obstetric Anesthesia Research Subcommittee
- 2008- Faculty of 1000 Medicine, Evaluation Board Faculty Member,
- 2007- SOAP Research Committee Member
- 2007 ASA Obstetric Anesthesia Practice Parameter Consultant
- 2006 International Anesthesia Research Society (IARS) Mentorship Initiative Mentor
- 2005- Foundation for Anesthesia Education and Research Medical Student Research Fellowship Mentor

Honors and Academic Awards:

- 2014 SOAP Annual scientific meeting: Best Paper of Scientific Meeting (First author)
- 2014 SOAP: Gertie Marx Symposium: 1st place (Senior Author)
- 2014 Stanford University Anesthesiology Department: Best Clinical Abstract
- 2012 Canadian Anesthesiologists' Society: Best Paper in Obstetric Anesthesia Award (Senior Author)
- 2012 SOAP: Best Paper of Scientific Meeting
- 2012 SOAP: Teacher of the Year
- 2012 SOAP: Gertie Marx Symposium: 3rd place (Co-Author)
- 2012 Stanford University Teaching Scholar Award
- 2011 SOAP Best Paper Finalist (Senior Author)
- 2010 SOAP Best Paper Finalist (Presenting Author)
- 2009 SOAP Gertie Marx Symposium 2nd place (Senior Author)
- 2007 Stanford University Anesthesiology Department: Attending of the Month Award
- 2007 SOAP Gertie Marx Symposium 3rd place (Senior Author)
- 2006 SPCTRM Intensive Clinical Research Course, Stanford University: Best Protocol
- 2006 Obstetric Anaesthetists Association: Best Abstract of Meeting (Senior Author)
- 2006 SOAP Gertie Marx Symposium: 1st place (Senior Author)
- 2006 Stanford University Anesthesiology Department: Attending of the Year Award
- 2004 SOAP Gertie Marx Symposium: 2nd place (Co-Author)
- 2003 SOAP Gertie Marx Symposium: 3rd place (First Author)
- 2003 Stanford University Anesthesiology Department: Attending of the Month Award

C. Contribution to Science

Cesarean delivery is associated with significant postoperative pain, and severe and persistent incisional pain after delivery can profoundly impact maternal and neonatal health. I developed and validated a technique to collect and assay wound exudate from the surgical site to profile biochemical mediator response. This discovery has helped scientists better understand the role of cytokines in incisional pain and wound healing postoperatively, and has facilitated the study of systemic and peripherally-administered analgesics. Our study data has provided evidence that wound instillation with a sub-therapeutic systemic dose of a non-steroidal anti-inflammatory is an effective anti-inflammatory and analgesic strategy. The series of studies provide a solid rationale for peripheral versus systemic administration of analgesics, as well as provide mechanistic evidence of the biological consequences of modulating local inflammatory events in surgical wounds. This research has been recognized by the Society of Obstetric Anesthesia and Perinatology by winning best research study of the meeting, and the Faculty of 1000 has also highlighted the impact of these studies to the sub-specialty of obstetric anesthesia and postoperative pain management. I served as the principal investigator on all of these studies.

- a. Carvalho B, Clark JD, Angst MS. Incisional Wound and Systemic Cytokines, Nerve Growth Factor, Prostaglandin E2 and Substance P Release Following Cesarean Delivery. *J Pain*. 2008;9:650-7
- b. Carvalho B, Clark JD, Qiao Y, Yeomans DC, Angst MS. The Effect of Continuous Wound Infiltration with Bupivacaine on the Local Release of Nociceptive and Inflammatory Mediators Following Cesarean Delivery. *Anesth Analg* 2010;111(6):1452-9
- c. Carvalho B, Clark DJ, Yeomans D, Angst MS. Collecting and Measuring Wound Exudate Biochemical Mediators in Surgical Wounds. *J Vis Exp*. 2012 Oct 20;(68)
- d. Carvalho B, Lemmens H, Ting V, Angst M. The Effects of Continuous Subcutaneous Instillation of Ketorolac and Hydromorphone on Wound Biochemistry in Surgical Wounds following Cesarean Delivery. *J Pain* 2013;14(1):48-56

There is vast variability among surgical patients in terms of pain and analgesic use. Another key area of my research interest has been to try and determine individual pain and analgesic requirements prior to labor or cesarean delivery. The ability to recognize patients at high risk of developing severe pain during labor or following surgery has the potential to facilitate the use of individualized anesthetic treatment plans. This advancement will allow analgesic dose selection based on specific needs and will facilitate the use of selective analgesics with potentially adverse side effects to patients most likely to benefit from them. I have conducted several studies examining whether quantitative sensory tests, genetic variance, and psychological questionnaires can reliably predict labor and post-cesarean delivery pain. My translational pain prediction studies have advanced our understanding of individual pain and analgesic requirement variances. These results have allowed us to make analgesic dose selection based on specific patient needs, and in the future develop individualized treatment protocols. I served as the principal investigator on all of these studies.

- a. Carvalho B, Zheng M, Aiono-Le Tagaloa L. Evaluation of Experimental Pain Tests to Predict Labor Pain and Epidural Analgesic Consumption. *Br J Anaesthesia* 2013;110(4):600-6.
- b. Landau R, Liu SK, Blouin JL, Carvalho B. The effect of OPRM1 and COMT genotypes on the analgesic response to intravenous fentanyl labor analgesia. *Anesth Analg* 2013;116(2):386-91
- c. Carvalho B, Hilton G, Wen L, Weiniger CF. Prospective longitudinal cohort questionnaire assessment of labouring women's preference both pre- and post-delivery for either reduced pain intensity for a longer duration or greater pain intensity for a shorter duration. *Br J Anaesth* 2014;113: 468-473
- d. Carvalho B, Zheng M, Aiono-Le Tagaloa L. A prospective observational study evaluating the ability of pre-labor psychological tests to predict labor pain, epidural analgesic consumption, and maternal satisfaction. *Anesth Analg*. 2014;119(3):632-40

A number of drugs are extensively utilized in expectant women and neonates, but these drugs have not been actually studied in the pregnant population. Due to physiological changes in pregnancy that may affect drug handling, there is a critical need to adequately study the pharmacokinetics and pharmacodynamics of drugs given to pregnant women and exposed neonates. I have completed a number of pharmacokinetics and pharmacodynamics studies of drugs administered to pregnant women including epidural morphine, cefazolin, ondansetron, fentanyl and magnesium. These research projects have produced valuable data to better appreciate pharmacokinetics and pharmacodynamics differences of drugs in pregnant women compared to non-pregnant women. The studies have also helped determine placental transfer and neonatal pharmacokinetic parameters of these drugs. Our data has significantly improved our understanding of perinatal

pharmacology of cefazolin and ondansetron. The research has been recognized by the Society of Obstetric Anesthesia and Perinatology by winning best research study of the meeting. These studies will in the future facilitate optimal maternal and fetal dosing protocols based on pharmacokinetics and pharmacodynamics mathematical modeling. Individualized dosing algorithms will significantly reduce maternal and neonatal side effects while maintaining therapeutic efficacy. I served as the principal and co-investigator on all of these studies.

- a. Atkinson L, Drover D, Carvalho B. The Pharmacokinetic and Pharmacodynamic Effects of Prior Epidural Lidocaine Administration on DepoDur® (extended-release epidural morphine) in Patients Undergoing Cesarean Delivery *Anesth Analg* 2011;113(2):251-8
- b. Elkomy MH, Sultan, P, Drover DR, Ekaterina E, Galinkin JL, Carvalho B. Pharmacokinetics of Prophylactic Cefazolin in Parturients undergoing Cesarean Delivery. *Antimicrob Agents Chemother*. 2014;58(6):3504-13
- c. Elkomy MH, Sultan P, Clavijo C, Galinkin JL, Carvalho B, Drover DR. Ondansetron Pharmacokinetics in Pregnant Women and Neonates: Towards a New Treatment for Neonatal Abstinence Syndrome. *Clinical Pharmacology & Therapeutics*. 2015; 97 (2):167–176

Labor and cesarean deliveries are associated with significant pain, and anesthetic and analgesic techniques to optimize the management are ongoing. My clinical research has helped improve how we administer labor epidural analgesia using patient-controlled epidural analgesia, as well as provide cesarean delivery anesthesia with optimal local anesthetic dosing, neuraxial opioids, and analgesic adjuvants. Many of my clinical studies have helped define current clinical practice of labor and cesarean delivery. My research has contributed to improved pain control during labor and after cesarean delivery of women throughout the world. Results of several studies have been recognized by Faculty of 1000 as making a significant impact to the sub-specialty of obstetric anesthesia. I served as the principal investigator on all of these studies.

- a. Carvalho B, Riley E, Cohen SE, Gambling D, Palmer C, Huffnagle HJ, Polley L, Muir H, Segal S, Lihou C, Manvelian G. Single-dose, sustained-release epidural morphine in the management of postoperative pain after elective cesarean delivery: results of a multicenter randomized controlled study. *Anesth Analg*. 2005;100(4):1150-8
- b. Carvalho B, Cohen SE, Giarrusso K, Durbin M, Riley ET, Lipman S. "Ultra-light" patient-controlled epidural analgesia during labor. *Int J Obstet Anesth*. 2005;14(3):223-9
- c. Carvalho B, Durbin M, Drover DR, Cohen SE, Ginosar Y, Riley ET. The ED50 and ED95 of intrathecal isobaric bupivacaine with opioids for cesarean delivery. *Anesthesiology*. 2005;103(3):606-12
- d. Carvalho B, Drover D, Atkinson L, Riley ET, Collins J. The ED50 and ED95 of Intrathecal Bupivacaine in Morbidly Obese Patients Undergoing Cesarean Delivery. *Anesthesiology* 2011;114(3):529-35

Pregnancy-induced analgesia is well-documented in animal studies; however the phenomenon is not clearly demonstrated in humans. I have conducted several studies to better understand the phenomenon of pregnancy-induced analgesia in women to determine the extent of hormonal changes in pain perception. Specifically we have demonstrated that heat pain tolerance was significantly increased in the pregnant women during pre and early post-delivery when compared with non-pregnant controls. We have found that conditioned pain modulation did not vary across phases in the menstrual cycle. Ongoing research is being conducted to determine if conditioned pain modulation and mechanical temporal summation changes during the course of pregnancy. These studies have facilitated a better understand of the role of hormones in endogenous analgesia and pain modulation. I served as the principal and co-investigator on these studies.

- a. Carvalho B, Angst MS, Fuller AJ, Lin E, Mathusamy AD, Riley ET. Experimental heat pain for detecting pregnancy-induced analgesia in humans. *Anesth Analg*. 2006;103(5):1283-7
- b. Wilson HD, Carvalho B, Granot M, Landau R. Evaluation of the temporal stability of conditioned pain modulation in healthy women over four menstrual cycles at the follicular and luteal phases. *Pain*. 2013 Dec;154(12):2633-8

A complete list of my published work can be found at:

My Bibliography *US National Library of Medicine*:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1LCY82v888j/bibliography/40989124/public/?sort=date&direction=ascending>.

D. Research Support (Past 3 years)

Ongoing Research Support

- 2014-2016 Covidien Ltd.
A study to determine the optimal technique to detect and monitor respiratory depression in women undergoing cesarean delivery with neuraxial opioids.
Role: Principal investigator
- 2012-2015 Child Health Research Institute (CHRI) Harman Faculty Scholar Award
A study to determine maternal and neonatal pharmacokinetic and pharmacodynamic models for antenatally-administered magnesium sulfate.
Role: Principal investigator
- 2012-2017 R01 HD070795-01A1
A study to investigate the role of ondansetron to prevent or minimize neonatal narcotic abstinence syndrome.
Role: Co-investigator

Completed Research Support

- 2013-2015 Child Health Research Institute (CHRI) Innovations in Patient Care Award
A study to determine optimal sepsis detection criteria and surveillance for the obstetric patients.
Role: Mentor, Senior Investigator
- 2011-2013 Australian and New Zealand College of Anaesthetists (ANZCA) Investigator-Initiated Grant
A study to investigate if methylnaltrexone prevents intrathecal morphine-induced pruritus after cesarean delivery.
Role: Co-investigator