

Journal für

Reproduktionsmedizin und Endokrinologie

– Journal of Reproductive Medicine and Endocrinology –

Andrologie • Embryologie & Biologie • Endokrinologie • Ethik & Recht • Genetik
Gynäkologie • Kontrazeption • Psychosomatik • Reproduktionsmedizin • Urologie



Management of Infertility: Past, Present and Future (from a personal perspective)

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J. Reproduktionsmed. Endokrinol 2013; 10 (Sonderheft
1), 13-22

www.kup.at/repromedizin

Online-Datenbank mit Autoren- und Stichwortsuche

Offizielles Organ: AGRBM, BRZ, DVR, DGA, DGGEF, DGRM, D-I-R, EFA, OEGRM, SRBM/DGE

Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz



ENDO FERTI FORUM

ENDOKRINOLOGIE & FERTILITÄT
FÜR KLINIK & PRAXIS

20.-21. März 2026

Universitätsmedizin Mainz

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Management of Infertility: Past, Present and Future (from a personal perspective)

B. Lunenfeld

■ Early Understanding of the Reproductive Process

The first systematic records besides the bible that deal with fertility to be studied were Egyptian papyrus documents: the Kahun Gynecological Papyrus (1825 BC) devotes approximately 25 pages to a range of interesting cures for women's ailments [1]. Diagnosis was based on the premise that the genital organs were in continuity with the rest of the body, and in particular with the digestive tract, a concept that was subsequently embraced by Hippocrates and medieval physicians.

The next recorded advance in knowledge about infertility came from the Arab school, 700–1200. Avicenna, or Ibn Sina (980–1037), was a Persian physician, philosopher and scientist who introduced the concept that infertility could be masculine or feminine in origin; it could be due to an abnormality of the genital tract, or to psychological troubles such as melancholy or apprehension [2].

This era was followed by a period of scientific progress during the Renaissance, particularly in Italy. Leonardo da Vinci's beautiful drawings illustrated detailed anatomy, and Vesale published his atlas *Humani Corporis Fabrica* in 1543 [3], which included cross sections of the female pelvis. The tubes, clitoris, vagina and placenta were described by Fallope [4], and the ovary and follicles by De Graaf in 1672 [5]. Contributions to the field of infertility continued between the 17th and 19th centuries, there were many contributors to our knowledge of the reproductive process. Some of them included: Antoine van Leeuwenhoek [6], a microscopist who, amongst his many other discoveries, was the first to conduct rigorous observations on human spermatozoa, Karl Ernst von Baer [7], an embryologist, identified the mammalian oocyte and Oscar Hertwig [8], who dis-

cerned that fertilization involved merging of two cell nuclei, egg + sperm cell.

■ The Beginning of Endocrinology (Fig. 1)

In 1849, Arnold Bethold found that a rooster's comb is an androgen-dependent structure. Following castration the comb atrophies, aggressive male behaviour disappears, and interest in the hens is lost. Importantly, Berthold also found that these castration-induced changes could be reversed by administration of a crude testicular extract [9]. This was followed by Claude Bernard, a French physiologist, who was the first to define the term „*milieu intérieur*“ in 1860 [10]. Finally the introduction of the term „hormone“ by Starling and Bayliss in 1905 [11] marked the beginning of endocrinology.

The observation of Crowe, Cushing and Homans in 1910 [12], suggesting the pituitary as having a role in regulating the gonads [13] can be described as the beginning of reproductive endocrinology (Fig. 2). They demonstrated that partial pituitary ablation resulted in atrophy of the genital organs. In 1912, Aschner [14] confirmed the findings of Crowe and observed that diseases, tumors, or injuries of the hypophysis, pituitary stalk, medulla oblongata or above lead to hypopituitarism and gonadal atrophy. In 1926, Zondek found that the implantation of anterior pituitary glands evoked a rapid development of sexual puberty in immature animals. In 1927 Smith showed that hypophysectomised immature male or female animals failed to mature sexually. Only 2 years later, Zondek [15] proposed the idea that the pituitary secretes two hormones that stimulate the gonads. He named these biological substances “Prolan A” and “Prolan B”. He postulated that Prolan A stimulated follicular growth, that Prolan A together with Prolan B stimulated the secretion of “folliculin”, and that Prolan B induced ovula-

tion, the formation of the corpus luteum and the secretion of lutein and folliculin. These two hormones induced glandular transformation of the endometrium, with endometrial proliferation, and also caused changes in the vaginal epithelium. Zondek realized that the dynamics of Prolan A secretion by the anterior pituitary and the correct timing of Prolan B discharge are responsible for the rhythm of ovarian function: this in turn controlled the proliferation and function of the endometrium to create optimal conditions for nidation of the fertilized egg. If we merely change the names of Prolan A and B to follicle stimulating hormone (FSH) and luteinising hormone (LH), and the names of folliculin and lutein to estrogen and progesterone, we can see that by 1930 Zondek had described the pituitary-gonadal relationship as we know it today. However the molecular mechanism of the action of gonadotropins was not known for another 3 decades. The „Utilization Theory of Gonadotropin Clearance“ had been proposed in the 1950's, but remained unproved [16]. In the 1960s it became clear, that normal follicular development, oocyte maturation and ovarian steroidogenesis are based on the “two-cell, two-gonadotropin theory” [17] and that

- under the influence of LH-activity, the theca cells convert cholesterol to androgens
- the resulting androgens are transferred to granulosa cells where, under the influence of FSH activity, they are converted into estradiol (via aromatase activity)
- LH also acts on granulosa cells during the late follicular phase
- the co-ordinated activity of FSH and LH between the follicular granulosa and theca cells results in oocyte maturation, follicular growth and estradiol production.

Following the report by Yalow and Berson of iodination of glycoprotein hormones [18] and after their visit to our

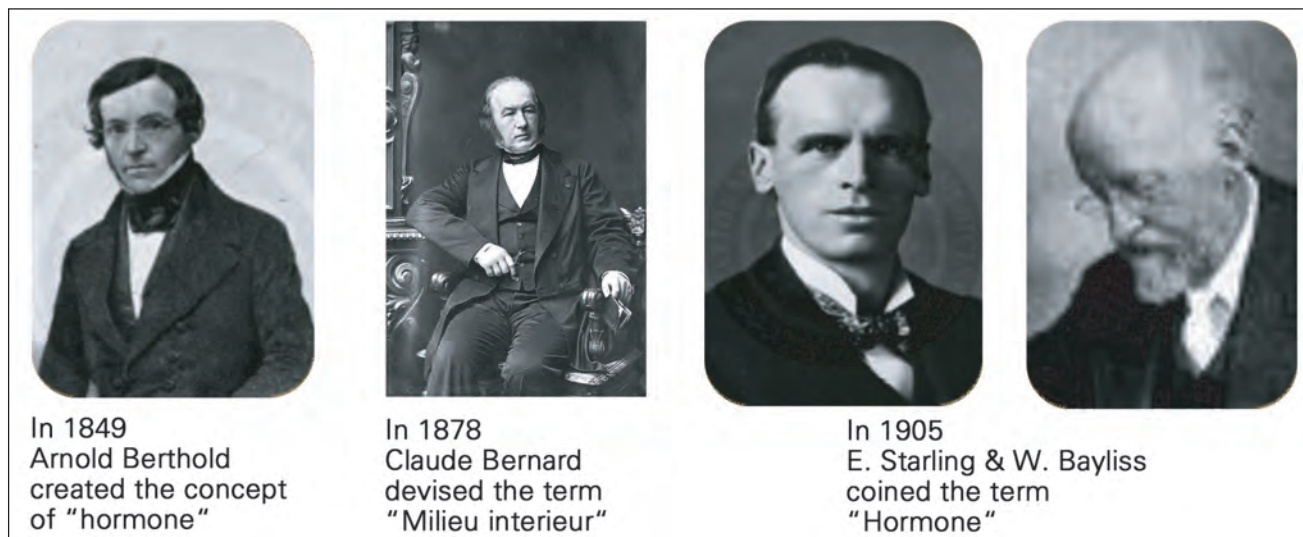


Figure 1. The "fathers" of endocrinology.

laboratory we labeled hCG with radioactive Iodine. We then injected the radio-labeled HCG to rat ovaries and demonstrated in 1967 specific uptake of hCG by the ovaries [19]. This was independently confirmed by Naftolin et al. [20]. Only 25 years later was the LH and hCG receptors cloned and shown to share a common receptor protein [21].

■ The Conquest of Hormone Dependent Infertility

The early discoveries in the 1930s revealing the physiological action of gonadotropins in the normal ovarian cycle tempted many scientists to seek gonadotropic extracts with sufficient purity to allow their use in the treatment of infertile patients suffering from gonadotropin deficiency.

Gonadotropins, such as pregnant mare serum gonadotropin (PMSG), were first introduced for ovarian stimulation in 1930 and the first pregnancy using the combination of PMSG and hCG was reported by Mazer et al. in 1945 [22]. However, use of PMSG lead to antibody formation, and had to be withdrawn.

While doing my PhD on the effects of estrogen and testosterone on menopausal symptoms with Professor De Watterville [23], we observed that urinary extracts from menopausal urine stimulated the growth of uteri and ovaries of immature mice and rats. Since menopausal urine contained no estrogens, it became clear to us that we extracted gonadotropins and that menopausal urine con-

tained elevated amounts of gonadotropins. In 1954 we demonstrated that, using the kaolin-acetone method for processing urine [24], it was possible to extract gonadotropins from menopausal urine. Menopausal gonadotropins (hMG) injected into immature rats were capable to stimulate follicular growth in ovaries and spermatogenesis in the testis [25]. Following these observations we predicted its future clinical use [26]. However this was met with skeptics as demonstrated by Frank Stabler's paper in 1954 [27] where he wrote: [...] *"I think I can say that I know of no hormone available to me that will make a woman ovulate naturally"*. It was extremely difficult to convince a pharmaceutical company to engage in a project that needed massive urine collections, safety concerns and the development of industrial extraction procedures based only on our animal experiments and our hypothesis. In 1957 I contacted Pietro Donini, then a senior scientist at Serravallo Institute, who had already extracted hMG and he invited me to visit Istituto Farmacologico Serravallo to discuss with their board of directors the possibility of mass production of hMG and the initiation of clinical trials. I presented our findings to the board, but could not convince them.

¹After the Italian government in 1969 restricted the Vatican tax freedom Pope Pius decided to transfer the Vatican fortune from Italy and Fabio Bertarelli bought a controlling stake from the Vatican in 1974 and by 1977 had moved the company to Geneva. Sidona, a famous tax attorney later murdered in prison in Italy having been deported from the USA was the intermediary.

Since 1952 the Vatican had a major share of the Istituto Farmacologico Serravallo and fortunately one of the directors, Don Giulio Pacelli, a representative of the Vatican and nephew of the Pope, was interested in my project and following long and interesting discussions with me and Dr. Donini returned to the board, declaring that old age homes of nuns would provide the required urine and thus convinced them to undertake this project. About 300 women participated in these collection centers and this permitted to produce enough hMG to start clinical trials. The purity of the available preparations was only 5%, containing both FSH and LH. However, in the absence of an alternative, they were accepted by both the regulatory agencies and the scientific community.

In 1959 with a grant (C 4377) from the National Cancer Institute United States' Public Health Service a workshop conference on human gonadotropins was held in Gatlinburg, Tennessee [28]. It was at this conference, that we reported our first clinical trials in hypo pituitary hypogonadic men and women with hMG [29].

In 1960 we presented the clinical effects of human post-menopausal gonadotropin in men and women at the First International Congress of Endocrinology, Copenhagen [30]. In 1961 we concluded that amenorrheic hypogonadotropic women needed 6.8–13.6 mg (75–150 IU/day), of hMG (Pergonal 22A,®) depending on individual sensitivity, in order to stimulate their ovaries to produce estro-

Early Discoveries in Human Reproduction



In 1910

Crowe, Cushing & Homans demonstrated that partial pituitary ablation resulted in atrophy of the genital organs



In 1912

Aschner observed that diseases, tumors, or injuries of the hypophysis, pituitary stalk, medulla oblongata or above lead to hypopituitarism and gonadal atrophy



In 1926

Zondek showed that the implantation of anterior pituitary glands evoked a rapid development of sexual puberty in immature animals



In 1930

Smith showed that hypophysectomized immature male or female animals failed to mature sexually

Figure 2. The “fathers” of human reproduction.

gens [31]. Treatment was monitored by daily 24 hour urinary estimations of estradiol, estron and estriol and the luteal phase confirmed by extracting pregnanediol and weighing the crystals. However, it took 7 years from our first animal experiments till we reported the first successful induction of ovulation followed by pregnancies in hypogonadotrophic anovulatory women, using a sequential step-up, step-down regimen with hMG-Pergonal 25E–35 [32]. The starting dose in our first patient was 240 mg of the international reference preparation of human menopausal gonadotropins (IRP-hMG). This corresponded to 150 IU daily, it was then gradually increased to 360 mg (225 IU), then to 480 mg IRP-hMG (300 IU), then gradually reduced to 360 mg and finally on day 11 and 12 to 240 mg IRP-hMG daily. Ovulation was induced by administration of 10,000 IU of hCG followed by 10,000 and 5000 IU of hCG on consecutive days (Fig. 3).

This hCG dose was sufficient to maintain corpus luteum function until endogenous hCG appeared about 13 days later. The entire pregnancy was monitored by weekly estradiol, estriol, estrone, pregnanediol and hCG determinations until the birth of a healthy child. The 2. and 3. case treated similarly aborted on day 90

and 93 respectable. These 2 cases represent for the first time the dynamics of an abortion due to corpus luteum deficiency. In both of these cases it is interesting to note, that although the level of hCG was still rising the daily Pregnanediol secretion decreased (Fig. 4), in the third case we tried to save the pregnancy with the administration of 10 mg medroxy progesterone acetate (MAP) and 0.1 mg ethinyl estradiol daily and an injection of 100 mg progesterone on day 55. This was followed by a rise in pregnanediol (probable metabolism of the injected progesterone) and a further decrease of estriol, estrone, and estradiol followed by an abortion on day 93 (Fig. 5) [33].

Donini and myself convinced Fabio Bertarelli, then a senior executive at Istituto Serono, to provide hMG-Pergonal 25E–35 to my colleagues in France and the USA. Our results on ovulation induction followed by pregnancies were then confirmed by Palmer and Dorangeon [34] as well as by Salomon and Netter [35] in France, Rosenberg and colleagues [36], Jones [37] and Taymor et al [38] in the USA. Furthermore a similar result was obtained by Karl Gemzel using gonadotropins extracted from pituitary glands of cadavers [39]. Apostolakis, Bettendorf and Voigt then demonstrated that ovulation followed by pre-

gnancy could also be induced in hypophysectomized women [40]. Very quickly it became evident that ovulation induction with gonadotropins has an increased risk of multiple pregnancies and ovarian hyperstimulation syndrome [41, 42].

In 1972 the World Health Organization (WHO) Expert Committee on biological Standardization under my chairmanship defined the international unit (IU) for FSH and the IU for interstitial cell stimulating hormone (ICSH) (LH) as the respective activities contained in 0.2295 mg of the IRP-hMG [43]. This permitted to use standardized doses of gonadotropins. Monitoring treatment with the cervical score helped to reduce the number of estrogen estimations and excessive stimulation [44].

In 1973 the WHO convened a scientific group meeting in Geneva, chaired by myself [45]. During this meeting, guidelines for the diagnosis and management of infertile couples were developed and a classification system of amenorrheic states was recommended [46] (Fig. 6a). The effective daily dose for hypogonadotrophic patients was reported to be in the range of 150–225 IU, and for anovulatory normogonadotrophic patients 75–150 IU. It was also noted, that the ratio of FSH to LH varies in different HMG

preparations, but the available evidence indicated that preparations with ratios of 0.1–10 were acceptable therapeutic agents provided that a sufficient total dose of FSH was administered to the patient [45].

In 1961 [47] we succeeded in producing antibodies to human gonadotropins, and in 1967 [48], by using an immune-purification technique with polyclonal anti-hCG antibodies (cross reacting with LH), an FSH preparation free of LH could be obtained from hMG. The final product (Metrodin) contained 150 IU of FSH and < 1 IU of LH per mg of protein. We could demonstrate that purified FSH preparation was capable of stimulation follicular development in immature mice, without causing stimulation of the uteri [49]. This supported the “2-cell, 2-gonadotropin” theory, previously suggested by Ryan [17]. Our findings confirmed that FSH without LH is incapable

of initiating steroid production which is responsible for uterine growth.

Further technological advances made it possible to replace polyvalent antibodies with highly specific monoclonal antibodies. As a result of the improved processing, this FSH preparation (Metrodin HP) contained less than 0.1 IU of LH activity and less than 5% of unidentified urinary proteins. The specific activity of the FSH was increased from approximately 100–150 IU/mg of protein in purified urinary FSH preparations (Metrodin) to about 9000 IU/mg protein in the highly purified product (Metrodin HP). The purity was also increased from 1–2% to 95%.

Yalow and Berson developed a system by which they “tagged” a known sample of insulin with a radioisotope, then mixed a blood sample of unknown content with a complex of that tagged insu-

lin and its antibody [50]. Because the antibodies regularly abandoned the tagged hormones for any “naturally occurring” hormones of the same sort, they found that the amount of “stranded” radioactive hormones in the final mixture reflected precisely the amount of the same hormones occurring in the sample being tested. This was to become the starting point for radioimmunological determination of insulin and, later, for all peptide as well as steroid hormones in blood, other fluids and tissues.

The advancement of radio-immunoassays for steroids, ultrasonography to monitor follicular development [51] and well standardized preparations of gonadotropins permitted to develop different treatment protocols. The low dose regimes with the combined use of serial ultrasonography and estradiol measurements have reduced hyperstimulation risks significantly.

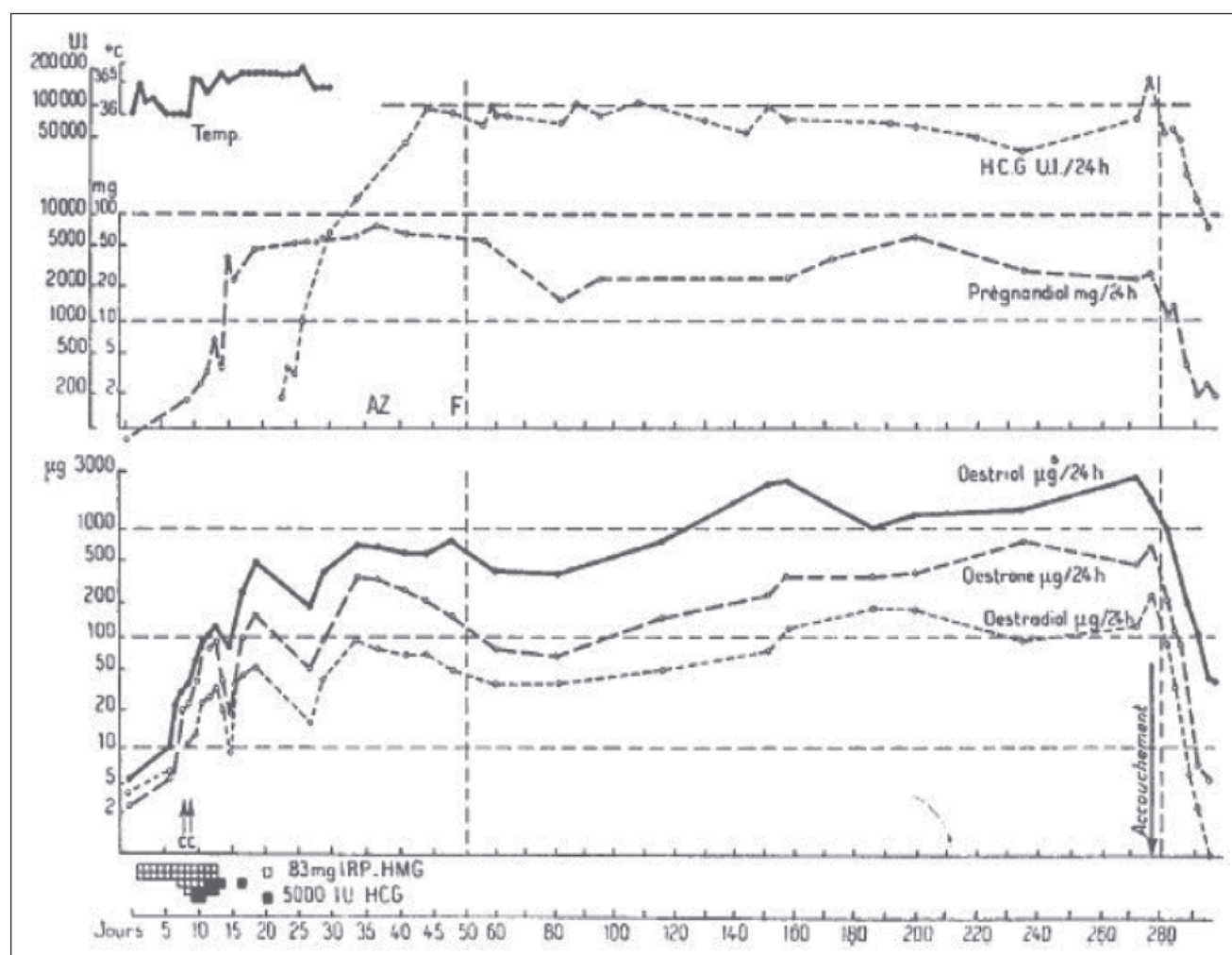


Figure 3. Hormonal pattern during follicular phase, ovulation, luteal phase and pregnancy following stimulation with hMG (step up, continuous and step down) of a primary amenorrhic patient with hypopituitary hypogonadism. Mod. from [33].

On April 20th, 1985 I had scheduled a meeting with Karl Gemzell in New York. In the early morning I read in the news paper that 3 deaths had occurred in individuals, who were treated with the pituitary growth hormone (GH) 8 years earlier. At lunch Karl said to me “*what happened with GH may also happen to pituitary FSH*”. He was correct. The hPG preparations were abandoned when cases of iatrogenic Creutzfeld-Jakob disease (CJD) were recognized [52, 53] in patients who were treated with them.

In 1961, Greenblatt et al [54] demonstrated, that clomiphene citrate (CC) was capable of stimulating follicular development followed by ovulation in unovulatory women (WHO II). In 1966, we could demonstrate that ovulation could also be induced with CC in amenorrheic women with galactorrhea [55]. At the same time we discovered that ergocornine inhibited prolactin in rabbits and assessed the effect of ergocornine administration to women [56, 57]. But only 10 years later, in 1973 [58], Br-ergocryptine (CB 154) was shown to be safer and could restore ovulatory function and fertility in women with elevated prolactin levels.

In 1963 Guillemin described the partial purification of an hypothalamic factor (LRF) stimulating the secretion of pituitary luteinizing hormone (LH) [59] and demonstrated induction of ovulation by purified LRF in animals rendered anovulatory by hypothalamic lesion [60]. In 1971 the group succeeded in the total synthesis by solid phase of a decapeptide stimulating the secretion of LH and FSH pituitary gonadotropins [61]. At the same time Schally et al [62] structurally identified the gonadotropin releasing hormone (GnRH) as (pyro)Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂ and synthesized it. He also demonstrated that this peptide represents the hypothalamic hormone regulating the secretion of both LH and FSH.

In 1975 our attempt to induce follicular growth by continuous nasal administration of GnRH failed. However, we were able to demonstrate that it was possible following follicular stimulation with hMG to induce ovulation with intranasal self-administered gonadotropin releasing hormone [63]. Only after Knobil and his group showed that continuous GnRH

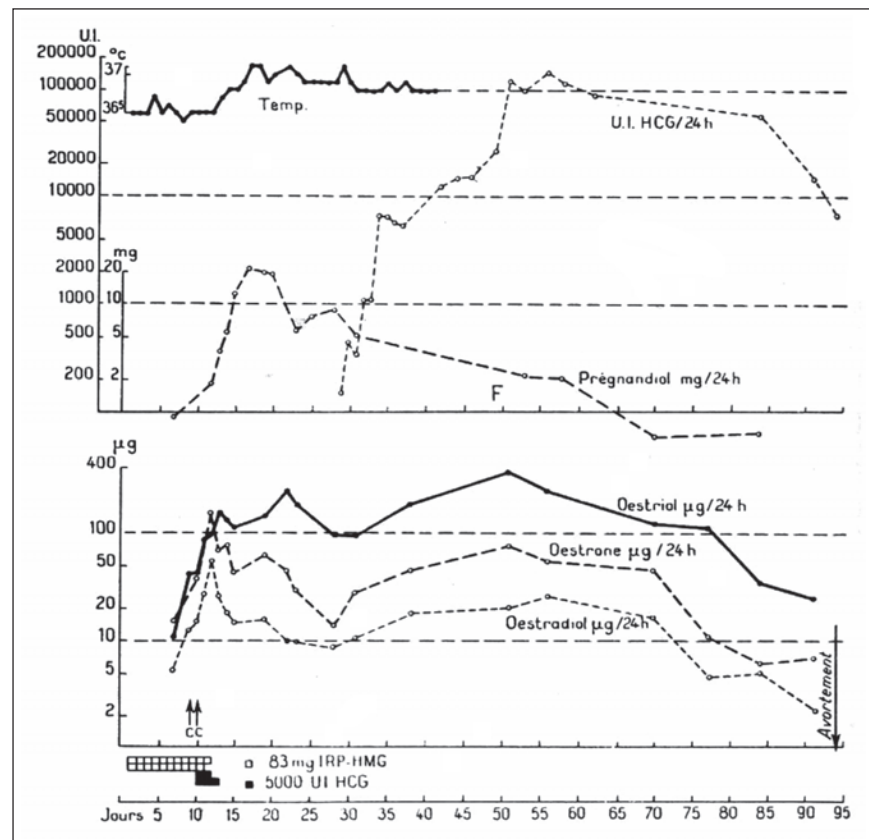


Figure 4. Hormonal following treatment with hMG followed by ovulation and Corpus luteum deficiency and abortion in a primary amenorrheic patient with hypopituitary hypogonadism. Mod. from [33].

administration inhibited gonadotropin and only pulsatile GnRH administration stimulated gonadotropin secretion [64], Leyendecker reported the successful induction of pregnancies with pulsatile administration of GnRH patients with severe hypothalamic amenorrhea [65].

Thus in the mid 1980s, there was a consensus that replacement therapy with the administration of GnRH in a pulsatile rhythm corrects the deficiency of endogenous GnRH secretion and stimulates via stimulation of gonadotropins the function of peripheral target organs. If given continuously, GnRH leads to desensitization of pituitary GnRH receptors and inhibition of LH and FSH secretion. Potent and long-acting agonistic GnRH analogs have been synthesized which are capable of producing a selective gonadotropin inhibition.

Having learned to control gonadal activity by inhibiting gonadotropins by GnRH or stimulating gonadal activity by gonadotropins the last 50 years have seen an unprecedented leap of knowledge to control the reproductive processes. With the availability of hMG, clo-

miphene citrate, ergot derivatives GnRH agonists and antagonists, algorithms were developed for their optimal utilization. These developments contributed to the conquest of hormone dependent infertility in both men and women.

The main agents for controlled ovarian stimulation for assisted reproductive techniques (ART) were gonadotropins and GnRH analogues. Recombinant DNA technology now allows the production of pharmacologically active pure FSH, LH and hCG preparations in unlimited quantities, minimizing the risk of disease transmission via biological contamination. The introduction of recombinant gonadotropins with more than 99% purity, is gradually replacing hMG preparations world wide.

■ The Conquest for Mechanical and Unknown Causes of Infertility (Fig. 7)

However for mechanical causes of childlessness only surgical and microsurgical procedures were available. Vithal Nagesh Shirodka, a reputed Indian Obste-

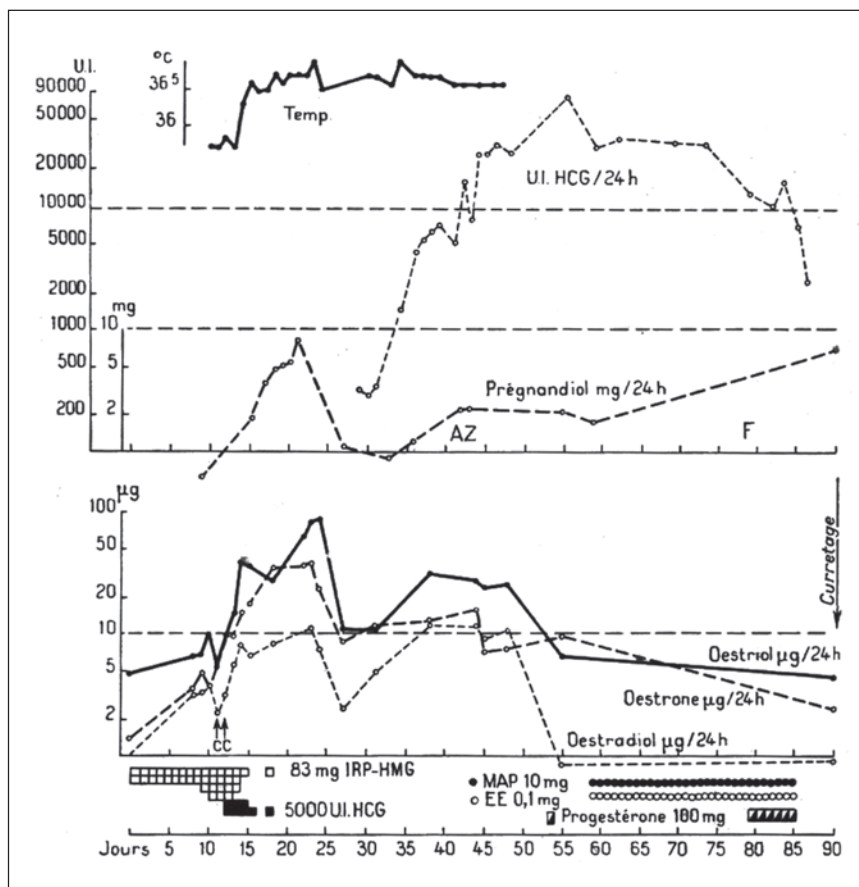


Figure 5. Hormonal following treatment with hMG followed by ovulation and Corpus luteum deficiency and attempt to treat corpus luteum deficiency with E = P in a primary amenorrheic patient with hypopituitary hypogonadism. Mod. from [33].

trician and Gynecologist [66], Buxton and Mastroianni [67] in the USA and Victor Gomel [68] in Canada were some of the pioneers of these procedures. However these methods were not very effective.

Following Leopold Schenk's observation that cell division occurred in cultures after sperm were added to ova (in rabbits and guinea pigs [69], Heape's first rabbit embryo transfers in 1880 [70], Pincus's attempts at IVF in Rabbits 1934 [71], Menkin and Rock in vitro fertilization of human eggs in 1944 [72], Chang's rabbit birth following IVF [73] the first human pregnancy following IVF (unfortunately ending in a miscarriage) was reported by Trounson et al. in 1973 [74]. In 1978, Edwards and Steptoe reported the birth of the first human IVF [75] in a natural cycle. This was followed by Jones et al., reporting in 1981 the first series of children born after IVF using the method we described earlier namely hMG to stimulate the development of follicles and hCG to obtain ovulation. This method with some minor

modification remained the standard method for IVF till today [76].

One of the main drawbacks with these protocols was premature LH surge. GnRH analogues suppress LH fluctuations and produce a condition of hypogonadotropic hypogonadism. This action combined with treatment with human menopausal gonadotropins (hMG) was then exploited in programs of induction of follicular growth in infertile women for both in vivo and in vitro fertilization. There is improved clinical control over the process of ovulation and the phenomenon of premature luteinization could be eliminated [77].

■ The Conquest of Male Factor Infertility

The next technological brake-through permitted to tackle male factor infertility. In 1984 Temple-Smith et al. described how spermatozoa were collected by microaspiration from the *corpus epididymidis* of a man with secondary obstructive azoospermia and used for in

vitro fertilization [78]. They claimed that this technique will provide a useful alternative for the management of some infertile men with obstructive azoospermia. Patrizio et al. in 1989 then reported the first 2 babies born after epididymal sperm aspiration for men with congenital absence of the vas deferens and named the technique MESA [79].

In 1988 Ng, Bongso, Ratnam et al. reported the first pregnancy after subzonal insemination [80]. This was followed in 1992 by Palermo et al. reporting pregnancies after intracytoplasmic injection (ICSI) of single spermatozoon into an oocyte [81]. This procedure permitted to treat couples with infertility because of severely impaired sperm characteristics.

Pregnancy obtained with human testicular spermatozoa in an in vitro fertilization program was then reported by Schoysman et al. [82]. Silber et al. then wrote in 1995: "When epididymal spermatozoa cannot be retrieved, a testicular biopsy can be performed and the few barely motile spermatozoa thus obtained can be used for ICSI. It appears that all cases of obstructive azoospermia can now be successfully treated" [83].

■ The Introduction of Recombinant Gonadotropins

The introduction of gonadotropin protocols in IVF and ICSI increased the demand for menopausal urine significantly [84]. At the beginning of this millennium, 120 million liters of urine were necessary to satisfy the worldwide need. It then became evident, that there would never be a sufficient urine supply to cover the increasing world demand. Recombinant DNA technology now allows the production of pharmacologically active pure FSH, LH and hCG preparations in unlimited quantities, minimizing the risk of disease transmission via biological contamination.

In 1997 Agrawal et al. [85] reported the first birth following stimulation of follicular growth in a hypopituitary-hypogonadotropic woman (WHO Group I) with recombinant FSH and recombinant LH; recombinant hCG was used to induce ovulation. In 2002, Donderwinkel et al. [86] reported a pregnancy follow-

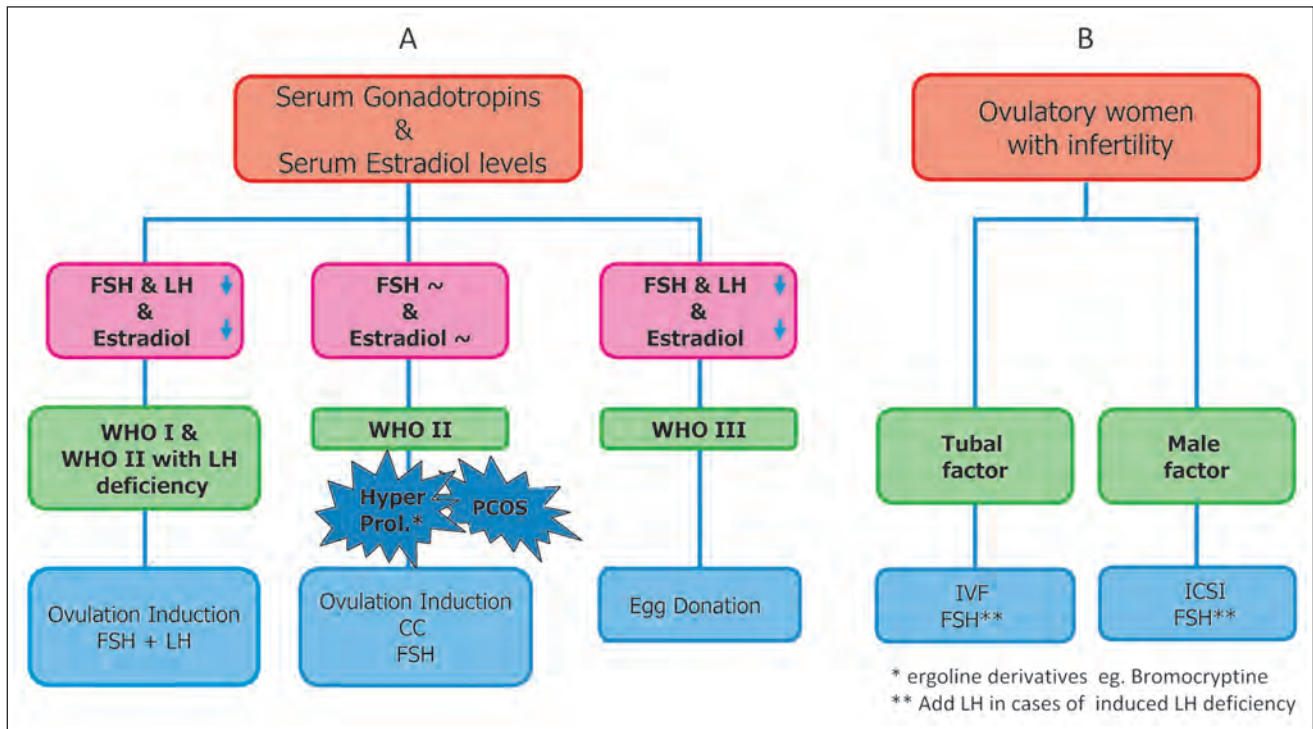


Figure 6. Classification of infertile patients.

ing ovulation induction with rFSH in a patient with polycystic ovaries. Recent advances in the manufacturing process for the rFSH (follitropin alfa) result in high batch-to-batch consistency in both isoform profile and glycan species distribution. The most significant advantage of this preparation over urinary-derived FSH is that it permits FSH to be quantified reliably by protein content (mass in mg) rather than by biological activity; this indication of purity offers optimal risk reduction as well as superior quality assurance and batch-to-batch consistency. The coefficient of variation for an in vivo bioassay is typically 20%, compared with 2% for physico-chemical analytical techniques such as size exclusion high-performance liquid chromatography [SE-HPLC; Driebergen et al., 2002]. As a result, Serono International now quantify their rFSH (Gonal-Fw) protein by SE-HPLC, a precise and robust assay that results in a significant improvement in batch-to-batch consistency over batches quantified by the Steelman-Pohley bioassay [87].

Since 2007 there exists a fixed 2:1 combination of rec-hFSH (150 IU) and rec-hLH (75 IU). Experiences in daily use of this combination for the stimulation of follicular development in women with

severe FSH and LH deficiency, in poor responders and older women shows promising results [88–90]. By avoiding the need for two separate injections or mixing of gonadotropins prior to injection, the 2:1 formulation of follitropin alfa and lutropin alfa offers potential benefits.

Recombinant DNA technology permits the design of potent therapeutically active gonadotropin agonists and antagonists by altering key proteins and carbohydrate regions in the α - and β -subunits of FSH and LH. FSH has a relatively short half-life, and hCG has a relatively long half-life. Site-directed mutagenesis and gene transfer techniques made it possible to fuse the carboxyterminal extension of hCGb (CTP) to the 30 end of the FSH coding sequence and produce an FSH-like product with a longer elimination half life. One injection is able to keep the circulating FSH activity above the threshold necessary to support multi-follicular growth for an entire week and induces sustained multiple follicular development during the first week of IVF treatment. In fact, one single injection of corifollitropin alfa replaces the first seven daily injections of rFSH. The first live birth after ovarian stimulation using this chimeric long-acting human rFSH

agonist (rFSH-CTP) was reported by Beckers [91]. The clinical trial program for corifollitropin alfa, that includes engage, ensure and others, is presently the largest in ART and includes more than 2500 patients in 78 IVF centers in 23 countries. These trials demonstrated that the treatment with a single injection of corifollitropin alfa was safe and well tolerated. The dose of 150 μ g of corifollitropin alfa is the most appropriate dose for achieving an optimal outcome in terms of the number of oocytes for patients with a body weight > 60 kg. In women weighing $\leq$ 60 kg a lower dose of 100 μ g showed similar results [92–96].

■ The Development of Orally Bioavailable Gonadotropin Mimetics

For companies committed to developing a wider range of innovative medicines for infertility, a generation of orally bioavailable gonadotropin mimetics has been the “holy grail” of drug development research for several years. As knowledge about the activating sites of gonadotropin and GnRH analogues has increased, it has become possible to create small, non-peptide molecules that induce signal transduction without binding to the extracellular domains of membrane proteins. Such molecules will ulti-

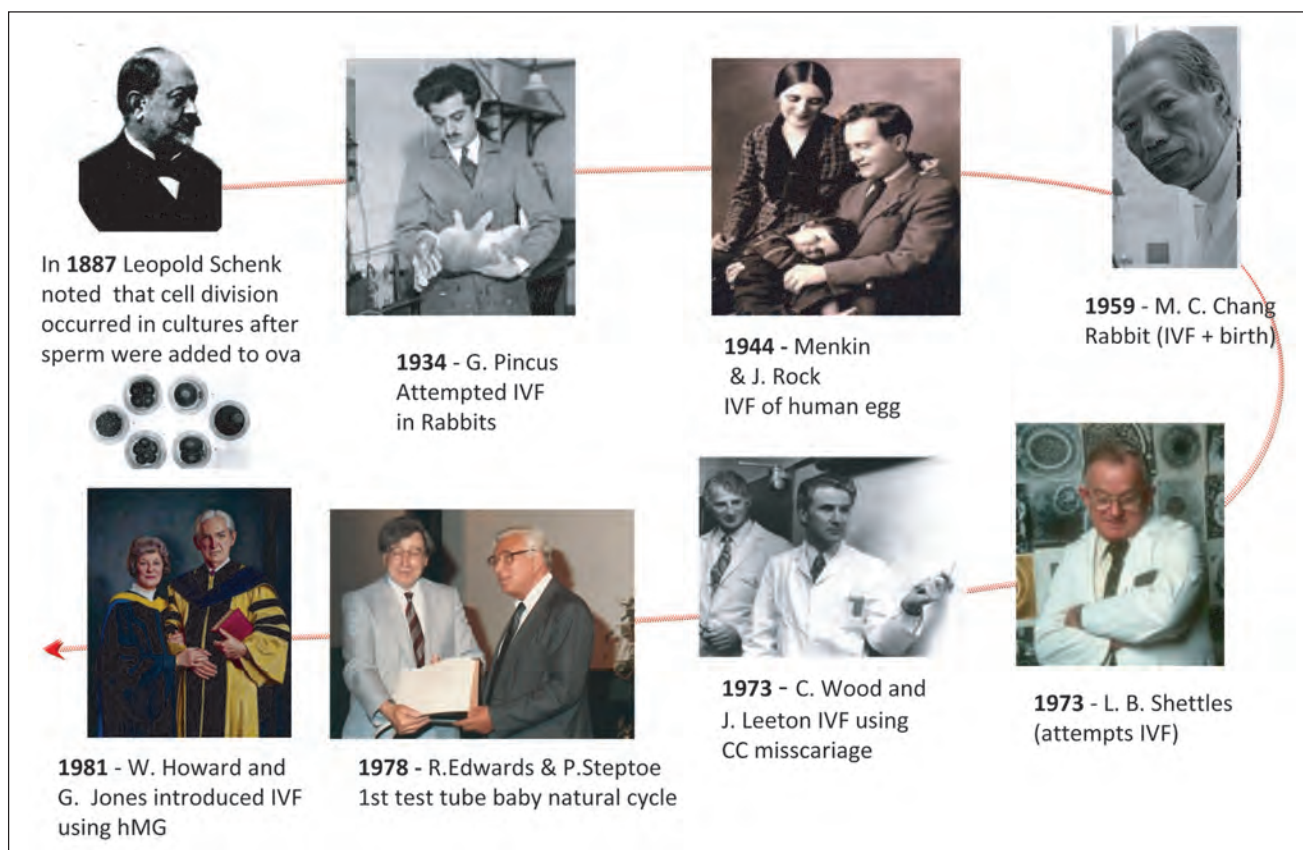


Figure 7. The “fathers” of in vitro fertilisation.

mately be converted into highly potent orally active therapeutic preparations, and will either replace the dimeric glycoprotein hormones or act as antagonists. The first report of a bioactive low molecular weight (LMW) gonadotropin described an FSH-R antagonist [97] as a potential compound for female contraception. Others reported small molecule modulators of the FSH receptor [98] and LMW compounds (thiazolidinones) with high affinity for the FSH receptor [99, 100].

The first report of a LMW (Org 43553) compound with a nano molar potency on the LH-R, showing oral bioavailability and ovulation induction in various animal was reported by van de Lagemaat et al. [101]. This compound has been developed as a safe oral alternative to the current injectable LH/hCG preparations for clinical use to induce ovulation or oocyte maturation for both in vivo and IVF therapy.

Conclusion and Thoughts for the Future

I think there is consensus that the use of hormones together with the basic tech-

niques described above helped to develop protocols (Fig. 6 a and b) which enabled more the 90% of infertile couples to have their genetic offspring and it is estimated that more than 10 million children have since been born with the help of gonadotropins. We now need to encourage our colleagues not only to develop and improve methods to permit infertile couples to have healthy offspring, but to encourage them to prevent infertility.

Prevention is cheaper than cure, “even using the mildest stimulation protocols”. It may be less profitable to the service providers and pharmaceutical companies but this must not our concern. Prevention of STD by the use of condoms, delaying adolescence pregnancies and unwanted pregnancies by contraception and sex education in schools, may all reduce mechanical causes of infertility for which IVF was created.

We create better and safer methods for IVF and a mayor part of budgets toward women’s health are spent for these important issues, and a large part of congress programs are filled with these issues. Should we not spend some time

and money to prevent the conditions which make IVF necessary?

ICSI was a blessing, but again we were so impressed with a method that could help nearly all men to have genetic heirs, that we forgot to invest in andrology, and in quite a number of countries positions for andrology in medical school disappear and they are replaced by high grade technicians who will attempt to find a few sperms and will try with sometimes sophisticated method to select the best. Practical no one invests in the science of andrology anymore.

Dear colleagues, let us promote health education, fight the global epidemic of obesity, promote a healthy life style with proper nutrition and physical exercise and help to reduce stress – this might be a very good investment and may decrease hypothalamic-pituitary and metabolic conditions related to male and female subfertility or infertility.

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