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From HMG through purified urinary FSH preparations to recombinant FSH: a substitution study

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Drugs produced through the use of recombinant DNA techniques have become an integral part of medical practice. Before recombinant FSH (rFSH) was introduced in 1996, FSH purified from the urine of postmenopausal women had been commercially available since the 1960s. We analysed the diffusion and the substitution patterns of the different FSH preparations in The Netherlands. The fact that rFSH preparations have batch-to-batch consistency, are free from urinary protein contaminants and have the potential to be produced in limitless quantities, is advantageous. The question whether newer, more pure FSH products are beneficial from the clinical perspective, has not been settled beyond reasonable doubt. The price of rFSH is three times as high as the price of the former FSH preparations. Due to the introduction of rFSH, total FSH expenditures have grown from €5.0 million in 1995, to €26.8 million in 2000, while the volume increased by <100%. Both the pharmaceutical companies and purchasers (government, insurers) have influenced the patterns of substitution of existing FSH products by biotech equivalents. In general, the risk of increasing pharmaceutical costs without clear clinical benefits has to be set against the risk of strangling innovations. Therefore, a continuous process of technology assessment is necessary.

Key words: drug policy/FSH/HMG/IVF/technology assessment

Introduction

Since 1982, with the advent of recombinant human insulin, biotechnology drugs produced through the use of recombinant DNA techniques have become an integral part of medical practice. However, this has not happened without a fight. As McKelvey described in her book on the development of recombinant human growth hormone, biotechnology as a new means to produce pharmaceuticals initially could not always count on a warm welcome (McKelvey, 1996). Public opinion on biotechnology is still not entirely positive, although most opposition is directed at its application in the food industry. At the same time, high expectations have been placed on the young biotech industry since its emergence in the 1980s. The euphoria subsided somewhat during the 1990s, but at the beginning of this century, with the completion of the Human Genome Project, expectations rose again. With pharmaceutical recombinant proteins being around for almost 20 years, the question of how these products are taken up in medical practice can now be raised.

In this paper we describe and analyse the case of one specific biotechnology drug, namely recombinant FSH (rFSH)

and its diffusion into Dutch medical practice. This case touches on a topic which has previously been identified as an important issue in the assessment of biotechnology drugs, namely that rFSH constitutes an alternative option for already existing medicines purified from an organic source (van Rijkom *et al.*, 1999). FSH extracted from the urine of postmenopausal women has been commercially available since the 1960s, before rFSH was introduced in 1996. Similarly insulin, growth hormone and clotting Factor VIII, respectively derived from animal pancreas, human pituitary tissue and plasma from blood donors, had already been in use long before the recombinant versions of these products became available. In this study we will depict the diffusion patterns of the different FSH preparations and the consequences of the introduction of the recombinant products. Data on the sales of FSH products were kindly provided to us by two of the pharmaceutical companies involved. Information on pivotal articles published, product introductions and withdrawals, reimbursement decisions, and the like, will be examined along with diffusion data to obtain insight into the processes underlying the adoption of these products by clinical practice.

Table I. FSH containing gonadotropin preparations on the Dutch market

	HMG	uFSH	uFSH-HP	rFSH
Full name	Human menopausal gonadotrophin	Urinary FSH	Highly purified urinary FSH	Recombinant FSH
Source	Urine from postmenopausal women	Urine from postmenopausal women	Urine from postmenopausal women	Genetically modified cells from Chinese hamster ovary
Ingredients	FSH + LH	FSH	FSH	FSH
Purity	<5%	<5%	>95%	99%
Administration	i.m.	i.m.	i.m. or s.c.	i.m. or s.c.
Brands	Humegon® (1963, Organon) Pergonal® (1970, Serono) Menogon® (1997, Ferring)	Metrodin® (1986, Serono)	Metrodin HP® (1995, Serono) Follegon® (1995, Organon)	Gonal-F® (1996, Serono) Puregon® (1997, Organon)

FSH and IVF

FSH containing gonadotrophin preparations have been commercially available since the 1960s. Their first use was in ovulation induction in women with anovulatory disorders. Since 1978, however, when the first IVF baby was born, they have been used increasingly in assisted reproductive technologies such as IVF and intra-uterine insemination (IUI). Now, ovulation induction comprises only 10% of gonadotrophin usage, while 90% is used for ovarian hyperstimulation in assisted reproductive technologies (about half for IVF and half for IUI in stimulated cycles) (Merkus, 1996). In The Netherlands, a total of 200 000 babies are born each year and 1 in 70 of them is conceived using IVF techniques (Anonymous, 2000). IVF starts with ovarian hyperstimulation using gonadotrophin preparations, containing FSH alone, or combined with LH. In the normal menstrual cycle out of a cohort of 10–20 antral follicles only one obtains dominance over the others and shows continued growth until ovulation takes place. In IVF, through the administration of FSH (for on average 10 days, starting on day 2–3 of the menstrual cycle), the maturation of a larger part of the antral follicle cohort is aimed for. During the stimulation phase pituitary desensitisation with a GnRH agonist is accomplished to prevent premature LH activity and ovulation. Those follicles which will grow until the preovulatory stage, will then be exposed to a surrogate midcycle LH peak (by using exogenous HCG) and be punctured under transvaginal ultrasound observation in order to harvest the oocytes contained in the follicles (oocyte retrieval). In the laboratory the oocytes will be fertilized and, after in-vitro culture for 3–4 days, transferred into the uterus, at which time the embryos will be at the 8–64 cell stage (embryo transfer).

Products

FSH containing gonadotrophin preparations can be divided into four groups (see Table I): (i) HMG, containing both FSH and LH; (ii) urinary FSH (uFSH); (iii) highly purified urinary FSH (uFSH-HP); and (iv) recombinant FSH (rFSH). Both HMG and uFSH contain a lot of, mainly undefined, urinary protein contaminants, rendering their purity <5%. Through

the application of immunochromatography with monoclonal antibodies against FSH, an increased purity of >95% is achieved in uFSH-HP preparations. Because of the increased purity, both uFSH-HP and rFSH can be administered s.c. as well as i.m.

Urinary derived preparations contain both intact FSH dimers as well as inactive FSH subunits. As such, mass is not a good indicator of urinary FSH content and the amount of gonadotrophin in each product is usually expressed in international units (IU) of FSH activity, as measured in a standardized bioassay.

Although both FSH and LH are required for normal follicular growth and maturation, the precise role of LH is at present still uncertain. Since it was shown in the late 1980s that too high a concentration of LH might have a negative effect on fertilization and embryo quality, the idea arose that pure FSH preparations might be superior to HMG preparations (Daya *et al.*, 1995; Agrawal *et al.*, 2000). This hypothesis was tested in several clinical trials comparing uFSH with HMG with respect to pregnancy rates per IVF treatment cycle. Statistical significance was not reached in any of these individual studies (Daya *et al.*, 1995; Agrawal *et al.*, 2000). However, in 1995 a meta-analysis by Daya *et al.* was published, which included eight studies and demonstrated a significant difference in favour of uFSH (Daya *et al.*, 1995) (see Table II). A few years later this finding was contradicted by a meta-analysis by Agrawal *et al.* who argued that meta-analyses should take into account the different pituitary desensitisation protocols used (Agrawal, *et al.*, 2000). When pooling together 11 trials with the most commonly used GnRH agonist protocol (the long protocol), the overall odds ratio for comparing FSH and HMG was not significant. Although this meta-analysis was criticised on the issue of study selection bias, re-analysis following the inclusion and exclusion of selected studies did not change the overall results of the study (Agrawal and Jacobs, 2000; Balasch, 2000; Daya, 2000).

A second issue that has been addressed in scientific literature, is the comparison between rFSH and urinary FSH (uFSH or uFSH-HP). The fact that recombinant preparations have batch-to-batch consistency, are free from urinary protein contaminants

Table II. Published meta-analyses

Meta-analysis	Preparations compared	Number of trials included (period)	Pregnancies per cycle (confidence interval)	P-value
Daya <i>et al.</i> (1995)	uFSH HMG	8 (1986–1994)	OR = 1.71 RD = 8.5%	0.013 0.009
Out <i>et al.</i> (1997)	rFSH uFSH/HMG	3 (1995–1996)	– RD = 4.9% (0.1–9.6%)	– 0.044
Daya and Gunby (1999)	rFSH uFSH/uFSH-HP	12 (1993–1998)	OR = 1.2 (1.02–1.42) RD = 3.7% (0.5–6.9%)	0.03 < 0.05
Agrawal <i>et al.</i> (2000) ^a	uFSH HMG	11 (1993–1997)	OR = 0.77 (0.58–1.05)	NS

^aOnly the meta-analysis for trials using the long protocol for gonadotrophin-releasing hormone (GnRH) analogues is included.

OR = odds ratio; RD = absolute risk difference; NS = not significant.

and have the potential to be produced in limitless quantities is advantageous. The question whether rFSH also leads to more clinical pregnancies per IVF cycle has been addressed by several clinical trials, none of which reached statistical significance. However, two meta-analyses pooling together the results of several trials, did show significant treatment effects in favour of rFSH (Out *et al.*, 1997; Daya and Gunby, 1999). The interpretation of these meta-analyses is still debated, since they compare two types of rFSH (the alpha and beta variant), as well as different types of urinary FSH (uFSH and uFSH-HP, and in Out's meta-analysis one study with HMG was also included). In Daya's analysis, which received Cochrane status, an absolute increase in pregnancy rates of 3.7% [95% confidence interval (CI) 0.5–6.9%] was demonstrated comparing rFSH with uFSH/uFSH-HP (see Table II).

Clinical pregnancy rates are influenced by the fact that in most IVF clinics only a limited (usually 2–3) number of embryos are transferred into the uterus to prevent large multiple pregnancies. The surplus of embryos is usually frozen, and subsequently they can be thawed and used in another IVF cycle without follicular stimulation (cryopreservation). Therefore, it has been suggested that the number of oocytes retrieved or the number of cumulative pregnancies, including those from frozen-thawed embryo transfer cycles, might be more appropriate endpoints. Oocyte retrieval was shown to be significantly higher for rFSH compared with uFSH/uFSH-HP in several individual trials (Out *et al.*, 1995; Bergh *et al.*, 1997; Frydman *et al.*, 2000; Schats *et al.*, 2000). The reason for this is not yet fully understood (Schats *et al.*, 2000). With regard to cumulative pregnancy rates including cryopreservation, a significant difference in favour of rFSH has been shown in one large trial by Out *et al.* (Out *et al.*, 1995). In many other trials (Bergh *et al.*, 1997; Frydman *et al.*, 2000; Schats *et al.*, 2000) and in the latest meta-analysis (Daya and Gunby, 1999) this endpoint was not addressed. The long-term effects of IVF on the growth and development of derived children are not yet totally clear. Cryopreservation and thawing involve major cellular changes and may cause (additional) adverse effects. Although the limited data available on this topic are reassuring, more data are needed to be able to weigh the advantages of using cryopreserved embryos for transfer without the need

for hyperstimulation, against the possibly negative effects on the children (Buitendijk, 2000).

Data on the third possible comparison, between rFSH and HMG, are scarce. The studies that have been conducted so far found no statistically significant differences with respect to ongoing pregnancy rates (Out *et al.*, 1996; Gordon *et al.*, 2001; Strehler *et al.*, 2001).

The evidence available at this time, comparing the different FSH containing gonadotrophin preparations, concerns their usage in IVF. However, almost half of all gonadotrophins are used in other settings, such as IUI. Very little data are available comparing the preparations for this indication.

With respect to adverse effects of exogenous FSH administration, no significant differences have been found between products. The main risk associated with the use of FSH containing gonadotrophin products is the development of the ovarian hyperstimulation syndrome (OHSS). This is a serious condition characterized by increased vascular permeability and liquid accumulation in the peritoneal, pleural, and pericardial cavities, which occurs in 1–2% of cases (Buitendijk, 1993). The incidence of OHSS does not differ between products (Out *et al.*, 1995; Bergh *et al.*, 1997).

Patterns of substitution

Before 1995

Since the 1960s two HMG products have been available on the market: Humegon[®] from Organon, and Pergonal[®] from Serono. The first change in the market came in 1986 with the introduction of uFSH (Metrodin[®], Serono). In 1991, a reference pricing system was introduced in The Netherlands for the reimbursement of prescription drugs through community pharmacies. This means that all pharmaceuticals are clustered into groups with the same therapeutic efficacy. Then a price reference is set as a reimbursement limit in such a way that there is enough opportunity for the insured to receive proper medication without co-payment. uFSH was categorized in the same cluster as HMG with a maximum reimbursement level of €10 per 75 IU.

1995–1996

The uFSH-HP preparations were introduced to the Dutch market in February 1995. As can be seen in Figure 1A and

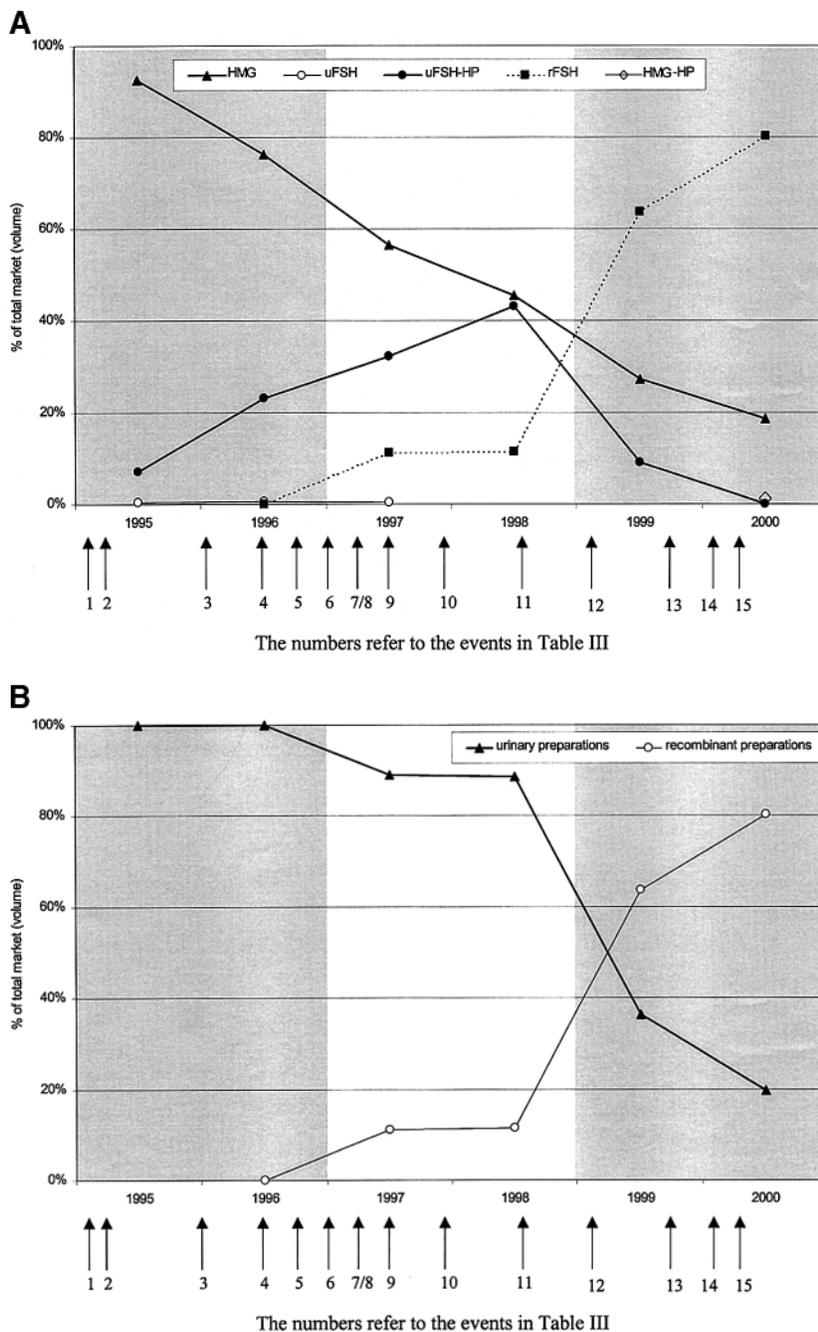


Figure 1. (A) Diffusion of gonadotrophin preparations in The Netherlands. (B) Substitution of urinary products by recombinant products.

Table III, uFSH-HP and HMG divided the market between them, leaving only a negligible share for uFSH. While in 1995 HMG products held a >90% share of the market volume and uFSH-HP <7%, in 1996 uFSH-HP had increased to a 23% market share. Metrodin HP® was by far the largest uFSH-HP provider (>95%); the contribution of Follegon® to the gonadotrophins market has been negligible. The question can be raised whether the growth of uFSH-HP at the expense of HMG preparations was supply driven or demand driven. Probably it was both. On the one hand, the meta-analysis presented by Daya *et al.* in 1995, which concluded that FSH alone was more effective than HMG, may have increased the demand for FSH-only products (Daya *et al.*, 1995). Since Serono phased out Metrodin® when Metrodin HP® was intro-

duced, uFSH-HP was the only available pure FSH option. On the other hand, the increased use of FSH-only products may also have partly been forced on the market, since there was a shortage of HMG products. In May 1995, Serono sent a letter to all Dutch gynaecologists explaining the decreased production of Pergonal® (capacity problems and a shortage of urine due to the production of Metrodin HP®) (Snyman, 1995). One year later, in May 1996, the Newsletter of Freya, the patient federation for fertility problems, reported that the production of Pergonal® for The Netherlands had been totally abandoned (Anonymous, 1996). Organon experienced difficulties as well, with the production of its HMG product Humegon® (Boerma, 1995, 1996). The shortage of HMG products may have forced doctors and their patients to use uFSH-HP; a worry that was

Table III. History

No.	Date	Event
(1)	February 1995	Introduction of Follegon [®] and Metrodin HP [®]
(2)	April 1995	Presentation of meta-analysis by Daya <i>et al.</i> (Daya <i>et al.</i> , 1995) conference (publication follows in August 1995)
(3)	1995–1996	Shortages of HMG (Pergonal [®] and Humegon [®])
	May 1996	Delivery of Metrodin HP [®] directly to certain pharmacies below the official price
(4)	July 1996	Production of Pergonal [®] has been stopped (Daya and Gunby, 1999)
(5)	September 1996	Metrodin [®] removed from Z-index
(6)	January 1997	Introduction of Gonal-F [®]
(7)	March 1997	Introduction of Puregon [®]
(8)	April 1997	Introduction of Menogon [®]
(9)	July 1997	Start of Puregon [®] restitution action
(10)	November 1997	Meta-analysis Out <i>et al.</i> (Out <i>et al.</i> , 1997)
(11)	August 1998	Start of Metrodin HP [®] action: now available at a price equal to reimbursement level
(12)	February 1999	Report by Study Group Recombinant Gonadotropins sent to Health Insurance Fund Council
		rFSH gets a separate reimbursement cluster: now fully reimbursed
		End of Puregon [®] restitution action
		End of Metrodin HP [®] action
(13)	September 1999	Meta-analysis Daya <i>et al.</i> (Daya and Gunby, 1999)
(14)	February 2000	Meta-analysis Agrawal <i>et al.</i> (Agrawal, <i>et al.</i> , 2000)
(15)	May 2000	Metrodin HP [®] removed from Z-index

Table IV. Product availability

Product	Brand	Supply	75 IU price (€)
1990–1995			
HMG	Humegon [®]	OK	10
	Pergonal [®]	OK	10
uFSH	Metrodin [®]	OK	15
1995–1996			
HMG	Humegon [®]	shortage	10
	Pergonal [®]	shortage	10
uFSH	Metrodin [®]	phased out	16
uFSH-HP	Metrodin HP [®]	OK	18
	Follegon [®]	OK	16
1997–1998			
HMG	Humegon [®]	shortage	10
	Menogon [®]	OK	10
uFSH-HP	Metrodin HP [®]	OK	16
	Follegon [®]	OK	22
rFSH	Gonal-F [®]	OK	30
	Puregon [®]	OK	34
1999–2000			
HMG	Humegon [®]	shortage	10
	Menogon [®]	OK	10
uFSH-HP	Metrodin HP [®]	phased out	16
	Follegon [®]	OK	22/10
rFSH	Gonal-F [®]	OK	34
	Puregon [®]	OK	34

indeed expressed by Freya (Anonymous, 1996). Freya was all the more concerned, since uFSH-HP products required a co-payment. Like uFSH, uFSH-HP had been included in the same cluster as HMG with a maximum reimbursement level of €10 per 75 IU. This meant that for Metrodin HP[®] patients had to pay a co-payment of €8 per 75 IU ampoule, which gave an average co-payment of €160–240 per cycle (150–225 IU for 10 days) (see Table IV). In some selected pharmacies, however, patients were able to purchase the product at a reduced cost, since Serono, the producer of Metrodin HP[®], made direct deliveries to these pharmacies, thus circumventing the wholesaler's margin. IVF centres were informed to refer

their patients specifically to the selected pharmacies. This construction soon had to be abandoned, since it caused a lot of criticism, especially from the Royal Dutch Association for the Advancement of Pharmacy (Arts, 1996; Briedé, 1996a,b; Vlottes, 1996).

1997–1998

The rFSH products Gonal-F[®] and Puregon[®] were introduced in September 1996 and January 1997 respectively and in the subsequent 2 years they conquered 11% of the total FSH market. The volume of uFSH-HP continued to increase, and HMG further decreased so that both had an ~45% market share in 1998 (see Figure 1A).

The 11% market share of rFSH obtained within 2 years appears relatively modest. There may be two reasons for this. First, the clinical benefits of rFSH were debated. The discussions centred around the clinical trials being industry-sponsored or -associated, the potency of rFSH preparations (should 50 IU rFSH be regarded as equipotent to 75 IU urinary FSH?), and the quality of the harvested oocytes (Balén *et al.*, 1999; Bergh, 1999; Meniru, 1999; Out *et al.*, 1999; Hernandez, 2000). In any event, it appears that at first the evidence that had to support the superiority of rFSH was convincing to neither the Dutch Health Insurance Fund Council or to the Minister of Health, as they decided to categorize rFSH in the same reimbursement cluster as the urinary preparations, setting its reimbursement level at €10 per 75 IU. This is the second reason to explain the relatively slow uptake of rFSH: the co-payment for rFSH products could amount to €700 per cycle. Organon, the producer of Puregon[®], started a campaign in which patients could submit the receipt of their co-payment and get a refund of about 75%. At the same time, Serono started a similar campaign, not for its rFSH product Gonal-F[®], but for Metrodin-HP[®]: temporarily this could be obtained from Serono's distributor by all Dutch pharmacists at a price of €10 per 75 IU (official price was €16) (Serono Benelux BV, 1997).

Another important event was the introduction of a third HMG preparation, Menogon[®], by a new player in the field, Ferring. While Organon and Serono brought down or even abandoned the production of HMG preparations, either voluntarily or forced by circumstances, the introduction of Menogon[®] made HMG available again. For sure, this has played a significant role in the persistence of HMG as one of the available products in this class.

1999–2000

In March 1998, the Study Group Recombinant Gonadotropins, in which were represented among others the patient federation Freya and the Dutch Association of Gynaecologists, sent a report to the Health Insurance Fund Council entitled 'Therapeutic Value of Recombinant Gonadotropins'. The Study Group concluded that recombinant gonadotrophins are safer, and that they carry therapeutic and economic benefits, compared with the urinary gonadotrophins (Study Group Recombinant Gonadotrophins, 1998). The goal was to convince the Health Insurance Fund Council (HIFC) and the Minister of Health to create a separate reimbursement cluster for the rFSH preparations. In an advice to the Minister, the HIFC adopted the increased efficacy of rFSH, but not the economic benefits nor the increased safety profile [Centrale Medisch Pharmaceutische Commissie (CMPC), 1998]. Based on this advice, the Minister decided to introduce a separate cluster for rFSH with a reimbursement level of €34 per 75 IU. As a result, from February 1, 1999 onwards, rFSH was fully reimbursed. Both the Puregon[®] and the Metrodin HP[®] campaigns of refunding patient's co-payments were stopped immediately by Organon and Serono respectively.

As a consequence of this development, the volume of rFSH increased explosively to a 64% market share in 1999 (see Figure 1A). The growth levelled off in 2000 (80% volume for rFSH). The large increase of rFSH was mainly at the expense of uFSH-HP, which dropped to 9% volume share in 1999, and 0% in 2000. The market share of HMG continued to decrease to 19%, with Menogon[®] providing more than 70% of the total HMG market in 2000.

In 1999, the market share of uFSH-HP started to decrease for the first time since 1995. In 2000, Metrodin-HP[®] even disappeared from the market. An important explanation for this is of course that Metrodin-HP[®] was the only product for which a co-payment was still required.

It seems that in 2000 the growth of rFSH levelled off, and that the decrease of urinary preparations slowed down (see Figure 1B). While in 1995–1999 the idea ruled that uFSH was probably superior to HMG for use in ovary stimulation for IVF, in 2000 this was questioned again, mainly through the meta-analysis by Agrawal *et al.* (Agrawal *et al.*, 2000) Agrawal argued that some exposure to LH may be beneficial, and indeed her meta-analysis of 11 trials using the long GnRH agonist protocol showed that HMG and uFSH yielded similar results. On the other hand, Daya's analysis (Daya and Gunby, 1999) pointed in the direction of rFSH being superior to urinary FSH.

Current developments

For each IVF cycle, women need a once-daily injection for an average 10 days and in The Netherlands almost all the women administer these themselves. In the period 1995–1999, the products described were marketed as a lyophilised powder (generally 50, 75, 100 or 150 IU) with a separate container of 1 ml solvent. Thus, before injecting themselves, the women first had to dissolve the lyophilised FSH powder in the solvent. Since June 2000, Puregon[®] has been available as a ready-made solution (Puregon[®] Solution). This makes its administration easier and, moreover, the volume has been decreased from 1 ml to 0.5 ml. Generally, a smaller volume is associated with less pain upon injection. In addition, Organon has introduced a pen for self-injection, similar to the ones used by diabetics to administer insulin. The Puregon[®] Pen is to be filled with cartridges of 300 or 600 IU (for multiple injections) and has a dosing mechanism, which can be adjusted in steps of 25 IU. For 50 IU, the volume of injection is only 0.06 ml. The pen can be re-used and costs €23, although many gynaecologists received copies for free distribution among their patients. In April 2000, Organon sent a letter to all Dutch gynaecologists stating that the availability of Humegon[®] would be terminated on July 1, 2000 (Drees, 2000). Serono introduced Gonal-F[®] 600 IU/ml Multidose to the Dutch market in June 2001. This lyophilised powder of 1200 IU (retrieval 1050 IU) has to be dissolved once in the accompanying solvent and can subsequently be used for several days. The injection volume is small. However, the increased convenience for patients of these newly introduced rFSH products may come at a cost, since the increased amount of rFSH per package (minimum 300 IU for Puregon[®] Pen and 1050 IU for Gonal-F[®] Multidose) might lead to more waste.

In July 2000 Ferring introduced a new product: Menopur[®]. This consists of highly purified (purity >97.5%) urinary FSH 75 IU and LH 75 IU (HMG-HP). It is marketed as a lyophilised powder with a separate container of 1 ml solvent. The price is €23 per 75 IU, which means that a co-payment of €13 is required per ampoule, since the product is clustered with the other, less pure, HMG products. However, Ferring has started a campaign through which patients can receive a complete refund of their co-payments. In 2000, the market share of Menopur[®] was 1%.

Discussion

Decision-making about (biotechnology) drugs takes place at different levels (Zwart-van Rijkom *et al.*, 2000). On the macro level, politicians, regulators and health insurers have to decide about the licensing and reimbursement of pharmaceuticals. On the intermediate level, decisions are made by specialist organizations, e.g. in developing good practice guidelines, and formulary committees. Ultimately, on the micro level, physicians and patients make choices about individual treatments. Together, all these decisions determine the fate of a biotechnology drug, and its diffusion into society and medical practice. When looking at the diffusion of rFSH, the most crucial decision-making has taken place on the macro level, namely the decisions about its reimbursement. The uptake of

rFSH was held back by the fact that a substantial co-payment was required and as soon as this matter was resolved, the switch towards rFSH assumed high proportions. Apparently, gynaecologists and patients (on the meso and micro level) were already in favour of rFSH, but not enough to accept the accompanying co-payment. That is why they brought together the Study Group Recombinant Gonadotropins, which successfully requested the Minister of Health to reconsider a separate reimbursement cluster for rFSH.

In addition, the pharmaceutical companies constitute an important influence in the diffusion process. Regularly, the topic of the influence of the pharmaceutical industry on the medical community is discussed in medical scientific journals (Lexchin, 1993; Bodenheimer, 2000; Wazana, 2000). In the case of rFSH, the influence of the FSH producing companies is easy to point out. The fact that the production of HMG and uFSH in the period 1995–1996 remained far behind the needs at that time, benefited the adoption of uFSH-HP. At a later stage, this influence was somewhat constrained by the entry of a third player to the market (Ferring), which marketed HMG as its only gonadotrophin product. During the period 1997–1998, both Serono and Organon put together policies to reduce co-payments for patients. By choosing the products for which these actions were installed, they could influence the adoption patterns. Organon chose to focus on rFSH, while Serono put its bet on uFSH-HP.

The first biotech substitutes, which were introduced in the 1980s, namely recombinant insulin and recombinant growth hormone, have never really needed to show superiority compared with the previously used products they were replacing. When recombinant human growth hormone (GH) was granted a marketing authorization in 1985, the previously used pituitary derived products had just been withdrawn from the market due to contamination with the agent causing Creutzfeldt-Jakob disease. As such, recombinant GH automatically gained a 100% market share. Regarding insulin, the debate was not whether recombinant insulin was better than animal insulin, but whether it was not worse. Namely, recombinant insulin was suspected to raise the risk of hypoglycaemia as compared with animal insulin (Berger *et al.*, 1987, 1989; Egger *et al.*, 1991). In spite of this discussion, during the 1980s virtually all diabetic patients switched to recombinant insulin and since the early 1990s animal insulin has not even been available in the Netherlands. Again, similar to the rFSH case, the pharmaceutical companies played a major part in this, since they simply withdrew their animal insulin from the market (Gale, 1989). Reimbursement was less of an issue at that time, since the reference pricing system was not yet in place and recombinant insulin was only a little bit more expensive than animal insulin (<10%).

At the time of the introduction of rFSH, however, the reference pricing system was in place and evidence of clinical superiority was very important. When comparing rFSH with uFSH/uFSH-HP, an absolute increase in pregnancy rates of 3.7% (95% CI 0.5–6.9%) has been demonstrated in Daya's meta-analysis (Daya and Gunby, 1999). The discussion still centres around the question whether this difference is clinically relevant. A 3.7% absolute difference means that the number

of women needing treatment with rFSH instead of uFSH/uFSH-HP in order to gain one additional pregnancy is 27 (95% CI 14–200). The fact that two types of rFSH (the alpha and beta variant) are compared with two types of urinary FSH (uFSH and uFSH-HP) further complicates the discussion. Another potential comparison, rFSH versus HMG, initially was not given much attention. Apparently, in the early period after introduction of rFSH, it was commonly assumed that if rFSH could be demonstrated to be superior to uFSH/uFSH-HP, it was also superior to HMG. Given the results of Daya's meta-analysis (Daya *et al.*, 1995) this seemed logical indeed. However, since: (i) a subsequent meta-analysis (Agrawal *et al.*, 2000) pointed in the opposite direction, (ii) uFSH is hardly available anymore, and (iii) a HMG-HP preparation has been introduced to the market (Menopur[®]), the question about the comparison between rFSH and HMG (and HMG-HP) has started to become relevant. Overall, the background of several studies using different comparisons and endpoints gives occasion to the fact that the discussion and assessment of the different gonadotrophin preparations remains complicated.

That the superiority question is not an easy one to answer is illustrated also by the changeable decisions of the Dutch government. Initially, the Dutch Minister of Health was not convinced of rFSH's superiority and included it in the cluster of the urinary gonadotrophins. A few years later, however, its opinion was altered and a separate reimbursement cluster for rFSH was created. In the meantime a report by the Dutch Health Council had been written, in which it was stated that cryopreservation had become an accepted part of IVF cycles (even though the effects on the resulting 'cryo-children' were unknown and further research on that topic was required). This made it possible for the Minister to accept the efficacy endpoint of cumulative pregnancies, including pregnancies from cryo-cycles. The meta-analyses by Daya (Daya and Gunby, 1999) and Agrawal (Agrawal *et al.*, 2000) were published after the Minister's decision in 1998, and as such the debate on the clinical benefit of rFSH is still ongoing (Balen *et al.*, 1999; Bergh, 1999; Meniru, 1999; Out *et al.*, 1999; Hernandez, 2000). It can be anticipated that further clinical trials and meta-analyses comparing rFSH and HMG (or HMG-HP) will be published in the future. Moreover, the debate about the cost-effectiveness of rFSH will continue. The incremental cost-effectiveness ratio of rFSH compared with uFSH-HP has been estimated at about 12 000 US dollars per additional ongoing pregnancy, assuming an absolute increase in pregnancy rate of 6.4% (including thawed embryos) (Mantovani *et al.*, 1999). When a 0.5% difference was assumed the estimate was about 70 000 US dollars (Mantovani *et al.*, 1999). In spite of the ongoing debate, the total FSH market has grown from €5.0 million in 1995 to €26.8 million in 2000 (>400% increase), while the total volume increased by <100% in that same period. This can of course be explained by the fact that rFSH is >3 times more expensive per unit than urinary preparations. In 1999, the ovulatory inductive medicines caused the fourth biggest cost increase for pharmaceuticals after gastric acid inhibitors, cholesterol lowering agents and antidepressants (Anonymous, 2000).

In addition to the data provided to us, this study is based

on only published literature, written reports and correspondence filed in the archive of the patient federation Freya. We did not acquire inside information from the parties involved, such as government officials, doctors and the pharmaceutical companies. This of course could constitute a valuable addition, to further deepen the insight into the processes underlying the diffusion patterns that we observed.

In general, the development of recombinant substitutes for already existing compounds was based on several factors, such as potential scarcity of the 'classical' product (future shortages had been forecasted for animal insulin and for plasma derived Factor VIII) (Galloway, 1980; Pierce *et al.*, 1989; Bins *et al.*, 1991) and fascination with genetic engineering, but also on the assumption that distinct benefits would result from the use of products which were as pure as possible. With respect to pharmaceutical quality, the increased purity and batch-to-batch consistency of the recombinant proteins can be considered a breakthrough. To the pharmaceutical companies it means a more efficient and well-controlled production process. It frees the companies of the complicated logistics of collecting large amounts of pancreas, pituitary tissue, urine or blood plasma, the supply of which may be uncertain, since it depends on the willingness and co-operation of donors. Moreover, the use of urine as a source for medicines raises concerns about potential contamination with pathogenic micro-organisms. Plasma derived Factor VIII, for example, has infected many haemophilia patients with HIV and hepatitis C. Especially in the current era of 'prion scare', this may be an important argument in favour of biotech substitutes. On the other hand, urinary derived gonadotrophins have been available since the beginning of the 1960s, and so far prion or other infectivity has never been ascribed to them. Notwithstanding the pharmaceutical advantages, significant medical benefits in clinical practice have never been convincingly demonstrated for biotech substitutes, such as recombinant insulin and recombinant Factor VIII, and for rFSH the debate is still ongoing (Gale, 1989; Mauser-Bunschoten *et al.*, 2001). As such, the adage 'the purer, the better' may be of limited value from the clinical perspective.

Appraising innovations only on their immediate apparent clinical benefits is not a very profound method of technology assessment. Recombinant insulin, as such, did not have relevant clinical benefits over animal insulin (Gale, 1989). However, it has been an important incentive to continue the development of other valuable biotechnology drugs and vaccines, such as erythropoietin and hepatitis B vaccine. As a rule innovations take place gradually. If the first biotechnology drugs had not have been given a fair chance, we might not have had the knowledge, the experience and the new biotech drugs in development that we have now. Similarly, if recombinant human insulin had not been given a chance in the 1980s, the short acting insulin analogues, such as insulin lispro and insulin aspart, would today probably not be available. The gonadotrophin market is also still innovating, with the introduction of ready-made solutions and pens for injection, although these are not necessarily biotech related. Still, these products may represent a considerable step forward to the patients who are using them. In general, the risk of increasing pharmaceutical

costs without clear clinical benefits has so be set against the risk of strangling innovations (van Rijkom *et al.*, 1999). This, of course is not an easy judgement to make, especially at the beginning of the life-cycle of a new pharmaceutical product. Usually, the real advantages and disadvantages of a new medicine become apparent only after it has been used for some time. Therefore, a continuous process of technology assessment is warranted.

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