Using the Fetal Gastrointestinal Tract to Overcome Neonatal Disease

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Dr. Buchmiller-Crair is the recipient of the **IFFGD 2003 Research Award to Pediatric Investigator, Basic Science**. She performs the full spectrum of pediatric surgery with a particular interest in minimal access surgery, management of the short bowel syndrome, and fetal surgical diagnoses and prenatal counseling. Her recent basic science and clinical work reflect her continuing interest in fetal gastrointestinal development and the mechanisms of GI absorption and motility during the last trimester of gestation.

Basic science is the fundamental approach to understanding how systems work. Basic research takes place in the laboratory. From this body of knowledge is drawn the means to investigate practical applications and to formulate clinical practices.

As a practicing Pediatric Surgeon, I have been struck by the challenges of dealing with severe neonatal growth retardation and gastrointestinal problems after birth. The gestational period before birth provides an intriguing time for possible maternal-fetal interventions, which could hopefully minimize, or eliminate the developing baby's problems. As the Director of the Pediatric Surgical Research Laboratory at the Weill Medical College of Cornell University, I have had a dedicated focus over the past 10 years investigating these concepts in the research laboratory and was recently honored by the IFFGD as the recipient of their first Pediatric Basic Science Investigator Award. I would like to share a few of our ideas and progress in the laboratory in studying fetal gastrointestinal development during the last trimester of gestation. This time period correlates to the 6^{th}–9^{th} month of human pregnancy.

Fetuses are surrounded by amniotic fluid *in-utero* (in the uterus, before birth), which they swallow throughout the last half of gestation. This fluid passes through the gastrointestinal tract, and the developing baby digests the nutrients and hormones that it contains. This passage of amniotic fluid, a form of fetal nutrition, appears necessary for normal gastrointestinal development. Many human infants born prematurely, or those with surgical conditions such as intestinal atresia (where the bowel ends abruptly and is discontinuous) or gastroschisis (where the bowel floats outside the baby's abdomen) suffer after birth from prolonged gastrointestinal dysfunction with impaired motility and nutrient absorption. Indeed, these children can ultimately need bowel transplantation, as the gut is not able to support the nutritional needs of the child. The understanding of the underlying mechanisms of neonatal gastrointestinal dysmotility and impaired absorption are essential if effective treatments are to be devised.

Using animal models over the past 10 years, we have conducted live (in-vivo), in-utero studies of intrauterine growth retardation (IUGR) that closely parallels human IUGR and have created models of pediatric surgical diseases such as pure esophageal atresia and gastroschisis. Experiments have supported our original hypothesis that the passage of amniotic fluid throughout the gastrointestinal tract is essential for the normal development of the gut in-utero.

We next sought to determine if we could add nutrients and hormones to the swallowed amniotic fluid to even further improve fetal gut function. Growth factors such as epidermal growth factor (EGF) and gastrin were given throughout the last trimester through surgically placed catheters. Even further upregulation of these digestive and absorptive processes occurred, but were surprisingly most pronounced in growth-retarded fetuses, exactly the fetuses we wanted to target for intervention.

We are currently studying the fetal development (ontogeny) of motilin, a peptide with promotility effects in the stomach and small intestine. We have defined levels of the peptide throughout the gastrointestinal tract during the last trimester and have compared both normal and IUGR fetuses.

Preliminary results have shown depressed levels of this motility hormone in the growth-retarded fetuses. Further studies will evaluate the importance of gut continuity on the development of motility in both normal and IUGR fetuses.

Lastly, this work must be validated in a larger animal model before consideration of human studies can be

entertained. We are initiating studies to evaluate a novel method of providing an internalized system of chronic access to the amniotic fluid cavity during the last one-third of gestation. If successful, this will allow the above studies to be performed in a larger animal model, with minimal risk to both fetus and mom.

Summary

Understanding GI function in-utero will help us differentiate what processes and disease states can be manipulated before birth, from those which are preset, and must be dealt with after birth. We have described above several models of in-utero study, which form the foundation for potential human application. Ameliorating the devastating effects of an immature gastrointestinal system in the preterm and growth-retarded newborn remain our vision, and our laboratory is very thankful for the gracious support of the IFFGD in our endeavors.

[Note: In the U.S. institutions that use laboratory animals for research or instructional purposes are required by law to establish an Institutional Animal Care and Use Committee (IACUC) to oversee and evaluate all aspects of the institution's animal care and use program. In Dr. Buchmiller-Crair's lab, all animal procedures are done with the approval of the Institutional Animal Care and Use Committee as overseen by Weill Cornell Medical College as well as Federal oversight agencies to ensure compassionate use of animals under the direct supervision of a Veterinarian.]