

ICSI Fathers May Transmit Genetic Disease Risk

BY BETSY BATES

Los Angeles Bureau

SAN DIEGO — Infertile men undergoing intracytoplasmic sperm injection display an elevated rate of genetic variations that may predispose them to pass on traits associated with neurodegenerative diseases, according to a study presented at the annual meeting of the Endocrine Society.

"This technique overcomes tremendous genetic barriers to reproduction and allows men with genetic disorders to achieve a pregnancy. It is therefore our concern that they will transmit these diseases to offspring," said Francesca Gordon, a research associate at Baylor College of Medicine, Houston.

Ms. Gordon, Dolores J. Lamb, Ph.D., and their associates at Baylor and Monash Medical Center, Melbourne, obtained DNA samples from 647 infertile men whose partners were undergoing in vitro fertilization (IVF) with intracytoplasmic

sperm injection (ICSI) in Houston and Melbourne and 369 normal controls from the same cities.

Polymerase chain reaction was used to analyze the lengths of triplet repeat tracts, also known as microsatellites, for three alleles associated with neurodegenerative disease: spinocerebral ataxia type 1 (SCA1), spinocerebral ataxia type 2 (SCA2), and dystrophia myotonica.

Several triplet repeat diseases such as Kennedy syndrome and myotonic dystrophy are associated with infertility.

The researchers hypothesized that expanded (normal, but unstable) microsatellite lengths associated with other triplet repeat diseases might be more common in infertile men, potentially putting at risk their children conceived through ICSI.

There was a significantly increased incidence of unstable alleles associated with dystrophia myotonica in infertile men in the study population.

Ms. Gordon explained that there is a spectrum of repeat triplet lengths for each allele, ranging from normal to expanded-normal—a pattern that might pose a "pool of instability for future generations"—to

a long expanse of triplet repeat tracts, associated with the development of symptoms. The length of the repeat correlates with disease severity and the age of onset. In general, the longer the triple repeat, the

more severe the illness and the earlier symptoms occur.

There was a significantly increased incidence of unstable alleles associated with dystrophia myotonica in infertile men in Houston and Melbourne, compared with study controls.

Infertile men in Houston had an elevated incidence of unstable SCA2 alleles, compared with fertile control men. Conversely, only the men in Melbourne had a significantly elevated incidence of unstable SCA1 alleles, when compared with men in the control group.

Several of the patients exhibited repeat lengths in the mild to moderate disease range, whereas none of the control men did. The incidence of these unstable alleles varies by ethnicity and region, with SCA1 being more common in the general Australian population.

The incidence of dystrophia myotonica in the general population is estimated to be 5 in 100,000 people (0.00005%).

Infertile men in Houston had evidence of increased incidence of mild disease alleles, compared with men in the general population.

The estimated incidences of SCA1 and SCA2 are 0.006% in the general population.

Infertile men from both Houston and Melbourne had a higher incidence of SCA2 disease alleles than normal control samples. SCA1 disease alleles, in contrast, were increased, compared with controls only in the Melbourne population.

These results indicate there may be an increased risk of microsatellite expansion in infertile men using ICSI to father children. These men could then transmit these expanded alleles to their children, resulting in an increased risk of microsatellite expansion of neurodegenerative disease alleles in these individuals as well. ■

Study: IVF Children Are Taller, Have Better Lipid Profiles

BY BETSY BATES

Los Angeles Bureau

SAN DIEGO — New Zealand school-aged children who were conceived using in vitro fertilization were taller and had more favorable lipid profiles than those conceived naturally, a case-control study concluded.

Harriet Miles, M.D., and associates at the Liggins Institute of the University of Auckland studied 50 healthy children conceived via in vitro fertilization (IVF) with fresh embryos and 60 matched controls, when the children were 7-9 years old.

Participants were singletons, born at term, she said in an oral presentation at the annual meeting of the Endocrine Society.

After controlling for midparental height, members of the IVF group were considerably taller than the naturally conceived children. "This is surprising, as 15% of the IVF group were born small for gestational age, defined as weight below the 10th percentile," said Dr. Miles, a pediatric endocrinologist.

According to standard growth prediction models, the IVF group would be up to half a standard deviation shorter than their naturally conceived peers, yet they were more than half a standard deviation taller.

"Another interesting finding is sexual dimorphism, with difference in height being more marked in females," she said.

There were no differences in body composition between the two groups of children, yet IVF-conceived children had significantly higher insulin-like growth factor I (IGF-1), IGF-II, and insulin-like growth factor-binding protein 3 (IGFBP-3).

Their lipid profiles were more favorable, even when researchers controlled for age, sex, height, and percentage of body fat.

For example, the mean HDL cholesterol for IVF-conceived children was 1.61

mmol/L, compared with 1.51 mmol/L in naturally conceived controls.

There was a trend toward lower triglycerides and significantly lower LDL cholesterol in IVF-conceived children.

"Differences in growth and lipid metabolism in IVF children may be due to changes in genes influencing these factors, which are known to be imprinted," Dr. Miles said.

She hypothesized that imprinting of these genes might be influenced by alterations in methylation patterns in the first few days after conception, as in the preimplantation period. A candidate gene to test this hypothesis has been found, and a future study will examine expression of this gene in IVF- and naturally conceived children.

In an interview, Dr. Miles explained that something as simple as the culture used during IVF may have an impact on methylation and expression of imprinted genes involved in growth and metabolism. The culture used in Australia and New Zealand contains glucose, for example.

Eric Surrey, M.D., president of the Society for Assisted Reproductive Technologies and a reproductive endocrinologist from Englewood, Colo., said in an interview after the conference that he found the study results "intriguing, but preliminary."

Most studies of children conceived by IVF have focused on developmental issues and have found an occasional "blip," but no significant, consistent differences between them and naturally conceived children. This may be the first study to address metabolic differences, he added.

"This is a small study, and I'm not sure any conclusions can be drawn from it. But anything suggesting differences in outcomes between children born using assisted reproductive techniques and those conceived naturally is very important to follow up on," he said. ■

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