



FETAL PROGRAMMING IN DIABETES

Researching the link between mother and child using sheep models

By Susan McGinley

Babies born to women who have high blood sugar (gestational diabetes) during pregnancy face a greater risk for developing obesity and Type 2 diabetes later on. Although elevated blood sugar levels can be mild for diabetic mothers who take precautions, the excess glucose crossing the placenta into their babies may seriously affect the

pancreatic beta cells, which are involved in insulin secretion.

Not enough is known about exactly how or when the mother's gestational diabetes affects the fetus to the point where it can impair the child for life. Scientists at the University of Arizona are conducting research to fill in the gaps in knowledge regarding the fetal response to mild sugar overload.

"Since 1991, the working hypothesis has proposed that what you're exposed to in utero can define your life," says Sean Limesand, an assistant professor in the University of Arizona Department of Animal Sciences. "The developmental period is essentially when your organs are forming, establishing the functions they will have after birth. The

pancreas is one of the organs important for metabolism."

Focusing specifically on the way the pancreas develops before birth, Limesand measured different types and levels of hyperglycemia in sheep models to help establish a baseline for eventual clinical guidelines in treating pregnant women with gestational diabetes. The year-long study was conducted in collaboration with Ronald Lynch, a professor in the Department of Physiology and funded through a Science Foundation of Arizona New Opportunity Investment award.

The timing is critical: The incidence of mothers with gestational diabetes has doubled over the past eight years, while at the same time cases of non-insulin dependent diabetes have risen

in children. In Arizona, a study conducted among the Pima Indians by the Phoenix Epidemiology and Clinical Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases has shown links between fetal exposure to diabetes during pregnancy and greater risk for developing diabetes in adulthood.

The landmarks of development in sheep are very similar to humans, Limesand says. “For the study, we’re looking at a level of diabetes that is not severe. Clinically, the concentrations chosen reflect the upper limits of what would be within an acceptable range for a mother with controlled diabetes.”

During their study, Limesand and Lynch, working with postdoctoral student Alice Green, infused glucose at varying amounts into sheep for two weeks to mimic the

intermittent, pulsing form of mild diabetes human mothers may experience during the day after meals. They compared the diabetic mothers to control sheep receiving saline.

The beta cell function, measured by decreased insulin secretion, was 45 percent less in diabetic fetuses. Thus exposure to even mildly elevated glucose concentrations can alter beta cell function during fetal life. Upon analysis, the impaired insulin secretion in the fetuses was found to be associated with accumulation of reactive oxygen species—a type of free radical containing oxygen. The findings indicate oxidative stress may be causing the beta cell impairment, because if reactive oxygen species are not cleared rapidly or properly, they will damage cellular proteins, DNA and lipids.

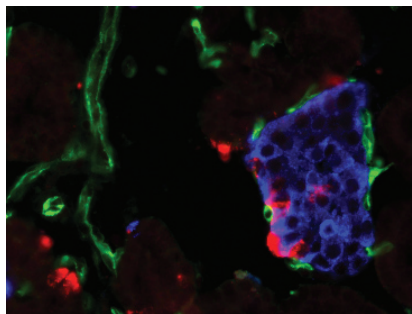
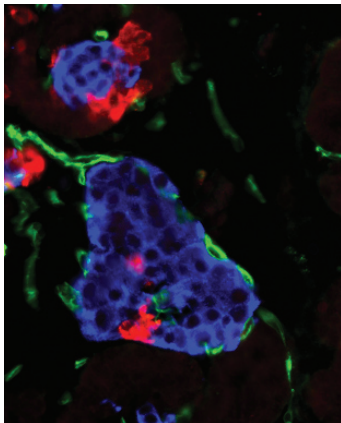
THE COST OF DIABETES

More than 284,000 Arizonans have been diagnosed with diabetes, accounting for more than 91,000 hospitalizations and \$2.5 billion in health care costs—and the number of cases could double by 2020 if the current prevalence rates continue. National figures published in the journal *Diabetes Care* in November 2009 note that the number of people with diagnosed and undiagnosed diabetes totals about 24 million and will nearly double to 44 million by the year 2034. Related medical costs are projected to rise from \$113 billion to \$336 billion in 2007 dollars.

“Now that we’ve defined the model, we need to figure out how to circumvent these outcomes,” Limesand says. “That may not be by controlling glucose. Our next stage is to find some way to manage the fetus so it’s not compromised by repeated exposure to hyperglycemia—possibly by infusing antioxidants into it to block the effects.” ☼

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Lab photos of Islets of Langerhans in sheep pancreas show immunofluorescent staining for insulin (blue), vasculature (green) and other endocrine hormones (red for alpha, delta and F cells).

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