

A shot at contraception

In India, a nonagenarian renews testing of a birth control vaccine

By Killugudi Jayaraman



Matt Hansen/SpringerNature

The idea to try to revolutionize birth control came to Gursaran Pran Talwar during a trip in 1972 to the holy city of Varanasi on the banks of the Ganges. There, in the crowded streets, the Indian biochemist bumped into groups of emaciated women herding their large broods of children.

Why did they not limit their family size when the government offered a basket of birth control methods for free, Talwar, who then worked at the All India Institute of Medical Sciences (AIIMS) in Delhi, wondered. A brief conversation with them revealed the reasons: using birth control pills required remembering to take them daily and the intrauterine devices (IUDs) available at the time caused excessive bleeding. A surgical procedure involving ligation of the fallopian tubes, known as ‘getting your tubes tied’ in other parts of the world, caused permanent infertility and was therefore not preferred until later in their reproductive lives. Their husbands, meanwhile, were reluctant to use condoms.

That set Talwar thinking. Why not devise a reversible contraceptive option for women that didn’t require daily dosing and was free of many of the side effects associated with traditional birth control, such as unexpected mid-cycle bleeding, mood changes and headaches?

He believed that a vaccine targeting the hormone called human chorionic gonadotropin (hCG) would be ideal. hCG is made by the embryo early after fertilization and isn’t produced until the onset of pregnancy. This unique aspect of hCG is the very reason why it is used as a reliable test of pregnancy. Importantly, hCG is essential for implantation of the embryo in the uterine lining. So, if a vaccine were to generate antibodies neutralizing hCG, Talwar reasoned, implantation of the embryo would be blocked, thereby preventing development of a fetus.

Now, after more than four decades and having developed three different successively improved versions of an anti-hCG vaccine, Talwar, 91, thinks his idea is finally becoming reality.

In late November, he got the news he was eagerly waiting for. The Indian Council of Medical Research (ICMR), the country’s primary funding and coordinating body for biomedical research, informed him it would fund and conduct the clinical trials of his latest vaccine. A total of 120 women will participate in the testing—50 in the phase 1 trial and 70 in the phase 2 trial—at two hospitals in Delhi. Talwar expects the phase 1 trial to start by March, and, according to the ICMR letter he received, the trials are approved to “determine the safety and

immunogenicity of the vaccine in sexually active healthy women and prove its ability to prevent pregnancy without impairment of ovulation and derangement of menstrual regularity and bleeding profiles.”

Other scientists have taken note of the upcoming trials. “It is gratifying to hear the hCG vaccine has been revived,” says John Schiller of the US National Cancer Institute, who a decade ago had considered hCG as a potential ‘payload’ for a vaccine platform that he had developed, although he did not end up moving ahead with this particular application. Jeffrey Jensen, director of the Women’s Health Research Unit at Oregon Health & Science University in Portland, who has followed Talwar’s work since the late 1980s, is also watching to see what happens. Although he stresses that some of the immune system’s reactions to the vaccine have to be better understood, he told *Nature Medicine* that “a vaccine approach could become an additional option for birth control in India” and would likely be accepted in other countries, too.

But Sharon Batt, a bioethicist at Canada’s Dalhousie University, fears that the vaccine, if it becomes available, will inevitably be deployed among the poor where large families are most common. “It masks, rather than addresses,

the social and economic reasons that poor, undereducated women have large families, including a dependence on children for economic security,” she says.

For his part, Talwar hopes that the vaccine, when released, will have women opting for it because of its contraceptive benefit without the unpleasant side effects of ‘the pill’. “I am sure there would be plenty of women who would like to take three or four doses of vaccine and be free for about two years,” he says. “A role for vaccines undoubtedly exists as an aid to birth spacing, particularly in developing countries.”

An alternative choice

References to fertility regulation in women exist in historical records stretching back to ancient times, but it was only in the twentieth century that a basket of efficient and secure methods of birth control became available. The first oral hormonal pill of this sort, Enovid, was first marketed as a contraceptive in 1960. IUDs appeared in the 1920s, but it was only in 1988 that the new-generation copper IUD was first introduced to the US market, and hormonal IUDs came later in 2001. Altogether, 18% of the world’s contraception users rely on hormonal methods. But Talwar says that his vaccine offers an advantage in that it doesn’t control women’s menstruation cycles or hormones as the pill does. And he believes that modulating the immune system should be better for temporary contraception than IUDs, which require surgery for implantation and removal.

The number of women using contraception globally has already surpassed 770 million¹, with high growth in use projected for all regions of Africa and in southern Asia. However, according to the World Health Organization (WHO), 214 million women of reproductive age in developing countries who want to avoid pregnancy are not using a modern contraceptive method. The need for increasing contraceptive options was noted in a December study² by the Guttmacher Institute in New York. This study found that, in India, half of the 48 million pregnancies in 2015 were unintended and that more than 15 million ended in abortion. “Our findings confirm and reinforce the need for more effective contraceptive methods for women to choose from,” Susheela Singh, the study’s author and the institute’s vice president for international research told *Nature Medicine*.

Talwar’s vaccine targets hCG, which has two subunits—alpha and beta. Ideally, a contraceptive vaccine would use both to stimulate an immune response, but the alpha subunit of hCG is common to other non-pregnancy hormones produced by the pituitary gland, so its incorporation in the intended vaccine could provoke an autoimmune response against this



Forging ahead: Talwar in his office with a photo of his aunt, Vimal Raghuraj, who raised him.

Gauraran Pran Talwar

whole range of vital pituitary hormones. Talwar therefore chose to make the vaccine out of the beta subunit and chemically attached it to the tetanus toxoid protein to help trigger the body to become immunized against this subunit.

In 1974, he launched a phase 1 clinical trial that included four Indian women who had completed their families and had their fallopian tubes tied to prevent further pregnancies. In these women, the vaccine made antibodies against both hCG and tetanus with no disruption of regular menstruation. Their antibody levels steadily rose to reach a plateau, which was maintained for about three months, after which antibody levels began to decline, indicating that the vaccine’s effects wear off over time^{3,4}. The safety and ability of the vaccine to induce anti-hCG antibodies were confirmed by Population Council-sponsored trials in the late 1970s using the same vaccine in Finland, Sweden, Brazil and Chile⁵ on 15 healthy women.

Besides Talwar, another scientist named Vernon Stevens at the Ohio State University had been working since the early 1970s on a similar approach for birth control. However, unlike Talwar who designed his vaccine to employ the whole beta subunit, Stevens ultimately designed a vaccine based on only a tiny fragment of the beta subunit for the WHO Task Force on Vaccines for Fertility Regulation.

Even though the idea of a birth control vaccine was gaining traction outside India, this did not assuage all skepticism to the approach in Talwar’s homeland. “Back home, people felt that this was a crazy idea that could make women permanently sterile,” he says, reminiscing about the early days that, fairly or not, generated significant debate on ethics. “Vaccines were made against infections and not contraception,” Sarojini Nadimpally, a feminist bioethicist and the founder of Sama,

a Delhi-based resource group for women and health, told *Nature Medicine*. The result, says Talwar, was that he “could get no research grant or support from his peers to go ahead.” Talwar’s distress was, however, short-lived. The break came in 1983 when he became the director of the newly established National Institute of Immunology in Delhi, where he resumed the voyage that he started a decade earlier at AIIMS.

Talwar was aware of the main drawback of his prototype vaccine: the antibody levels it produced were insufficient to neutralize hCG. To make it more powerful, in 1988, he combined the hCG beta subunit (which was prepared from hCG purified from the urine of pregnant women) with a sheep-derived version of the alpha subunit of another reproductive signaling molecule known as luteinizing hormone. The rationale behind the updated design was that the latter hormone, being a foreign molecule, would stir a greater immune response in humans.

In a 1990 phase 1 trial, this second-generation anti-hCG vaccine produced higher antibody titers than its predecessor. The phase 2 efficacy trial on 148 women during 1991–1993 in three centers in India demonstrated the feasibility of preventing pregnancy in a reversible manner without impairment of ovulation. The women had IUDs implanted until it was demonstrated that their antibody levels were high enough to prevent pregnancy. Once the IUDs were removed, there was only one implanted pregnancy (which was terminated upon the subject’s request) occurring in 1,224 menstrual cycles⁶. The response to the vaccine was reversible. Four women in the trial, who desired another child and who did not take a booster after having remained protected for a year or more, did conceive and delivered normal babies⁷. A news report in *Science*⁸ described the

trial as a “landmark” and hailed it as the “first demonstration that women can be vaccinated against pregnancy.”

Evoking a response

Although the phase 2 trial of Talwar’s second-generation birth control vaccine provided proof of concept, only about two-thirds of women in the trial produced antibodies above the desired threshold, thought by Talwar to be sufficient to prevent pregnancy, for a duration of at least three months. So, it was Talwar’s next task to enhance the vaccine’s ability to evoke an immune response. But he suddenly faced another barrier that again held up the vaccine’s progress: in October 1994 he had to retire from the National Institute of Immunology, whose authorities could not extend his emeritus position nor provide him working space. Parting from the institute also meant that he had to leave behind a Canadian grant he had received for developing the vaccine.

The bad news kept coming. Around the same time, news arrived that a WHO task force trial undertaken on women in Sweden testing the vaccine developed by Vernon Stevens was suspended because the first seven of the 30 trial participants all experienced severe and unexpected side effects⁹. The study was not published.

Talwar says he “was left injured” when asked to quit midway. But a remedy arrived quickly in the form of a new grant from the Rockefeller Foundation in New York and an offer of laboratory space by the National Institute of Immunology’s neighbor, the International Centre for Genetic Engineering and Biotechnology (ICGEB). The honeymoon, however, lasted for just four years, as the space given to him was subsequently needed to house the National Brain Research Centre. The prospect of an imminent ouster from ICGEB when his project was midway completed put him in a fix.

But nothing could deter Talwar, an incurable optimist who is no stranger to difficulties. He lost his mother when he was eight days old and, as a youth, had to flee to Delhi from riot-torn Hissar—his birthplace—following the partition of India. Talwar completed his final year of college by staying in a camp set up for migrants. All this didn’t stop him from winning a fellowship for graduate studies at the Pasteur Institute in Paris, where he got his doctorate, and becoming the second faculty member to join the newly launched AIIMS in Delhi in 1956. This indomitable spirit drove him to carry on working on his dream vaccine, even after eviction from ICGEB, in a laboratory he built near his residence with his own funds. Thanks to a grant from the Indo-US Committee on



Early days: Talwar as a graduate student at the Pasteur Institute.

Contraception Research in 2006, his research program that had remained inactive for about 12 years was revived.

His third-generation vaccine, now awaiting clinical trial, is a recombinant vaccine that consists of the hCG hormone’s beta subunit fused with a portion of a protein derived from *Escherichia coli* bacteria that is thought to be more capable of stirring an immune response than the inactivated tetanus toxin used as a carrier in earlier versions. This version of the vaccine passed toxicological studies in rodents and marmosets and was ready in 2010 for human testing, but it has taken eight years to pass through India’s National Review Committee on Genetic Manipulation and the Drugs Controller General of India to reach the clinical trial stage. Bharat Biotech in Hyderabad will produce the vaccine and make it available free of charge for the clinical trials.

Will it prevent pregnancy? Talwar is optimistic but adds that “how long the protection will last will only be clear after the trials.” He notes that, in clinical trials of the second-generation vaccine, many women remained protected for as long as two and a half years by taking boosters an average of every three months to maintain the desired antibody levels⁶. Talwar does not believe there is a risk of long-term infertility from the vaccine and says a woman can conceive a child by skipping the boosters and waiting until her antibody levels drop below a certain level.

“It is exciting news,” Rajesh Naz, who is vice chair of research and professor of obstetrics and gynecology at West Virginia University’s School of Medicine, says of the new trial launch. “If successful,” adds Naz, who was Talwar’s

PhD student decades ago, this vaccine “will revolutionize the field of contraception all over the world, especially in India where presently the population explosion is a pressing issue.”

But not everyone is buoyant about the vaccine’s prospects. Aaron Hsueh, a reproductive biologist at the Stanford University School of Medicine who is familiar with the story of the hCG vaccine, says he is “surprised that Talwar is still working on this project.” He questions the need for a vaccine given the safe contraceptive options available for women, including the so-called ‘morning after pill’. Sharon Batt of Dalhousie University says that, although there is no evidence of harm from the earlier versions of the vaccine to animals, mothers or offspring, the numbers of subjects and extent of follow-up are not adequate to conclude safety. “If this trial goes ahead,” she says, “Talwar and his colleagues would be advised to welcome a very public system of external oversight.”

There are still skeptics in Talwar’s home country as well. “I do not think there is any likelihood of this vaccine being accepted as a reversible form of contraception,” says Jacob Puliyel, a pediatrician at St. Stephens Hospital in Delhi and a member of India’s National Technical Advisory Group on Immunization. But all this doesn’t worry Talwar. “When it was decided to conclude the phase 2 trial in 1993, many participants offered to pay for the vaccine to continue to be immunized,” he says, even though he and his fellow scientists could not continue administering the vaccine after the trial’s end. “It reflects in a way that they were happy and satisfied with this mode of contraception.”

Reflecting on his decades-long scientific journey, which began in the holy city of Varanasi, the nonagenarian Talwar posits that another hand might be helping to bring this type of vaccine forward: “Maybe God has given me long life to see this vaccine become the first birth control vaccine for preventing pregnancy, if it succeeds in the clinical trials.”

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