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## Review

# Charles Thibault and assisted reproduction in France\*\*

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**Abstract** – Charles Thibault was liked by French gynaecologists. There was not a year that Charles Thibault did not attend clinician gynaecology conferences. He made great strides in research on in vitro fertilisation, being the first to perform in vitro fertilised (IVF) oocyte transfers in rabbits. Later, in 1978 the first human pregnancy following IVF was achieved in the UK when Louise Brown was born. In 1980, two French teams, one at the Sèvres hospital and the other at the Clamart University Teaching Hospital, carried out egg retrievals in patients with natural cycles, after determination of the urinary LH peak, under general anaesthesia and by laparoscopy. The Clamart team developed LH SIR, which enabled a more accurate determination of the ideal time for egg collection. In 1983, the same team reported the first ambulatory oocyte retrievals by ultrasound, under local anaesthesia. This new technique did not require general anaesthesia. Finally, in 1983, the rate of births, per transfer, for the Sèvres team rose to 5.31%. 1984 showed considerable improvement: 13.83%. The first step in establishing IVF in France was completed with the Carghese symposium, in September 1984, where Charles Thibault pleaded for animal experimentation before human clinical trials. It was only later that ART developed significantly, necessitating a legislative framework and organisations such as GEF and FIVNAT.

### **in vitro fertilisation / embryo transfer / human**

Charles Thibault was liked by French gynaecologists – I would even say *adored* by French gynaecologists. He returned their appreciation and proved it on many occasions. There was not a year that Charles Thibault did not attend clinicians' gynaecology conferences. There was never a meeting where he spoke, that not every seat was filled and that people didn't have to stand. Why? Because he was the man who, after the 1960s and 1970s, the dark ages for fertility in gynaecology, gave us knowledge that the universities would not; he provided us with the latest information on a day-to-day, month-to-month basis. Thanks to him,

the French gynaecological profession was kept abreast of what was happening in research and the possible practical applications. I would like to truly honour Charles Thibault today, because if French gynaecology is to this day internationally renowned, it is in great part thanks to Charles Thibault and his instruction.

Here are two examples of Charles Thibault's dedication. Firstly, Charles Thibault was invited to all of our meetings. He gave clinicians ideas for topics. He was president of the *Société française d'étude de la fertilité* [French society for the study of fertility]; that is where I first met him.

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\*\* This text is the transcription of the oral communication presented at the symposium.

I became president long after him and we enjoyed years and years of work together on the executive committee. He was a major influence in the choice of topics, subjects and authors, and it is thanks to him that there was such an amazing collaboration between research and clinical medicine, which also exists in the United Kingdom, I believe. Outside of these two countries, I cannot think of an example of such invaluable cooperation.

Secondly, Charles Thibault asked me to give a course to students in the reproduction module and talk to them about clinical matters that they had seen at the theoretical level. I did this for twelve years, arriving with clinical slides and human clinical films; this gave students an opportunity to see the application of their research, which I think was absolutely fundamental. I have therefore retained a truly glorious, marvelous memory of Charles Thibault.

I will honour him today by speaking on the beginnings of ART in France.

The birth of Louise Brown opened a new path in human clinical medicine, which I do not need to indicate here, but it was the culmination of years and years of work. I like this slide because it shows how slowly ideas progress. When we think that we discovered spermatozoa and follicles 250 years ago, that we've known about fertilisation for 150 years and that we've been performing artificial insemination for more than 100 years, we can wonder that it took all this time to come up with in vitro fertilisation.

Charles Thibault made great strides in research on in vitro fertilisation, being the first to perform oocyte transfers. Chang, in 1959, also performed a transfer in rabbits. However, Robert Edwards, who is with us today, was the great pioneer and father of this research in humans.

I'll only speak briefly on the patience of Bob Edwards in working on in vitro fertilisation. When he asked clinicians from Cambridge and London for help, he was turned down. He was forced to go see Howard Jones in the United States in 1964 where he

was allowed to obtain oocytes by laparoscopy. He returned in 1967, only to find that the gynaecologists in Cambridge and London still wouldn't help him. He then met Patrick Steptoe, who at the time was a department head in Oldham, 180 miles from Cambridge. They began to work together, with Bob Edwards taking the train back and forth, 180 miles to Oldham, and 180 miles back, to get oocytes and bring them back to Cambridge to fertilise and develop, then take them back to Oldham to put them in a uterus. It required an incredible amount of patience and conviction.

In 1975, the first pregnancy was achieved, an ectopic pregnancy; 32 transfers later, in 1978, Louise Brown was born. During this time, I met Charles Thibault on the executive committee of the *Société française d'étude de la fertilité*, where, knowing that Bob Edwards was already working on IVF, I expressed a desire to do the same in France. Some female monkeys had been made available to Alex Psychoyos and me at INSERM in Saint-Antoine, where I was a TA to Professor Merger. I remember asking Charles Thibault if he would lend us a few of his students to help us perform the in vitro fertilisations. I must say that Charles Thibault did not believe in IVF, didn't think it was likely to work in humans. However, when Louise Brown was born, Charles Thibault demonstrated extraordinary tolerance, clear-sightedness and an ability to admit he was wrong; he called me personally and told me "I have two students, Jacqueline Mandelbaum and Michèle Plachot, who can work with you at the hospital in Sèvres". That is how the Sèvres team was born. René Frydman, disappointed with the results of tubal infertility microsurgery, began working on IVF in 1977 after a meeting with Ondine Bomsel sparked his interest in human follicles and oocytes.

There were two French teams – since I was asked to give a brief history of ART in France – there was the Clamart team with mainly René Frydman and Jacques Testart, and the Sèvres team with Jacqueline

Mandelbaum, Michèle Plachot and myself. In 1979, we were not very successful. In Clamart, they had worked with 25 natural cycles, 9 fertilised eggs, and no pregnancies. In Sèvres, we had 5 natural cycles and 65 HMG/HCG cycles, and 6 fertilised eggs. Both teams greatly progressed, with the Clamart team being the first to demonstrate the exact moment of ovulation so that oocyte retrieval by laparoscopy could be performed just before ovulation, as well as when the oocyte was mature and ready to be fertilised. Clamart showed that it was 36 to 40 h following the LH peak – at the time, we were using urinary LH peaks. Then we too were successful, first demonstrating that the ovarian follicle could be monitored by ultrasound – that was the very beginning of ultrasound. Michèle Plachot did some groundbreaking work on chromosomal abnormalities in oocytes, showing that more than 35% to 40% of the oocytes extracted were incapable of developing correctly. Today this research is still a reference the world over.

In 1980, the Clamart and Sèvres teams, realising that they had thus far achieved nothing individually, decided to collaborate – the first pregnancy was the fruit of this joint effort. We took a patient from Sèvres, performed oocyte retrieval in Sèvres, fertilisation in Clamart and transferred her back to Sèvres. She got pregnant, but we didn't know whose the baby was! However, she had a miscarriage, which removed any need for argument. In 1982, the first two French babies were born, at a three-month interval. They were Amandine in Clamart and Alexia in Sèvres.

That is how the first two French teams were born, one at the Sèvres hospital (*Hôpital intercommunal non universitaire*) under Dr Loffredo, and the other at the Clamart University Teaching Hospital under Prof. Papiernik together with J. Testart, who headed the biological team.

Both teams carried out egg retrieval for natural cycles after determination of the urinary LH peak. This meant performing lapar-

oscopies day and night, Sundays and public holidays included. Their enthusiasm as pioneers in the field is what kept the physicians, biologists and hospital staff persevering despite the difficult conditions. Let us not forget that, in 1978, very few physicians or biologists understood immediately what IVF meant for the future of reproductive medicine. But those at Sèvres and Clamart were inspired by a desire to succeed, innovate, understand their failures and to know why a rival team had succeeded where they had not. There was not a lot in the way of resources, but there was dedication and faith in success that brought together the first teams from the four corners of the world. The friendships developed during this time still remain today. A spirit of friendly competition existed during the first few years of IVF techniques in France. The first successful birth was not until 1982 but there was much collaboration in the years prior to that. In 1980, an article was published on the effect of gonadotrophins on the human follicle in vitro. The authors included: J. Testart, A. Gougeon, R. Frydman, O. Bomsel and Jean Cohen [1].

Both teams worked in public establishments and the patients did not have to pay for their attempts at IVF. The medicines and research were reimbursed by the French public healthcare system and hospital stays were free, as were any medical procedures performed during those stays.

The Clamart and Sèvres teams oriented themselves towards specialised research. From this time until 1981, remember, egg retrievals were performed on patients with natural cycles, under general anaesthesia, by laparoscopy. There was much uncertainty surrounding the determination of the preovulatory LH peak. R. Edwards used Higonavis to test urine samples every 4 h. The reactant used was expensive and there were a great number of urine samples to be tested. Egg collection was performed at any time of day or night and during the laparoscopy, ovulation was sometimes discovered to have already occurred. Both teams soon

received assistance from the *Fondation de recherche en Hormonologie* [Foundation for research in hormonology] which had for several years expertly carried out most hormone assay in Paris, first based on urine samples, and, later on, serum. As we saw previously, the Clamart team developed LH SIR, which enabled a more accurate determination of the ideal time for egg collection [2]. Most importantly, it was now possible to determine the time of ovulation according to the beginning, rather than the peak, of the LH surge. This allowed for more effective collection.

In the early days of IVF at the intermunicipal hospital of Sèvres, setting up a laboratory on site was materially impossible. Jacqueline Mandelbaum and Michèle Plachot, however, had the technical capacity at the INSERM unit headed by Professor de Grouchy at Necker Hospital. In 1981, we adopted a protocol to allow us to transport oocytes collected (by laparoscopy at first) in an ordinary thermos at 37 °C. In most cases, it was the biological father who transported the thermos to the lab, by taxi, as fast as possible (90 min on average). The resulting embryos were brought back by the biologists in the same thermos, then transferred. We did achieve some success in this way, obviously, with a few inconveniences. These included changes in temperature which were discovered upon arrival at the laboratory (sometimes > 38–40 °C, which lowered the fertilisation rate) and, on rare occasions, husbands who got lost on their way to the laboratory! This technique, also used by J. Testart and W. Feichtinger, proved very useful and effective at the beginning of IVF for teams that did not have laboratory facilities. Getting started was difficult. You had to go abroad to purchase Higonavis kits to detect LH in urine.

Yves Menezo (1976) developed the first B2 culture medium in the world. It was widely used by French teams and therefore known as “French milieu” abroad. Menezo’s B2 is a specific medium that mimics follicle, tubal and uterine media in sheep, rabbits

and humans. The beginnings of IVF in France enjoyed the assistance and extensive experience in animal research of INRA researchers. Professor Thibault headed the Animal Physiology Station, where Y. Menezo, M. Plachot and J. Testart also worked, along with many other, younger, biologists. French IVF centres thus benefited greatly from biologists specialising in animal research.

As early as 1979, in cooperation with J.P. Pez, we began to monitor the growth of follicles by ultrasound. In a study on 40 patients [3], we demonstrated that there existed a good correlation between observations made by ultrasound and those made by laparoscopy. Already at this point we had suggested that ultrasound diameter was a better indication of follicle maturation than hormone assay.

In France, the first IVF baby, Amandine, was born in February 1982 in Clamart; the second, Alexia, was born in June of the same year, in Sèvres. The two years that followed saw an expansion of IVF centres in France. J. Salat Baroux (Tenon) also began to work jointly with the biological team of J. Mandelbaum and M. Plachot.

Meanwhile, in Montpellier, Bernard Hedon in the department headed by Jean L. Viala, together with Olivier Flandres performed IVF for the first time in 1981. The third transfer resulted in pregnancy, which was aborted at Christmas 1981 and, finally, the group’s first birth took place in July 1983. On 3 September 1981, Bob Edwards, Patrick Steptoe and Jenny Purdy invited the “pioneers” of IVF to Bournhall, in particular those who had already achieved pregnancies: H. Conti, and G. Jones, W. Feichtinger, S. Szalay, J. Testart, R. Frydman, P. Lieberman, J. Dyer, J. Cohen, M. Plachot, L. Hamberger, L. Nilsson, T. Hillensjö, L. Mettler, V. Baukloh, A. Lopata, I. Johnston, A.L. Speirs, A. Trounson, J.F. Leeton, S. Fishel and J. Webster. (Jacqueline Mandelbaum was giving birth in France at the time.) At the time, oocyte collection was carried out with natural cycles, so the major difficulty

**Table I.** The notes of J. Cohen – September 4, 1981.

	Melbourne Johnston	Austria Feichtinger	France Frydman	France II Cohen	USA Jones	UK Steptoe	Germany Metler
Laparoscopy	130	68		77	31	330	149
Follicles	368						
Eggs	265		109	52	50		
Laparoscopy at least 1 oocyte	114			35	27	263	98
Fertilisation	154	24	59	16	16	203	70
Laparoscopy with 1 or more embryos	93					197	29
Transfers	78	19	24	5	12	195	3
Pregnancies	4	4	5	2	2	44	0
Abort	1		2	2		7	
Clin ab	2 before		2	1		9	
>10 weeks continuing	1		1		2	28	

The results of A. Trounson are not figured.

was determining the exact time to puncture the follicle, using the only measurements available, that is, oestradiol assay, LH assay and progesterone assay. I will mention just a few important points from my handwritten notes. The first major discussion dealt with how many hours following the LH peak retrieval should occur. "Anywhere from 2 to 6 h is suggested and Lopata indicates a period of 26 to 36 h after the initial surge, determined by ultrasound. R. Edwards suggests 26 h after the first LH-positive urine test. Maturing in vitro is suggested by Steptoe when collection is premature, which A. Trounson agrees with; he says eggs may be collected up to 12 h in advance in animals. R. Frydman speaks about Clamart's experimentation with LH SIR."

Most noteworthy was the discussion on the use of ovulation stimulants. "A. Trounson and J. Leeton say they use clomiphene to obtain more oocytes, therefore more embryos and more pregnancies. They indicate that a good follicle produces 300 pcg of E<sub>2</sub>; they are apparently already using follicle diameter for prognosis. R. Edwards and P. Steptoe remain sceptical, having experienced fail-

ures with clomiphene. J. Cohen speaks of French experiments with HMG outside of IVF. H. and G. Jones say they use HMG + HCG in patients with normal cycles. They consistently administer HCG at 7:30 p.m., then perform egg retrieval 36 h later. All the participants conclude that ovulation stimulation leads to more oocytes and therefore more pregnancies, and that it will improve retrieval timing."

The successful experiences of various teams, as discussed on 4 September 1981, are in Table I.

I do not have room here to go into the numerous discussions on embryo transfer, luteal phase treatment or the ethical problems which had only minor consequences later on.

In February 1982, J.P. Renard carried out mammalian embryo cryopreservation. In the months following, J. Testart and J.P. Renard developed a cryopreservation protocol that is still used today.

In 1983, J.H. Ravina and the Clamart team reported the first ambulatory oocyte retrievals by ultrasound, under local anaesthesia. This new technique was simpler,

less costly and did not require general anaesthesia.

M. Plachot's research starting in 1984 and particularly in 1986 [4] led her to publish the first long series of cytogenetic analyses of human oocytes and human embryos as well as the effects of fertilisation abnormalities on embryo development. Her work explained why implantation rates are so low in humans. Michèle Plachot also described, in 1986, the very first stages in timing fertilisation. In 1985, Jacqueline Mandelbaum and Dan Szollosi described the ultrastructural particularities of the human oocyte. These have become fashionable in recent years under the term "oocyte dysmorphisms" [5]. New indications for IVF were discovered: tubal abnormalities with stenosis, endometriosis, oligospermia and immunological infertility. Egg donation began to develop. At the time, stimulation protocols mainly involved clomiphene + HMG + HCG. Each team sought to understand the reasons for implantation failure. In 1982, we demonstrated the prognostic value of the HCG curve after embryo transfer [6].

Finally, in 1981, the rate of births for the Sèvres team was 2.08% and 6.25%, per oocyte retrieval and per transfer, respectively. The same rates rose to 2.52% and 4.78% in 1982 and to 3.22% and 5.31% in 1983. 1984 showed considerable improvement: 9.83% and 13.83%.

New centres were set up in various regions; it would be impossible to mention them all. Alain Audebert opened a centre in Bordeaux, with the first baby being born on 08 August 1983. In 1983, too, Jacques Montagut opened a centre in Toulouse and, in 1987, organised the first ESHRE ethics meeting.

GEFF (working group for in vitro fertilisation in France) was created in 1986, as was FIVNAT, the leading French IVF register, coordinated by INSERM Unit 292.

The first babies born following embryo cryopreservation were Australian (A. Trounson and L. Mohr) and Dutch (G. Zeilmaker), but it was Jacques Testart's team who, in 1985, published excellent

results using propanediol-sucrose as cryoprotectants for early-cleaved embryos, instead of DMSO. This is currently the most used protocol in the world [7]. In 1987, J. Mandelbaum [8] showed that embryos with morphological abnormalities were less resistant and demonstrated the damaging effects of blastomere loss on thawing. In 1988, she reported on the freezing of immature oocytes and the problems associated with it, which remain true today.

As early as 1983, J. Belaisch-Allart and the Clamart group suggested laparoscopy under local anaesthesia for egg collection [9].

In May 1983, a conference was held in Bari during which a total of 197 intrauterine pregnancies and 13 ectopic pregnancies were described.

As early as 1984, M.J. Mayaux and I, together with colleagues, took inventory of some 2 342 pregnancies between 1979 and 1984 in 55 international IVF centres. For the first time, it appeared that the rate of deformities (2.5%) had not gone up. The percentage of ectopic pregnancies in the series was 4.6%. We emphasised the higher frequency of ectopic pregnancies than in natural reproduction. We drew up several hypotheses and discussed the role of clomiphene which, at the time, was used in combination with HMG. We determined that there were 5.7% ectopic pregnancies when clomid was used versus 2.5% if HMG was used alone. The proportion of ectopic pregnancies today has diminished concurrently with the reduced use of clomiphene.

In 1984, P. Dellenbach [10] suggested ultrasound-guided transvaginal oocyte retrieval, estimating that it would be successful in 30% of cases. J.P. Pez [11] and I published a series of 85 egg retrievals with an 88% success rate and a 16% pregnancy rate per transfer.

In 1984, we published an article on 113 cycles in 88 patients [12] for which the luteal phase had been analysed after oocyte retrieval. We were able to show that E2 levels in the same patient with the same HMG

levels varied substantially from one cycle to another, as did levels of E2 and progesterone in the luteal phase. Nineteen endometrial biopsies analysed by J. de Brux did not show a correlation between anatomical criteria and hormone levels; nor did it provide an explanation for the implantation failures.

In early 1984, Robert Edwards suggested he might come to Sèvres to assist the biological team. We found him a very humble room in the hospital. During his time in France, he also took the opportunity to meet the biologists from Clamart. I invited R. Edwards several times to my house for dinner, where we discussed the European situation. In order to make their results known, European centres had to publish in the USA, either at the American Fertility Society's annual meetings, or in the journal *Fertility Sterility*. We agreed on the necessity of a European Society. Let us remember that, at that time, not everyone supported the idea of a European collaboration. R. Edwards and I, however, were confident, enthusiastic and determined. In May of the same year, at the Helsinki Congress, we put up a sign summoning anyone interested in a European Society to a meeting. One Friday morning at 11 a.m., without a meeting agenda, twenty people decided to create what would later become known as ESHRE.

In the early days of IVF, there were some egg donations made. Since there were no laws or regulations on donation, each team adopted its own policy. Anonymous donations were made in Clamart and Tenon. In Sèvres, we decided on the principle of voluntary, anonymous donations by patients having opted for an IVF cycle:

- One oocyte if 7 to 10 were collected.
- Two oocytes if more than 10 were collected.

Oocyte donations observed the same criteria as sperm donations, both being anonymous and free.

In September 1984, a symposium was held in Carghese (Corsica) to review the situation of assisted reproduction with advo-

cates of IVF and ultraconservatives. It was an opportunity to look at the experience we had gained as well as the uncertainties of the time\*.

Among the main ideas, I will cite just a few:

- C. Thibault's plea for animal experimentation before human clinical trials. R. Edwards and J. Testart were already pointing to differences in, for example, the use of clomiphene;
- the role of the dominant follicle by G. Hodgen;
- timing of HCG injections by R. Frydman and J. Testart;
- ultrasound-guided oocyte retrieval under general anaesthesia (J. Belaisch);
- human sperm fertility tests (J. Mandelbaum);
- oocyte fecundability (M. Plachot);
- embryo quality (Y. Menezo);
- embryo cryopreservation (J.P. Renard);
- luteal phase after IVF (H. Jones);
- oocyte donation (A. Trounson);
- calling into question of clomiphene and premature LH peaks (R. Edwards).

These were the major areas of interest for the scientific community at the time with regard to the conditions and consequences of follicular stimulation and parameters for growth and embryo quality.

To conclude, I would like to read a passage from an article Charles Thibault published in *Contraception Fertilité Sexualité* in 1998:

“Abnormalities observed in the gametes can also involve genes responsible for somatic

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\* I have arbitrarily chosen to stop this brief history of ART in 1984, because the first step in establishing IVF in France was completed with the Carghese symposium. It is only later that ART developed significantly, necessitating a legislative framework and organisations such as GEFF and FIVNAT. I have no doubt forgotten to mention several clinical or biological activities and apologise ahead of time to those whom I may have left out.

functions, enzymes in the mitochondria respiratory chain, recognition molecules and/or cell fusion, for instance. The fact that offspring are normal simply means that the abnormality is not dominant and that it will be expressed later on during fertilisation by a gamete carrying the mutated allele. This is the case with aplasia of vas deferens and cystic fibrosis. ICSI is therefore only acceptable when it is sure that the gametes used are not carriers of chromosomal or genetic abnormalities, which reduces the reasonable use of the technique and will continue to do so as new discoveries in molecular genetics are made. In all other cases, the acceptance of the couple who has been informed of the probable consequences for their offspring does not free the conscience of the gynaecologist, who, like any physician, is meant to cure disease and not contribute to the spread of it.”

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