ON April 6, 2016 a new chapter was scripted in human reproductive biology. A baby boy was born, not to the usual two parents, but to three parents – two women and a man – by a new procedure known as Mitochondrial Replacement Therapy to help women with genetic defects to have healthy babies. The people who made it possible were embryologist Dr. John Zhang and his team from the New Hope Fertility Center in New York City.

This is different from surrogacy, where also a man and two women are involved in the birth of a child. In surrogacy, the third woman only lends her womb for the growth of the fetus and delivers the baby. The child does not inherit her genetic material. But in the present case the child inherited genetic material from all the three.

The story relates to a Jordanian couple who had been trying to start a family for nearly 20 years. After several years the lady became pregnant. Unfortunately it ended up with miscarriage, followed by three more. In 2005, she gave birth to a baby girl. She was born with a disease known as Leigh syndrome, which affects the brain, muscles and nerves of the infant. The girl died at the age of six. This was followed by a second child with the same disorder who lived only for eight months.

It was at this time that the couple sought the help of Dr. Zhang, who tried for the first time a new procedure called Mitochondrial Replacement Therapy (MRT), which he had been working on for some time. This achievement is hailed as a new milestone in fertility medicine. So, what is MRT?

Well, human body cells contain an organelle known as mitochondrion – the power plant in the cell. It converts the energy from food to biochemical energy through a process known as oxidative phosphorylation to drive all the cellular functions. The specialty of mitochondria is that it is the only organelle in the cell other than the nucleus that contains its own DNA.

While the bulk of the DNA is in the nucleus in the form of 23 pairs of chromosomes with about 20,000 genes, the mitochondrial DNA is contained in only one circular chromosome with just about 37 genes that code for some of the enzymes needed for energy production. While the nuclear DNA exists as only one copy, a mitochondrion contains two to ten copies of its DNA and each cell contains hundreds of mitochondria.

We all inherit one copy of genes from the father and one copy of the genes from the mother. That is how we have two genetic parents. This is true with respect to nuclear genes only. Mitochondrial DNA is inherited in a different way. Both male and female offspring almost always inherit mitochondrial DNA only from the mother. This is because it is only the nuclear DNA that is delivered to the egg and not the mitochondrial DNA.

Just as nuclear DNA undergoes mutations and leads to inherited genetic diseases in the offspring, mitochondrial DNA also undergoes mutations. It is generally known that the mutation rates are higher in mitochondrial DNA than in the nuclear DNA. This is because the error checking ability, which corrects for errors in DNA sequence that occur during DNA replication, is less efficient in the mitochondrial DNA.
During each cell division the number of mitochondria doubles and segregates randomly between the two new cells and then makes more copies. Hence, as mitochondria proliferate within the cells, they may accumulate random mutations. So if the mother has mutated mitochondrial DNA, all her offspring will inherit them.

Mitochondrial DNA mutations are also associated with several inheritable diseases. These express mainly in organs that use lots of energy, leading to loss of muscle coordination, heart diseases, liver diseases, neurological problems, diabetes, deafness, dementia and so on. Many of these diseases may strike early in life and tend to get worse with age. It is reported that as many as one in 5000 children are born with mitochondrial diseases, the severity of which depends upon the proportion of defective mitochondria the mother passes on to her offspring. There is no cure for many of these diseases, but can only be treated for symptoms. Most patients die before adulthood.

Most mitochondrial diseases become clinically apparent once the number of defective mitochondria in the organ reaches a certain level. Therefore, a mothers with fewer defective mitochondria may not show any symptoms. However, when the offspring inherit those, mitochondrial divisions and proliferation may lead to more defects crossing the threshold. In the case cited above, the mother, though free of symptoms carried a mitochondrial mutation that caused Leigh syndrome, which affected the brain, muscles and nerves of the infants, causing their death.

How does one prevent mitochondrial diseases? The obvious way is to prevent the inheritance of the defective mitochondria. But mitochondria are so many in number and it is not possible to pick out the defective ones. The next alternative is to replace the mother’s entire mitochondria and provide the zygote with a healthy set.

Dr. Zhang and his team achieved this using a technique known as ‘maternal spindle transfer’. The procedure essentially involves three persons – the father, the mother and a healthy female donor. Eggs from the mother are harvested and the spindle complex which holds the nuclear chromosomes together in the egg is carefully taken out using a micro needle under a microscope, leaving behind the mitochondria and all other organelles. It is then inserted into the donor’s egg from which its own nucleus was removed earlier using the same procedure, but retaining mitochondria and all other organelles.

We know that the genetic material, DNA is contained in the nucleus of the cell structured into what are known as chromosomes. All cells in the body (except the red blood cells) contain 23 pairs of chromosomes. However, the germ cells (eggs from the female and sperm from the male) contain only one chromosome from each of the 23 pairs. During fertilization, the nucleus of the sperm enters the egg cell, thus providing the complete complement of the 23 pairs to the zygote, from which the baby is born. Specific sections of DNA in the chromosomes are identified as genes, which control all aspects of human development.
This reconstituted donor egg is fertilised with the father’s sperm using in vitro fertilisation techniques. The fertilised egg is then allowed to develop into an early embryo in the laboratory. The team produced five such embryos and implanted one of them into the mother’s womb. Nine months later the baby was delivered. Thus the baby contained genetic material from all three persons – nuclear genes from the father and mother and mitochondrial genes from the female donor. Dr. Zhang used the procedure for the first time on the Jordanian couple.

In an alternative procedure, the eggs from both the mother and the donor are first fertilised with the father’s sperm. The pronucleus formed by the fusing of both male and female nuclei from the mother’s fertilised egg is carefully removed and transferred into the fertilised egg of the donor from which the pronucleus was similarly removed. The reconstituted zygote is allowed to undergo a few divisions in the laboratory and implanted into the mothers’ womb. A three-parent baby with this procedure is expected to be born in the UK in 2017.

However, not all fertility experts are sure that either of the procedure will totally prevent the transmission of mitochondrial diseases. They argue that it may not be possible to make nuclear transfer completely free from the mother’s mitochondria. When Zhang and his colleagues tested the baby’s mitochondria they found less than 1 percent of them had come from the mother. Since it takes at least 18 percent of the mitochondria to be affected for the symptoms to show up, they hope the boy will be disease free.

Another area of concern is the possible mismatch between the mother’s nuclear DNA and the donor’s mitochondrial DNA. Though not much data are available on this aspect, experiments on mice have shown that a mismatch may lead to accelerated aging, metabolic disorders, and obesity in the offspring, though they appeared healthy when young. Hence, more births of this type and longer observation time alone can tell if these procedures can prevent the transmission of mitochondrial diseases to the future generations.

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