University of Michigan, Ann Arbor
Theme: Birth, muscle injury and pelvic floor dysfunction

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Center Abstract

This proposal seeks to improve care for the women who suffer the priority health conditions of pelvic floor dysfunction; problems that arise due to women's unique role in giving birth. It addresses the sex disparities that exist in these problems. Each year 3 million women deliver babies and 300,000 women need surgery for pelvic floor dysfunction. A lack of basic understanding of the mechanisms of birth-related injury and recovery during reproductive years and mechanisms of prolapse later in life block efforts to prevent damage, improve recovery, or improve treatment. We seek continued support for a broadly interdisciplinary group of researchers from 4 schools and 2 institutes to that has expedited development of new knowledge needed to improve treatment and prevention.

Project 1: "Birth Biomechanics" will test hypotheses concerning basic mechanisms of pelvic floor injury during vaginal birth; the single largest factor in causing pelvic floor dysfunction to identify specific situations may increase or decrease injury risk.

Project 2: "Injury Recovery" will identify risk factors associated with levator injury, test the hypothesis that these injuries are, in fact, related to vaginal delivery and determine early predictors of eventual recovery.

Project 3, "Mechanisms of Posterior Vaginal Prolapse" will use advanced imaging and deformation analysis to test hypotheses concerning the basic disease mechanisms responsible for posterior vaginal wall prolapse, one of the most common and strongly birth-associated pelvic floor dysfunction.

Core A: Administrative / Human Subjects / Biostatistics core provides project support by recruiting subjects, compiling and analyzing data and protecting subject safety. In Core A, two study groups will be formed concerning 1) Gender Impact and 2) Basic Science Futures to discuss expanding the issues raised by this research.

Core B: Measurement and Imaging core will provide technical support for the projects along with integrated analysis for 2 and 3 dimensional spatial data gathered across projects. This research will produce insights to address the women's health problem of pelvic floor dysfunction.

Project 1: Biomechanics of Birth-Related Injuries
Type: Basic

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Abstract
The overall goal of this research is to better understand the mechanisms of maternal vaginal birth related injury at the end of the second stage of labor. The main factor affecting the resistance of the pelvic floor muscles to stretch as they resist the downward descent of the fetal head is their viscoleastic material properties. The effect of term pregnancy on these properties has never been documented, partly due to the difficulty of obtaining sample of undamaged human pelvic floor tissues during birth.

In AIM 1, therefore, we will use equi-biaxial testing and stepwise stress relaxation assays to characterize the effect of term pregnancy on the constitutive law and mechanical behavior of mammalian pelvic floor tissues in rat and squirrel monkey. Uniaxial failure tests will also be conducted to determine the effect of pregnancy and test direction on the ultimate tensile stress in these tissues.

In AIM 2.1 we will develop a subject-specific, 3-D finite element biomechanical model of the second stage of labor from Station +2 on with representations of the fetal head, five major pelvic floor muscles and related soft tissues, as well as the time-varying maternal expulsive force.

In AIM 2.2 we will validate the model predictions by comparing them against the results of in vivo experiments in pregnant women. These involve the measured temporal displacement of a

posterior weighted speculum at C-section, and the time course of the increase in vaginal diameter upon fetal head crowning. In AIM 2.3 we will investigate the effect of (a) fetal head orientation, (b) cephalopelvic disproportion, (c) maternal sub-pubic arch angle, (d) epidural, (e) forceps use, and (f) episiotomy on the magnitude, direction and location of maximum pelvic floor muscle tissue stress. The ratio of that stress to the ultimate tensile stress is taken as a measure of the risk of tissue injury. These observations will yield insights into the factors associated with the greatest risk for injury, and should lead to better methods of preventing these injuries.

Project 2: Maternal Birth-Related Neuromuscular Injury and Recovery: Phase II
Type: Clinical

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Abstract

Magnetic resonance imaging data suggest a strong relationship between childbirth and structural pelvic floor injury, likely originating from stretch or crush of maternal tissues during the expulsive phase of labor. The pelvic floor muscle most vulnerable to injury is the striated pubovisceral muscle (PVM); 11-20% of parous women demonstrate a muscle defect at a year postpartum. A link between this defect and pelvic floor disorders has been found in our preliminary studies; women with prolapse and incontinence have a 4 fold and 2 fold- higher rate of PVM defects respectively. This finding offers a plausible causal link between pelvic floor disorders and a structural injury that occurs at childbirth. The cause of the defect is not yet known; nerve or muscle injury might be the underlying mechanism. Serial MRI offers the ability to observe PVM defects overtime and differentiate: 1) neurogenic injury (degeneration overtime), 2) myogenic injury (early and permanent avulsion), or 3) fully recoverable injury. Injury type can then be correlated with obstetric risk factors and functional recovery. This study's aims are to: 1) Establish the validity of factors used to identify women with greatest likelihood of PVM injury by estimating the probability of each injury outcome classified at 6 months postpartum in a sample (n=125) enriched for risk factors of long duration of 2nd stage, instrumented delivery, 3rd or 4th degree perineal lacerations, macrosomic infant. 2) Establish that PVM injuries are associated with vaginal births vs. pregnancy by comparing our 125 women who birthed vaginally to 50 women who birthed by elective Caesarean. 3) Determine the extent to which an array of clinical parameters observed at 6 weeks postpartum will predict long term (6 months) muscle outcomes. To do so, we will obtain MRI's at 2 weeks and 6 months postpartum and perform functional PVM testing at the standard 6-week postpartum evaluation. We will classify putative injury types and correlate with risk factors and functional parameters. We will

try to address the knowledge gaps identified at the March 2006 NIH convened State-of-the-Science Conference: Cesarean Delivery on Maternal Request, which highlighted the need for understanding the mechanisms and risk factors for PVM injury. The short-term goal is new insights on injury mechanism. The long-term goal is prevention of and better treatment for pelvic floor disorders.

Project 3: Mechanisms of Posterior Vaginal Prolapse
Type: Clinical

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Abstract

Posterior vaginal wall prolapse (PVP), including enterocele and rectocele, is an enigmatic condition whose pathophysiology is poorly understood. ORWH, NICHD and NIDDK have each identified that female pelvic floor disorders such as PVP are in critical need of pathophysiology research. Competing hypotheses have been proposed relating to the causal roles of endopelvic fascia or levator ani muscle failure. However, data to resolve these conflicts are not available and are needed to establish the relative contributions of fascial and muscular abnormalities to PVP. This study will test the mechanistic hypothesis that the occurrence of PVP is not explained by a single mechanism but involves the interaction between fascial and muscle abnormalities. To test these hypotheses, we will recruit 75 cases with PVP and 75 controls of similar age and race.

Aim 1. "Fascia", we will use mid-sagittal MR images made during maximal Valsalva to document the posterior wall location and morphology in 4 regions influenced by fascial support: 1) location of the posterior vaginal apex, 2) length of the posterior vaginal wall, 3) changes in the inclination of the distal vaginal wall, and 4) location of the perineal body. By comparing measurements between cases and controls, we will determine the contributions of abnormalities in each region to the occurrence and size of PVP.

Aim 2. "Muscle", we will use multiplanar proton density MR scans to compare 1) presence of visible defects in the levator ani muscles, 2) cross sectional areas of the muscle, as well as measuring and 3) pelvic muscle contraction force during a maximal contraction. Using these data we will determine the contribution of muscular abnormalities. We will then use statistical modeling to determine the relative contributions of fascial versus muscular abnormalities.

Aim 3. "Rectocele vs. Enterocele", we will test the strength of association between the 4 fascial and 3 muscle abnormalities and the two types of PVP using general linear modeling.

Aim 4. "Biomechanical Modeling", we will use biomechanical analyses of fascia and muscle interactions in computer-based models to investigate patterns of muscle and connective tissue support site failures that lead to PVP. These insights are needed to advance our understanding of disease mechanisms so that we can reduce the 30% recurrence rate of prolapse after surgery, and develop preventative strategies to reduce the need for surgery in 200,000 women each year.

CORES

Core A: Administrative, Human Subjects, Biostatistics Core

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Abstract

Core A will be responsible for the following four services to unify, support, and coordinate the 3 projects in this SCOR. Aim 1 Administration: Core A will provide administrative support to Projects 1, 2 and 3 for recruitment, subject scheduling, forms generation, IRB issues, organization and confidential filing. In addition, it will file group renewal reports, generate, manage and plan project budgets, schedule group meetings, discussion groups, and seminars. Aim 2: Fostering Sex and Gender Research: Core A will seek to stimulate further research with the following activities 2a) Gender Impact Studies Group discussion to consider the personal and societal impact of these problems unique to women, 2b) Support, maintain and expand the SCOR? Pelvic Floor Disorders Databank of over 12,000 images of over 600 research subjects from prior and ongoing projects 2c) convene an annual campus wide SCOR sponsored Pelvic Floor Research Day to foster interdisciplinary discussion 2d) Sponsor a National Workshop in Future Directions in Pelvic Floor Basic Science Research at the American Urogynecologic Society meeting. Aim 3 Biostatistics: Core A will manage data and work with project investigators to properly test study hypotheses. This will include overseeing data forms, data

entry and management, biostatistical analysis and data quality control. Aim 4 Human Subjects: The core will assure Human Subject safety through active involvement with our IRB committee. This involvement will assure compliance with institutional and national regulations, tracking and assessing subject safety by monitoring adverse events, providing information to our outside subject safety committee as necessary. Core A will prepare regular reports from centralized logs concerning adverse events across all projects to increase detection of infrequent events that may occur in different projects.

Core B: Measurement and Imaging Core

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Abstract

The Measurement and Imaging Core will assist with measurements of perineal geometry during the late second stage of labor in 50 women, and of pelvic floor load-displacement behavior in 32 women using a posterior weighted speculum at the time of pelvic surgery. The Core will assist with clinical measurements and standardized data sets from magnetic resonance (MR) imaging to be made on the 175 and 150 women completing Projects 2 and 3, respectively. In Projects 2 & 3, subject-specific pelvic floor model geometries will be developed from reconstructing the magnetic resonance (MR) images. Additionally, in Project 2 the post natal recovery of normal MR signal intensity will be tracked over time in the pubovisceral muscles. In Project 3, MR measurements of posterior vaginal wall geometry will be made. Lastly, the Core will provide bioengineering and technical support to each project. For Projects 2 & 3 it will provide technical support for all urethral pressure measurements (MUCPR and MUCPMvc) to be made using 8F catheter, maintain the hardware and software of the instrumented speculum used to measure levator ani contractile properties (LAR and I_AMVC,), and analyze and provide cleaned data sets to Core A for statistical analysis.