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MICE TIMES

In-vitro fertilization (IVF)

IVF a «monumental advance» – from animal to human

October 4, 2010

The Swedish Nobel Prize Committee announced this year's Laureate for Medicine. It is the British physiologist Robert Edwards. Today at the age of 85, he can look back on what was a sensational breakthrough more than 30 years ago. After fertilization of a human egg cell in the laboratory, Louise Joy Brown became the world's first «test-tube baby» when she was delivered by Caesarean section in July 1978. The parents of the baby girl had been trying for a baby for nine years. To no avail, because both fallopian tubes of Lesley Brown were blocked.

One in ten couples around the world is affected by infertility today for a diversity of reasons. It is no wonder that the technique of in-vitro fertilization (IVF) conquered clinics all over the world so quickly after the initial successes.

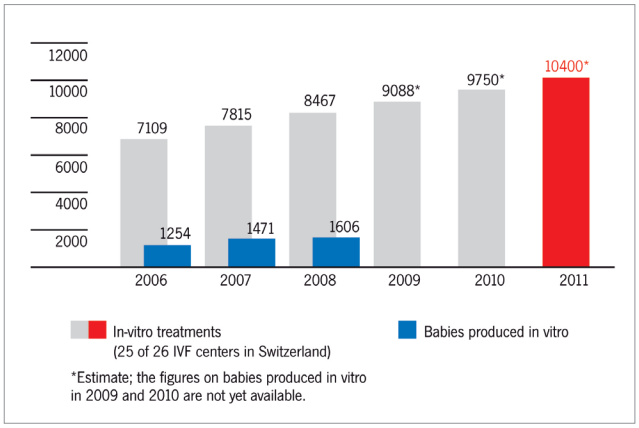

Fig.1: In-vitro treatments and artificial fertilization in Switzerland

To date a total of about four million babies have been born thanks to IVF. In Switzerland about 6000 women every year undergo in-vitro fertilization, and about five babies created in a test-tube are born every day.

The trend is rising both here and throughout the world, because more and more couples are putting off their plans for a family until after the age of 30, when fertility starts to decline quite sharply.

Knowledge of reproduction in animals is the basis of success

Why was it that Robert Edwards managed to achieved this «monumental advance» as the Nobel Committee expressed it? «Edwards knew an enormous amount about fertilization processes, because he had engaged in experiments for many years on reproduction in animals», says Christer Höög, cell biologist at the Stockholm Karolinska Institut and member of the Nobel Assembly, the committee that selects the Nobel Laureates. Stefan Schlatt, Director of the Institute for Reproductive Medicine in Münster, takes a similar view: «IVF was originally developed in animals. Only because it proved successful there was in-vitro fertilization eventually also a success in humans.»

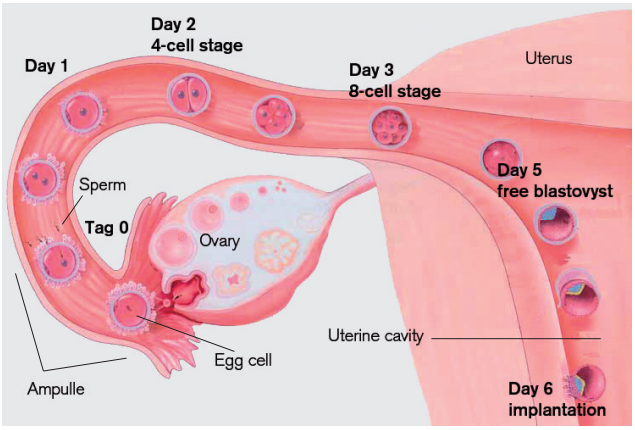

Fig. 2: Natural fertilization in the ampulla (= distal end) of the fallopian tube with migration of the fertilized egg cell through the fallopian tube. On Day 5, the free blastocyst reaches the uterine cavity. Implantation of the egg occurs on the 6th day after fertilization.

For a long time, researchers carried out animal studies in an effort to understand the miracle of reproduction. Since fertilization in mammals is a hidden process, it was first a roundworm in which Henry Nelson first observed the melding of egg and sperm cell in 1852. Seventy years before this, the Ita-

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lian priest Lazzaro Spallanzani had already carried out an «artificial fertilization» – albeit without knowing what actually happened. Using a syringe he injected sperm into the uterus of a poodle, which a litter of three small pups nine weeks later. Just a short time after this, doctors tried to help childless couples fulfill their wish for a baby in this way. Mostly without success. It was first necessary simply to understand more about the underlying processes of fertilization in humans and mammals.

Beginnings of artificial fertilization in the 19th century

Austrian embryologist Samuel Schenk started it in 1878: he isolated egg cells of guinea pigs and rabbits. But at this time he was not yet able to fertilize the eggs in a culture dish. Widespread reports of successes in the years that followed have to be viewed with caution from today's perspective. For example, the test protocol that American veterinary practitioner Gregory Pincus used in 1934 when he produced rabbits in the laboratory does not exclude the possibility that the actual fertilization may have taken place.

Only after the transfer of the «fertilized» egg cells by adherent sperm in the uterus. Important observations on the path to IVF were made by researchers during the 1950s in rats amongst other animals. It became clear here sperm first have to spend some time in the female genital tract before they are vigorous enough to swim and actually penetrate the protective membrane of the egg cell. In this phase the outer membrane of the sperm is remodeled and optimized for subsequent tasks.

As a result, the sperm are now first introduced into the uterus of the animals for a time before they are joined with the egg cell in the laboratory. Thanks to this trick, American Min Chueh Chang became the first person to report the birth of rabbits that had been produced in the culture dish in 1959. It was likewise Chang who eventually developed artificial media that conferred the necessary vigor on sperm even without having to spend time in the uterus. The medium that Robert Edwards used in 1969 and enabled him to fertilize human egg cells for the first time originally came from experiments with hamsters.

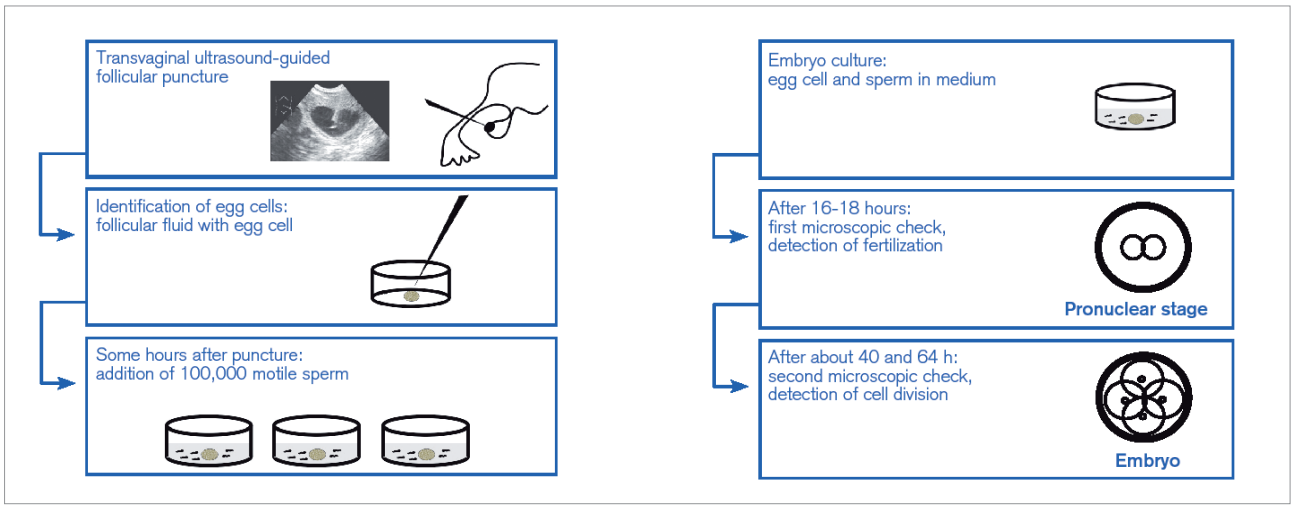

Fig. 3: In-vitro fertilization process, part 1 In-vitro fertilization process, part 2

First «test-tube baby»

But almost another ten years was to pass before the birth of the first «test-tube baby». Despite over a hundred transfers of fertilized egg cells, it initially proved impossible to start a pregnancy in women. Fortunately, Edwards had been working since 1970 with the gynecologist Patrick Steptoe, who managed to isolate egg cells at the right moment, i.e. when fertilization was possible, by means of laparoscopy.

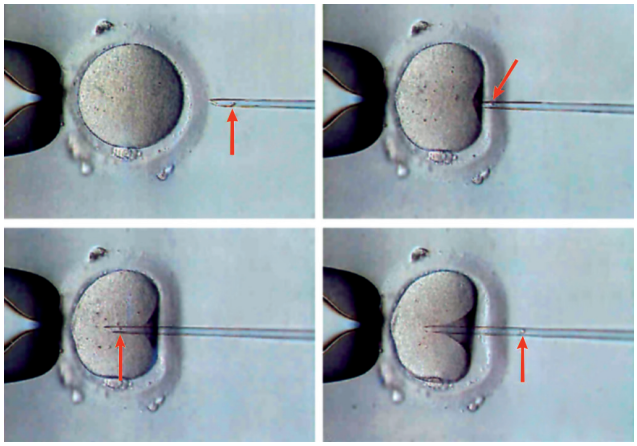

Fig. 4: (clockwise)
Intracytoplasmic sperm injection (micro-insemination). A vital sperm cell is transferred under the microscope into the inside of the egg cell. In ICSI the penetration process of a sperm cell through the various membranes of the egg cell is bypassed, so this treatment is used when the sperm quality is highly com promised.

After studies in mice, Edwards also developed the idea of using hormones to influence the maturation of egg cells before collecting them. The hormone treatment that was intended to promote the maturation of the eggs initially disturbed the implantation process and therefore had to be modified – in Lesley Brown it was decided to forgo the hormone treatment completely and an egg cells was obtained by laparoscopy during the natural cycle. But since 1981 the ovaries have been routinely stimulated by hormones in IVF, as a result of which several follicles mature at the same time. The chances of successful fertilization are increased, because several egg cells can be collected in a single step.

Fig. 5: Two embryos at the four-cell stage. At this stage the embryos are usually transferred back to the uterus.

The success rate of IVF is increasing

Improvements in culture media and the method overall have led to increased success rates in recent years. «Today we have much higher pregnancy rates after IVF than we did 20 years ago. Between 23 and 24 percent of transferred embryos become implanted in the uterus following IVF at our treatment center», says Maria De Geyter, Head of the Reproduction Biology Laboratory at the University Hospital Basel. Culture media and also new techniques are always tried and tested first in the animal model. Despite the great hopes raised in patient and doctor by new techniques, they must not be overhastily introduced into the daily clinical routine. «To date, new methods of assisted reproduction technology have often been propagated too quickly. The problem of malformation problems should have been

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better studied, for example in animal experiments, before ICSI (intracytoplasmic sperm injection) was widely introduced», write Bruno Imthurn and other Swiss specialists in reproduction medicine in the «Schweizerische Ärztezeitung» (no. 36, September 2010).

Every animal experiment must be well-founded

But in reproduction medicine, too, the principle applies that «For every experiment we perform as scientists with and in animals, we need damned good reasons», says Stefan Schlatt, reproduction researcher from Münster. He wants to establish why the production of egg and sperm cell can come to a standstill in cancer patients treated with chemotherapy or radiotherapy. In Münster they are therefore working with common marmosets (Callithrix jacchus) to gain a better understanding of the complex processes and develop methods to preserve fertility despite the cancer therapy.

It would be ideal if we could understand the complicated mechanisms of a body without stressful animal experiment. Unfortunately that is not yet possible today, although researchers have for a long time conducted countless experiments with cells and tissues and, in the age of system biology, are also increasing our knowledge by means of computer simulation. But the dilemma will remain for a long time to come: basic research without experiments in animals would mean abandoning any medical progress. Mausblick aims to explain why and therefore reports on medical success stories that were only possible thanks to animal experiments.

Mausblick is published in collaboration with the Basel Declaration.
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Sources:

Fig. 1: Tages-Anzeiger of January 4, 2011/Fivnat
Fig. 2: www.repro-endo.usz.ch/SiteCollectionDocuments/PatientenUndBesucher/Kinderwunschbroschüre%20D.pdf (page 6)
Fig. 3: www.repro-endo.usz.ch/SiteCollectionDocuments/PatientenUndBesucher/Kinderwunschbroschüre%20D.pdf (page 11)
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