

Managing Multiples

Twin births are surging, but they're high-risk. An eight-year, \$8 million trial will determine if Caesarean section is the best method of delivery

In July 2000, the Society of Obstetricians and Gynaecologists of Canada published a consensus statement on the management of twin pregnancies. Based on a literature review spanning more than two years by dozens of experts from across Canada and the world, the statement reflected broad agreement on the many complexities of twin pregnancies, and answered several questions. One question the panel couldn't answer, however, was the best way to deliver twins—vaginal birth or planned Caesarean section.

Twin and other multiple pregnancies—triplets, quadruplets and quintuplets—have much higher rates of premature birth and growth abnormalities than do singletons. But even in optimal circumstances, when the babies have reached full term without problems and the first twin is presenting head down, twins still have a threefold higher chance of dying. The expert panel, chaired by Dr. Yosef Barrett, an associate scientist at Sunnybrook Research Institute and director of the perinatal and gynaecology research program at Sunnybrook Health Sciences Centre, did agree that existing literature on the best method of delivering twins was inconclusive, despite preliminary evidence suggesting that Caesarean section may be better (especially for the second twin), and a drift toward it in obstetrical practice. They recommended further research on the subject, and it was from this Canadian seed that the global Twin Birth Study (TBS) was born.

Funded by an \$8.6 million grant from the Canadian Institutes of Health Research and led by Barrett, the TBS is an eight-year, international, multicentre, randomized controlled trial (RCT) coordinated by Sunnybrook Research Institute's Centre for Mother, Infant and Child Research. Its mission is clear: "We'll find the answer to this very basic but very important question of what's the best way to deliver twins," says Barrett in an interview between patients at the bustling Sunnybrook multiple births clinic. Although RCTs take a long time—this one in particular because the statistical differences between delivery options are likely to be small and therefore require

a high sample size—in the end, says Barrett, they're the only route to a definitive answer. "The RCT is the gold standard for evaluating clinical therapies. There's no other good way of doing it."

Finding that answer has become more important over the last 30 years because the rate of multiples has exploded. In Canada, from 1974 to 1990, twin births rose 35% (per 100,000 births). This change is similar to data from other developed countries, including the U.S., where the rate of twin births grew 70% from 1980 to 2005, climbing an average of 3% a year between 1990 and 2004. In Canada, there are now more than 4,000 sets of twins born each year. The incidence of other multiples has risen even more so; although rates have fallen slightly since the late 1990s, triplets increased almost 300%, and quadruplets over 400%, from 1974 to 1990. Multiples are, says Barrett, a "modern epidemic."

Two factors have contributed to the dramatic rise in multiples: more women choosing to have babies at an older age and new fertility treatments. Women in their thirties are more likely than younger women to have multiples spontaneously, and fertility treatments including assistive reproductive technologies (particularly in vitro fertilization), intrauterine insemination and ovulation stimulants have become common. Scientists estimate that fertility treatments account for about 16% of multiple births in Canada.

To manage this demand, Barrett, in addition to leading the study, helped found Canada's first multiple births clinic in 1999 at what was then known as Sunnybrook & Women's College (now Sunnybrook Health Sciences Centre). As a pregnancy clinic dedicated to seeing women with multiples, it was and still is unique because, according to Barrett, it's unusually multidisciplinary, involving doctors, ministers, midwives, dieticians and other support staff. Clinic staff created Canada's first electronic patient record, such that patients' data are entered directly into a computer—all the rooms are wired with computers, so staff can stream the data straight into a database server. The patient is also given a record, confidential between her and her doctor, which she carries. (It was the first medical clinic in Canada where patients could carry their own records.) The clinic has garnered Sunnybrook an outstanding reputation for multiple births care.



Dr. Yosef Barrett and Jessica Ganas, with her twins Peter (left) and Carys

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Although this new influx of women and their babies has helped make Sunnybrook the largest Canadian centre for the TBS (to date the clinic has enrolled 60 women), difficulty in finding participants has made reaching the study's recruitment goal of 2,800 a significant challenge. "As anyone who's done a randomized trial will tell you, the biggest challenge is recruitment, recruitment, recruitment," says Barrett. He has seen many patients with preconceived ideas about trials; some worry they won't receive the best care. Dalah Mason, a senior research coordinator for the TBS, seconds that experience. She also feels that preconceived ideas from patients' families or friends can sometimes hinder recruitment. "Occasionally women are interested, then go home and talk about it and later decide they're no longer interested," says Mason. She adds that although the TBS doesn't involve a new or untested treatment, many women don't like the idea of giving up the choice of how they deliver—another obstacle for this trial.

A further recruitment challenge lies in doctor equipoise, which Barrett calls "a fancy term for, 'I don't know what to do.' A patient comes to you because you're the doctor, and says, 'What's the best way to deliver my baby?' and you say, 'I don't know.' Well, it can be difficult to admit that, but it's the truth—right now, the literature is in that position of equipoise." Recruitment for the TBS was supposed to have reached 2,800 by June 2008, but enrollment is only halfway there.

Recruitment aside, two other challenges exist for the TBS: data collection and funding. Says Barrett, "We have to make sure the data are clean and accurate, which means hours of meticulous work with the data forms we get back from the centres." While a challenge for

any study, it's particularly daunting in this one, which has 87 centres in 22 countries, and requires two years of follow-up with each patient. Says Mason, "Follow-up is time-consuming, because people move away and need to be located, or they may lose interest. Then, we may lose them."

As another challenge, centres in Canada may be more hesitant to take on the work of a large trial like the TBS owing to Canada's funding structure. Although the Canadian Institutes of Health Research has provided significant funding for the study, all that money goes to running the grant, and none goes to investigators (unlike in the U.S. and some other countries). So, says Barrett, "it's up to individual universities, departments and practice plans to somehow pay people to do research, and that's a challenge."

This and other difficulties notwithstanding, Barrett is excited about the TBS and what it will reveal. An earlier RCT carried out by the Maternal, Infant and Reproductive Health Research Unit at Sunnybrook and Women's College Health Sciences Centre addressed a similar question—the best way to deliver breech babies—and the answer was Caesarean section. "Almost overnight, or at least within a year," says Barrett, "the practice internationally swung. It was one of the very few results of a study that globally, rapidly, changed the whole practice of obstetrics. And I have no doubt this trial will do the same thing." 

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