

# China's First Baby Conceived through In Vitro Fertilization-Embryonic Transfer, by Zhang Lizhu's Research Team

On 10 March 1988, China's first baby conceived through human in vitro fertilization (IVF) and embryo transfer (ET), commonly referred to as a test-tube baby, was born at the Peking University Third Hospital (PUTH) in Beijing. This birth was reported in numerous media reports as a huge step forward in China's long march to keep pace with global advances in science and technology. Led by gynecologist Zhang Lizhu, the PUTH research team had devoted more than four years to the human IVF-ET project. The team had to start by learning the basics of human egg morphology and embryology in order to design an IVF-ET strategy that was suited to the reproductive pathology affecting China's infertile population.

Zhang Lizhu, the director of the Department for Gynecology and Obstetrics Department in PUTH, took an interest in human IVF-ET technology in the early 1980s. Zhang led her PUTH research team in studying contraceptive technologies for two years, and she presented at international conferences about China's recently enacted One-Child Policy and its impact on global public health. As a well-known gynecologist, Zhang also received thousands of letters from infertile couples, mostly written by women, who pleaded for medical treatment in hopes of having their own biological children. Many of those couples had already consulted local hospitals as well as traditional healers, but to no avail. After many years of unfulfilled efforts, those infertile couples considered writing to the Department for Obstetrics and Gynecology at PUTH as a last resort. Zhang examined the causes of infertility in some of those prospective patients and began to consider human IVF-ET technologies as a potential resolution. Zhang learned that many infertile couples were able to have their own children in countries that offered IVF treatments, and started to review the literature about IVF, which was scarce in China in the early 1980s.

Funding for human IVF-ET research was elusive during the early 1980s in China. In 1984, Zhang and her colleagues at PUTH were slightly surprised when PUTH and two other hospitals were commissioned to study human IVF-ET as part of China's Seventh Five-Year Plan, the Party's goal-setting plan for national economical and scientific development for the period of 1986 to 1990. Under a research title that suggested little about fertility treatment, "Eugenics: the Protection, Preservation, and Development of Early Embryos," the National Foundation of Natural Sciences allocated 100,000 Chinese yuan (CNY) to PUTH, Central-South University Xiangya Hospital, and Peking Union Medical College Hospital for human IVF-ET research. Zhang's team in PUTH received slightly more than 30,000 CNY, then roughly equal to 15,000 US dollars.

In 1984, Zhang and her team began to explore ways to retrieve eggs for IVF purposes from infertile female patients, who often had obstructed or distorted fallopian tubes. The then standard ovum retrieval procedure established in clinics of other countries involved laparoscopy, a telescopic system that was inserted into the abdominal cavity through a small incision near the umbilicus to facilitate diagnosis and small surgeries in lieu of invasive abdominal surgery. With the aid of a laparoscope, IVF clinics in the West could retrieve ova from patients without inducing the significant pain and inconvenience that was then associated with open abdominal surgeries. Doctors could inspect the ovary, aspirate the ovarian follicles through a small incision, and then recover eggs from aspirated follicular fluid under the microscope.

Zhang and her team initially tried to retrieve eggs with the aid of laparoscopy, but found that the laparoscope could not make the surface of ovaries visible in a significant number of patients. Without

a visible ovary, she could retrieve no eggs. Extensive medical examination of women with ovaries inaccessible to laparoscopy often revealed medical histories of tuberculosis (TB) infections. A common infectious disease in China, TB frequently spread from the lungs to the pelvis, creating bands of scar-like tissues caused by inflammation (adhesions) in the pelvic cavity that damaged the fallopian tubes and uterus. Zhang determined from her cases that upward of one-third of female infertility cases in China resulted from tuberculosis, and concluded that laparoscopic egg retrieval would be an ineffective means of retrieving eggs in tuberculosis-affected patients.

Thinking about alternatives to laparoscopy, Zhang decided to try abdominal surgery to retrieve eggs, a procedure that she called intraoperative ovum pick-up. Such surgery made sense for TB-related infertility, Zhang reasoned, because the physician could remove excessive adhesions in the patient, thereby treating tuberculosis-associated pelvic disease and retrieving ovum in the same surgery. Even if the eggs could not be obtained through such surgery, the doctor could at least ameliorate the patient's pelvic conditions.

Zhang scheduled such surgeries thirty-two to thirty-three hours after injecting human chorionic gonadotrophin (hCG) into the women to stimulate ovulation. The timing was identical to the timing of ovum retrieval in laparoscope-aided protocols. In a typical surgery, Zhang would first remove pelvic adhesions, and then reach into the patient's abdominal cavity to access the ovary's surface. Zhang would then feel the ovary surface for protrusions generated from maturing, swollen ovarian follicles. Upon finding a protrusion, Zhang would quickly insert an aspiration needle to extract the follicular liquid. Zhang would aspirate the follicle filled with blood, which indicated that she had removed the ovum from the follicle. She collected the follicular fluid in glass tubes and placed it in insulated cups of warm water kept at body temperature. After retrieving four to six eggs, members of the research team would carry the insulated cups across the campus of PUTH to the Laboratory of Histology and Embryology to isolate and culture human eggs from the collected follicular fluid.

When Zhang started to perform ovum retrieval in 1984, she had never seen a human egg under a microscope. The textbook Zhang had used in her medical school only had pictures of pig eggs. To identify human eggs from follicular fluid, Zhang consulted an embryology professor working at the PUTH Laboratory of Histology and Embryology, Liu Bin, who soon became a collaborator for Zhang's team. Liu had studied mouse in vitro fertilization in the late 1970s with mammalian embryologist Jacques Mulnard at the Université Libre de Bruxelles in Belgium. During his study in Belgium, Liu had made a film capturing the developmental processes of mouse embryos in vitro and brought the film back to Beijing. In the video, the fertilized mouse egg divided into the four-cell and eight-cell stages, eventually reaching the blastocyst stage. Liu's video was a reference for Zhang's team, which also used images of human eggs published in Western literature. With those resources, Liu and Zhang examined follicular fluid meticulously, until they isolated and cultured human ova from the fluid.

In October 1985, after much trial and error, Zhang's team successfully fertilized a human ovum in vitro and brought it to the four-cell stage. As the media started to report about this initial success, Zhang became aware of public concerns about the social implications of the team's work. Many expressed the concern that it might be counterproductive to study test-tube baby technology in a country that endeavored to limit population growth. Some went further, explicitly denounced Zhang's work as a violation of the One-Child Policy. Zhang started to scrutinize the details written in population regulations and found that the policy not only encouraged gynecology workers to be skilled in contraception, but also encouraged them to treat infertility with proper means. Assured that national policy supported fertility research, Zhang and her team continued their work.

Confined by meager financial support, Zhang's team made numerous efforts to save money without impairing the quality of their work. The team made culture media from scratch and recycled culture dishes as well as other tools. When their few aspiration needles became blunt after many uses, Zhang had them sharpened in a nearby watch repair shop. Since the team did not have adequate equipment for safely transferring the four-celled embryos developed in vitro from Liu's laboratory to Zhang's operation room, they moved the whole operation facility to Liu's laboratory and conducted the embryo transfer operation in the same laboratory where in vitro fertilization and embryo development occurred.

In 1987, Zhang's team continued IVF-ET research, with the goal of pregnancy and delivery following embryo transfer. One day in May, a female elementary school teacher from rural area of Gansu Province, Zheng Guizhen, visited Zhang. Zheng was thirty-eight years old and had been married for twenty years. Zheng suffered from blocked fallopian tubes, which meant that traditional means of fertilization were unlikely to lead to successful pregnancy. Yearning to have a child, Zheng and her husband travelled to Beijing to visit Zhang's laboratory. Zheng's blocked fallopian tubes were a result of past TB infection, the condition for which Zhang had specifically designed her method of egg retrieval. Zhang's team discussed with Zheng and her family about the procedures and risks associated with IVF-ET. The research team explained that of the twelve embryo transfers prior to Zheng's case, only one had resulted in implantation, but that implantation was outside of the womb, resulting in an ectopic pregnancy that was not carried to term. Despite the history, Zheng was optimistic and persistent, and Zhang's team thus embarked on a new trial.

In June 1987, Zhang carried out ovum retrieval surgery and obtained four mature eggs from Zheng. During this surgery, the semen from Zheng's husband was washed and cultured for five hours, at which point the sperm capacitation was complete, which meant that the membranes surrounding the heads of the spermatozoa were destabilized to allow for better binding to the ova. Zhang's team then added the sperm to the egg culture. On 25 June, the researchers saw both male and female pronuclei under microscope, a sign indicating successful fertilization. On 26 June, the fertilized egg divided into four cells. On the same day, Zhang implanted all four developing four-celled embryos into Zheng's uterus, only one of which eventually underwent full development.

On 6 July, Zheng's urine test showed a high level of hCG, a hormonal indicator of early pregnancy. On 3 August, ultrasound images demonstrated the heartbeat of the embryo and on 1 September, the movement of the legs and arms was detected. Zheng's pregnancy culminated in the delivery of a baby girl, the first test-tube baby in Mainland China, through Caesarean section on 10 March 1988. To remember Zhang's work, Zheng named her daughter Mengzhu, which had the same character, zhu, as Zhang's name Lizhu.

Zhang's achievement was soon well known and celebrated throughout China. She was awarded the Beijing Science and Technology Progress First Prize and the National Science and Technology Progress Second Prize. The second test-tube baby in China soon followed, and was delivered in PUTH on 27 May 1988.

In June 1988, China's third test-tube baby was delivered in Central-South University Xiangya Hospital, another commissioned hospital of the 1984 human IVF-ET project, that also used surgical means for retrieving eggs. The hospital that concentrated solely on laparoscopy as a method, Peking Union Medical College Hospital, did not achieve a single case of in vitro fertilization that lead to the delivery of a test-tube baby.

During 1985 and 1986, several Western experts were invited to Beijing and Guangzhou to help treat infertile Chinese patients using IVF. The Western attempts at achieving pregnancy for infertile couples through laparoscopy-assisted IVF procedures also failed. As such, the abdominal surgery Zhang designed for TB-related infertility was seen as essential in the PUTH team's success. By 1988, however, Zhang sought less invasive methods for egg retrieval and started to experiment with what she called the ultrasonic-guided transvaginal ovum retrieval method; a technique that would in time significantly reduce the invasiveness of surgical egg retrieval.

In the 1990s, the IVF-ET fertility treatment in China was used in many hospitals and clinics and was gradually industrialized and standardized. As of 2011, IVF-ET fertility treatment in PUTH has its own Center for Reproductive Medicine that admits about one thousand patients daily from different areas of China. As IVF-ET technology has become more widely accepted and used, the stories of Zhang's research team have been detailed in newspapers and television programs, as well as in videos that play in the waiting rooms of the Center for Reproductive Medicine at PUTH.

## Sources

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