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DEBATE

Bye-bye urinary gonadotrophins?

The use of urinary gonadotrophins should be discouraged

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In view of concerns regarding the potential presence and infectivity of prion proteins in human urinary gonadotrophin preparations, together with the availability of both recombinant FSH and recombinant LH, it is argued that the use of urinary gonadotrophins should be discouraged.

Key words: BSE/new variant CJD/TSE/urinary gonadotrophins

Transmissible spongiform encephalopathies (TSEs), or prion diseases, are fatal degenerative disorders of the central nervous system that affect humans and animals. Although some TSEs, like scrapie in sheep, have been known to exist for centuries, bovine spongiform encephalopathy (BSE) was recognized only 15 years ago (Glatzel and Aguzzi, 2001). New variant Creutzfeldt-Jakob disease (nvCJD) of humans is probably caused by consumption of BSE-infected materials ('mad cow' disease). The nature of the infectious agent is not fully elucidated, but substantial evidence suggests that it is devoid of nucleic acids and consists at least in part of an abnormal form of a host protein termed PrP(C) (Glatzel and Aguzzi, 2001). Despite their rarity, prion diseases have become an important topic in public health and basic research because of the connection between nvCJD and BSE and also because of the unusual biological attributes of the infectious agent (Belay, 1999; Glatzel and Aguzzi, 2001).

It has been recently found that a prion protein isoform is present in urine of animals and humans affected with TSEs (Shaked *et al.*, 2001). Most important, this prion protein was also found in the urine of hamsters inoculated with prions long before the appearance of clinical signs. However, this urinary prion protein failed to cause prion disease in hamsters when inoculated intracerebrally (Shaked *et al.*, 2001).

Although infectivity by urine prions in humans or animals has not yet been documented, the aforementioned report raises serious concerns regarding the future use of urinary gonadotrophins. This is especially remarkable, since compared with recombinant FSH, urinary gonadotrophins have no evident clinical benefits (Daya and Gunby, 1999; Matorras *et al.*, 2000), whereas cost-effectiveness studies did not reveal considerable advantages (Balasch and Barri, 2001). Indeed with the recent commercialization of recombinant LH, the LH administration recommended by some authors in any IVF treatment (Levy *et al.*, 2000) can be obtained without using urinary gonadotrophins.

Thus, in our opinion, the use of urinary gonadotrophins should be discouraged.

References

Balasch, J. and Barri, P.N. (2001) Reflections on the cost-effectiveness of recombinant FSH in assisted reproduction. The clinician's perspective. *J. Assist. Reprod. Genet.*, **18**, 45–55.

Belay, E.D. (1999) Transmissible spongiform encephalopathies in humans. *Ann. Rev. Microbiol.*, **53**, 283–314.

Daya, S. and Gunby, J. (1999) Recombinant versus urinary follicle stimulating hormone for ovarian stimulation in assisted reproduction. *Hum. Reprod.*, **14**, 2207–2215.

Glatzel, M. and Aguzzi, A. (2001) The shifting biology of prions. *Brain Res. Rev.*, **36**, 241–248.

Levy, D.P., Navarro, J.M., Schattman, G.L., Davis, O.K. and Rosenwaks, Z. (2000) The role of LH in ovarian stimulation: exogenous LH: let's design the future. *Hum. Reprod.*, **15**, 2258–2265.

Matorras, R., Recio, V., Corcóstegui, B. and Rodríguez-Escudero, F.J. (2000) Recombinant human FSH versus highly purified urinary FSH: a randomized study in intrauterine insemination with husbands' spermatozoa. *Hum. Reprod.*, **15**, 1231–1234.

Shaked, G.M., Shaked, Y., Kariv-Inbal, Z., Halimi, M., Avraham, I. and Gabizon, R. (2001) A protease-resistant prion protein isoform is present in urine of animals and humans affected with prion diseases. *J. Biol. Chem.*, **276**, 31479–31482.

Risk of infection is not the main problem

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The risk of infection from prion proteins in urinary preparations of human gonadotrophins is uncertain—and is of lesser importance than the risk of multiple pregnancies and issues of cost.

Key words: prion proteins/recombinant FSH/urinary gonadotrophins

Compared with recombinant FSH, urinary gonadotrophins have no clinical benefits (Daya and Gunby, 1999; Matorras *et al.*, 2000), but they are less expensive. In fact, in some countries the cost of the two preparations is consistently different. For all customers, but especially for the 'public' programmes of ovarian stimulation, this is an important limiting factor, since the higher cost reduces the resources for other health programmes.

In addition, the urinary preparations of human gonadotrophins have been widely used for 40 years and no infections have been associated with their injection, even in the past when the urinary extracts were rather 'impure' (Donini *et al.*, 1949). No, the uncertain risk of infections currently does not represent the main problem of ovarian stimulation. Instead, the major concern is the real, well-known risk of twin pregnancies associated with the induced multiple ovulation (Gleicher *et al.*, 2000).

So, bye-bye urinary gonadotrophins? I am sure that these preparations will disappear as soon as cheaper recombinant ones become available. On the contrary, the risk of iatrogenic twinning will continue until a milder form of ovarian stimulation is used (Edwards *et al.*, 1997).

Curiously, reading the results of the publications in the area of gonadotrophin-induced cycles, multiple gestations are still wrongly reported as a therapeutic success. It is time to recategorize these as unwanted and feared complications.

References

Daya, S, and Gunby, J. (1999) Recombinant versus urinary follicle stimulating hormone for ovarian stimulation in assisted reproduction. *Hum. Reprod.*, **14**, 2207–2215.

Donini, P. and Montezemolo, R. (1949) Gonadotropina preipofisaria e gonadotropina preipofisaria-simile umana. *Rass. Clin. Terap. Sc. Affini,* **48**, 143–163.

Edwards, R.G., Lobo, R.A. and Bouchard, P. (1997) Why delay the obvious need for milder forms of ovarian stimulation? *Hum. Reprod.*, **12**, 399–401.

Gleicher N., Oleske, D.M., Tur-Kaspa, I., Vidali, A. and Karande, V. (2000) Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. *N. Engl. J. Med.*, **343,** 2–7.

Matorras, R., Recio, V., Corcóstegui, B. and Rodríguez-Escudero, F.J. (2000). Recombinant human FSH versus highly purified urinary FSH: a randomized study in intrauterine insemination with husbands' spermatozoa. *Hum. Reprod.*, **15**, 1231–1234.

Is there a risk of prion disease after the administration of urinary-derived gonadotrophins?

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Concern has been raised recently about the possibility of prion proteins appearing in the urine of animals and, possibly, humans affected by prion disease [scrapie, bovine spongiform encephalopathy (BSE) and Creutzfeldt Jakob disease (CJD)]. A debate has started in which the suggestion has been made that the purification of human urine for the provision of gonadotrophins should be discontinued. The alternative would be to use recombinantly-derived gonadotrophin preparations. The recombinant products, however, rely upon bovine serum during the cell culture process and could potentially also be exposed to abnormal prion proteins. It is reassuring that the different types of gonadotrophin preparations that are currently available are produced with either urine or bovine serum that is sourced from countries that at the present time appear to be free of BSE and new variant CJD. We can therefore be reassured that the gonadotrophins that we use therapeutically appear to be equally safe.

Key words: BSE/prion disease/recombinant gonadotrophins/urinary gonadotrophins/variant CJD

Introduction

The paper by Matorras and Rodríguez-Escudero (2001) is worthy of serious consideration and it is timely, once again, to consider whether we may be putting our patients at risk of infection with the drugs that we are administering (Matorras and Rodríguez-Escudero, 2001). There is a need for extreme vigilance when using biological products for therapy, particularly in reproductive medicine, when young women may be exposed to risks to their long-term health and potentially the health of their babies. In this short paper I present the view that the current evidence suggests that both urinary-derived and recombinant gonadotrophin preparations are safe with respect to the risk of transmitting prion disease.

Prion diseases—background

Creutzfeldt Jakob disease (CJD) is a chronic neurodegenerative disease, first identified in 1920, and has probably been in existence for many (hundreds) of years. CJD is a rare and fatal condition that affects the nervous system, and is one of a group of transmissible diseases known as the prion diseases or transmissible spongiform encephalopathies (TSEs). There are three major types of CJD: (i) sporadic CJD, which accounts for ~85% of all cases worldwide and for which the underlying cause is currently unknown (Department of Health, 2001a), although it may be due to a somatic mutation; (ii) familial CJD which is associated with a point mutation or insertion mutation in the human prion protein gene, and is inherited as an autosomal dominant condition; (iii) acquired CJD, which includes kuru, seen in the Fore tribe of Papua New Guinea and 'new variant' CJD, which results from the exposure to the bovine spongiform encephalopathy (BSE) agent. Also iatrogenic CJD may result after surgical procedures (Department of Health, 2001a).

Prions are pathogenic forms of proteins that are naturally produced by nerve cells and other cells. The normal protein isoform is referred to as prion protein cellular (PrP^{c}). All forms of prion disease are associated with the accumulation of an abnormal form of prion protein (scrapie, PrP^{Sc}) within the central nervous system (CNS). PrP^{Sc} is relatively protease resistant and so accumulates in plaques in the CNS. There is increasing evidence to indicate that the transmissible agent may be composed entirely of the abnormal form of prion protein (Department of Health, 2001a). Prions are not micro-organisms.

Between 1970 and December 2000, the National CJD Surveillance Unit identified 970 cases of classical CJD in the UK of which 888 were sporadic, 40 were familial and 42 were acquired as a result of treatment with human pituitary extract or brain membranes (National CJD Surveillance Unit, 2000). New variant CJD (vCJD) was first recognized as a distinct clinical entity in 1996 (Will *et al.*, 1996). This new disease is believed to be caused by the same abnormal 'prion' protein (PrP^{Sc}) that causes BSE and is thought to result from eating contaminated beef products. To 6th August 2001, there have been a total of 106 confirmed or probable cases of vCJD in the UK (Department of Health, 2001b). It is not known how many people have been infected but have not yet developed symptoms. Although there have been no documented cases of transmission of vCJD through medical interventions to date, it must be assumed that vCJD has the potential for transmission between patients as has been shown for classical CJD (Department of Health, 2001a). The incubation time for the emergence of the disease may be many decades (Bruce *et al.*, 1997).

Could human urine contain prion infectivity?

The extraction and purification of post-menopausal urine was pioneered in Italy in the late 1940s to result in the production of HMG. The first HMG extract that was sufficiently pure for human use was Pergonal® (Serono, Italy) or menotropin, in 1949 (Donini and Montezemolo, 1949). It took ten years for sufficient clinical interest to develop to require its commercial production. The first live birth was reported in 1962 (Lunenfeld *et al.*, 1962). Twenty to thirty litres of post-menopausal urine were required to treat one patient with one cycle of HMG. Over the next two decades purification processes were enhanced in order to increase the relative amount of active ingredient of HMG (menotropin) and uFSH (urofollitropin) (Hayden *et al.*, 1999; review).

The issue to tax us here is whether pooled urine from post-menopausal women might contain infective agents that could cause prion disease in women treated with gonadotrophins. There is particular sensitivity because of the development of CJD in patients treated both by gonadotrophins and growth hormone purified from cadaveric human pituitary glands. More than 80 cases of growth hormone related CJD have so far been reported in the UK, USA and France, with an incubation time of around 10 years (Committee On Safety Of Medicines, 1998). A genetic susceptibility to infection has been demonstrated. Gonadotrophins were prepared from human pituitaries for a shorter period of time than growth hormone and only four cases of CJD have been reported to date (all in Australia) (Committee On Safety Of Medicines, 1998).

The report that has stirred up the current debate is the finding of a protease resistant isoform of PrP in the urine of scrapie-infected hamsters, BSE-infected cattle and humans suffering from CJD (Shaked *et al.*, 2001). Most of the CJD patients were actually patients carrying the E200K mutation (Gabizon *et al.*, 1996). Urine from humans infected with vCJD was not examined. The conclusions drawn by Shaked and colleagues were that urine could be used to provide a simple, non-invasive test for prion diseases. They also demonstrated the appearance of PrP^{Sc} in urine before its accumulation in brain, thus inferring that the PrP urine test could be used during subclinical stages of infection.

There is no suggestion, however, that urine might contain an infective agent and furthermore, inoculation experiments have been performed (Shaked *et al.*, 2001) which failed to confirm infectivity. In their experiments hamsters were inoculated with either samples containing urine PrP from normal or hamsters with symptomatic scrapie or with brain samples from symptomatic-scrapie hamsters that had been diluted to contain similar concentrations of PrP^{Sc}. Whilst the animals inoculated with scrapie-infected brain samples suffered from fatal symptoms after about 80 days, none of the animals

Table I. Report of a World Health Organization consultation on medicinal and other products in relation to human and animal transmissible spongiform encephalopathies (World Health Organization, 1997)

Category	Infectivity level
Category 1	High infectivity Brain, spinal cord, (eye)*
Category 2	Medium infectivity Spleen, tonsil, lymph nodes, ileum, proximal colon, cerebrospinal fluid, pituitary gland, adrenal gland, (dura mater, pineal gland, placenta, distal colon)*
Category 3	Low infectivity Peripheral nerves, nasal mucosa, thymus, bone marrow, liver, lung, pancreas
Category 4	No detectable infectivity Skeletal muscle, heart, mammary gland, milk, blood clot, serum, faeces, kidney, thyroid, salivary gland, saliva, ovary, uterus, testis, seminal testis, fetal tissue, (colostrum, bile, bone, cartilaginous tissue, connective tissue, hair, skin, urine).

*Tissues in brackets were not titrated in the original studies (Hadlow, 1980, 1982) but relative infectivity is indicated by other data on spongiform encephalopathies.

inoculated with urine samples from hamsters with symptomatic scrapie developed clinical symptoms of prion disease up to 270 days—although they did test positive for the urinary PrP^{Sc} and one of three hamsters that was killed after 120 days showed low concentrations of PrP^{Sc} in the brain. This suggests that inoculation with urinary PrP^{Sc} *may* result in a subclinical or carrier state prion infection. The implications of this are unclear and there is certainly a need to repeat and confirm these observations (Professor R.Will, personal communication) before drawing conclusions about the putative infectivity of urine from prion-infected humans.

Transmission of prion disease

Prion disease, in particular vCJD, is thought to be due to the transmission of BSE to humans, predominantly by the ingestion of infected nervous tissue (brain, spinal cord). A critical factor in the pathogenesis of TSEs is the quantity of the prion present. Whilst the lymphoreticular system is essential for its pathogenesis, there is no evidence for transmission by the ingestion of tissue containing white cells/lymphoid tissue (e.g. spleen, lymph nodes). Transmission from individual to individual appears to be low, with a low within-herd incidence of BSE. Furthermore the current advice from the World Health Organization (1997—current on website December 2001) is that urine is thought to have zero infectivity (Table I), which is why precautions are not advised when handling urine from either infected animals or humans. Similarly other excreted bodily fluids are not thought to cause risk—hence the safety of milk (World Health Organization, 1997). There is, however, the potential risk of infection via leukocytes in bodily fluids, for example milk from cows with mastitis and, theoretically, from urine of women with cystitis (Professor R. Lacey, personal communication)—although neither of these situations has been demonstrated. With respect to blood products there is as yet no evidence that any form of CJD is transmitted by blood transfusion or via plasma derived medicinal products (Committee On Safety Of Medicines, 1998). Blood for human transfusion is now treated to remove leukocytes. Because of the problems that the recall of plasma-derived medicinal products has caused when donors were later found to test positive for CJD it was decided to source plasma products from countries free of vCJD (Committee On Safety Of Medicines, 1998).

Urinary gonadotrophins

Urinary gonadotrophins are currently derived from post-menopausal women who reside in countries free of BSE and vCJD (e.g. Argentina, Ferring Pharmaceuticals, personal communication). Furthermore, with respect to today's debate, *even if* urine were found to be infective it is highly unlikely that post-menopausal women with classical CJD would be in a position to be asked to donate urine and those individuals so far identified with vCJD have tended to be in a younger, pre-menopausal, age group (although they could potentially donate during the pre-clinical phase). The issue that a country is currently thought to be free of BSE is of course simply due to lack of detection of the disease amongst livestock combined with the absence of indigenous cases of vCJD in humans. There is the potential for this situation to change due to the fluidity and unpredictability of the condition.

Recombinant FSH

Recombinant FSH is derived from a Chinese hamster ovary (CHO) cell line that has been transfected with the gene for human FSH. Once the human FSH protein is produced the glycosylation process then occurs within the CHO cells (rhFSH Product Development Group, 1998). The cell culture medium requires the presence of fetal calf serum and, reassuringly, this is also obtained from countries where BSE is absent (Organon laboratories and Serono laboratories, personal communications). The fetal calf serum used in cell cultivation is removed by a validated purification process (Committee On Safety Of Medicines—personal communication). There are, in addition, tight controls placed by regulatory bodies, such as the Committee on Safety of Medicines in the UK, to ensure that all medicinal products are free of any potential risk of transmission of TSEs. There is not currently a reliable diagnostic or screening test for prion disease, although recently a plasminogen has

been developed which selectively binds to abnormal prions in the blood, and might even become a way for removing prions from blood products (Fischer *et al.*, 2000).

Both urinary derived and recombinantly engineered gonadotrophin preparations require purification. Procedures for ensuring that gonadotrophin preparations are free from contamination with infective agents include a number of filtration, anionic exchange chromatography and precipitation steps—detailed description of which is beyond the scope of this paper (Recombinant Human FSH Product Development Group, 1998; British Pharmacopoeia, 2001). Thus bacteria, viruses and prions may be physically removed from the final gonadotrophin preparation leaving FSH (and LH) as the only active ingredients. It is also reassuring to note that similar fractionation procedures that are used for the manufacture of human plasma products (e.g. albumin, immunoglobulins, factor VIII etc) contain steps that are capable of removing prion proteins (Foster, 2000).

Should the use of urinary-derived gonadotrophins be discontinued?

This debate concerns the putative risks of the transmission of prion disease from urinary-derived gonadotrophin preparations and is not concerned with either efficacy or the cost-benefit argument, which has been covered amply in recent months (Barlow, 2001; Daya *et al.*, 2001; Sykes *et al.*, 2001). Although, of course, in the wider debate it is necessary to consider every property of the available drugs (Balen *et al.*, 1999). The current evidence on the presence of PrP in urine does not appear sufficient to advocate the discontinuation of urinary-derived gonadotrophins. Caution needs to be exercised and further research undertaken. If Shaked and colleagues' work is verified it would be prudent to use the methods described to screen urine for PrP prior to its use for the extraction of gonadotrophins (Shaked *et al.*, 2001).

In conclusion, hundreds of thousands of women have been treated with gonadotrophin preparations, since the introduction of the urinary-derived HMG products in the early 1960s and the more recent introduction of recombinant FSH (and now LH) in the 1990s. All of the gonadotrophin preparations appear to have a good safety record without evidence of contamination with infectious agents, in particular, at the present time, with prions. The current procedures for sourcing of products from countries free of vCJD combined with a purification process that appears to minimise the risk of infectivity provides further reassurance. Extensive research is underway to identify reliable, non-invasive screening tests for prion disease together with methods for ensuring their elimination from biological products. In the meantime, we can be reassured that both urinary-derived and recombinant gonadotrophins appear to carry a minimal risk of prion infectivity and there is no evidence to change current prescribing habits.

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References

Balen, A.H., Hayden, C. and Rutherford, A.J. (1999) What are the value of the recombinant gonadotrophins? *Hum. Reprod.*, **14**, 1411–1417.

Barlow, D. (2001) Cost effectiveness modelling. *Hum. Reprod.*, **16**, 2479–2480.

British Pharmacopoeia (2001) Menotrophin 1067.

Bruce, M.E., Will, R.G., Ironside, J.W., McConnell, I., Drummond, D., Suttie, A., McArdle, L., Chree, A., Hope, J., Birkett, C., Cousens, S., Fraser, H. and Bostock, C.J. (1997) Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature*, **389**, 498–501.

Committee on Safety of Medicines, Scientific Committee on Medicinal Products and Medical Devices (1988) Opinion on the risk quantification for CJD transmission via substances of human origin.

Daya, S., Ledger, W., Auray, J.P., Duru, G., Silverberg, K., Wikland, M., Bouzayen, R., Howles, C.M. and Beresniak, A. (2001) Cost-effectiveness modelling of recombinant FSH versus urinary FSH in assisted reproduction techniques in the UK. *Hum. Reprod.*, **16**, 2563–2569.

Department of Health (2001a) First Annual Report 2000–2001 to the Joint Working Group on Transmissible Spongiform Encephalopathies of the Spongiform Encephalopathy Advisory Committee and the Advisory Committee on Dangerous Pathogens. (Department of Health Government Website, UK).

Department of Health (2001b) Monthly CJD Statistics published by the Department of Health at www. doh. gov. uk/cjd/cjd_stat. htm.

Donini, P. and Montezemolo, R. (1949) *Rassegna di Clinica, Terapia e Scienze Affini.* A publication of the Biologic Laboratories of the Instituto Serono., **48**, 3–28.

Fischer, M.B., Roeckl, C., Parizek, P., Schwarz, H.P. and Aguzzi, A. (2000) Binding of disease-associated prion protein to plasminogen. *Nature*, **408**, 479–483.

Foster, P.R. (2000) Prions and blood products (Review). *Ann. Med.*, **32**, 501–513.

Gabizon, R., Telling, G., Meiner, Z., Halimi, M., Kahana, I. and Prusiner, S.B. (1996) Insoluble wild-type and protease-resistant mutant prion protein in brains of patients with inherited prion disease. *Nature Med.*, **2**, 59–64.

Hadlow, W.J., Kennedy R.C., Race, R.E. and Eklund, C.M. (1980) Virologic and neurohistologic findings in dairy goats affected with natural scrapie. *Vet. Pathol.*, **17**, 187–199.

Hadlow, W.J., Kennedy R.C. and Race, R.E. (1982) Natural infection of Suffolk sheep with scrapie virus. *J. Infect. Diseases*, **146**, 657–664.

Hayden, C.J., Balen, A.H. and Rutherford, A.J. (1999) Recombinant gonadotrophins. *Br. J. Obs. Gynaecol*., **106**, 188–196.

Lunenfeld, B., Sulmovici, S., Rabau, E. and Eshkol, A. (1962) L'induction de l'ovulation dans les amenorrhees hypophysaires par an traitment combine de gonadotrophines urinaires menopausiques et de gonadotrophines chorioniques. *C. R. Soc. Francaise de Gynecol.*, **5**, 1–6.

Matorras, R. and Rodríguez-Escudero, F.J. (2002) Bye-bye urinary gonadotrophins? The use of urinary gonadotrophins should be discouraged. *Hum. Reprod.*, **17**, xxxx.

National CJD Surveillance Unit (2000) Ninth Annual Report 2000. Creutzfeldt-Jakob Disease Surveillance in the UK. The National CJD Surveillance Unit. www.cjd.ed.ac.uk

Recombinant Human FSH Product Development Group (1998) Recombinant follicle stimulating hormone: development of the first biotechnology product for the treatment of infertility. *Hum. Reprod. Update,* 862–881.

Shaked, G.M., Shaked, Y., Kariva, Z., Halimi, M., Avraham, I. and Gabizon, R. (2001) A protease resistant PrP isoform is present in urine of animals and humans affected with Prion diseases. *J. Biol. Chem.*, **276**, 31479–31482.

Sykes, D., Out, H.J., Palmer, S.J. and van Loon, J. (2001) The cost-effectiveness of IVF in the UK: a comparison of three gonadotrophin regimens. *Hum. Reprod.*, **16**, 2563–2569.

Will, R.G., Ironside, J.W., Zeidler, M., Cousens, S.N., Estibeiro, K., Alperovitch, A., Poser, S., Pocchiari, M., Hofman, A. and Smith, P.G. (1996) A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet*, **347**, 921–925.

World Health Organization (1997) Report of a WHO Consultation on Medicinal and other Products in Relation to Human and Animal Transmissible Spongiform Encephalopathies.

The conflict between effective and affordable health care—a perspective from the developing world

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The recent introduction of recombinant FSH into the clinical management of patients suffering from infertility appears to be associated with several treatment benefits when compared with urinary human menopausal gonadotrophin. However, from the perspective of the developing world the associated increase in cost is a cause for concern—particularly if the 'cheaper' urinary gonadotrophins are no longer marketed. The need for infertility care in Africa is significant, but health resources are very limited. The commonest cause of infertility in Africa is tubal disease, so that assisted reproductive techniques, and therefore exogenous gonadotrophins, are central to effective management. The conflict between affordable and effective health care is addressed.

Key words: assisted reproductive technology/developing countries/infertility care/recombinantFSH/urinary gonadotrophins

The ongoing development of more effective and safer pharmacological compounds is driving fundamental changes in medicine (Anonymous, 2001). In the field of reproductive medicine this is demonstrated by the pharmacological development of gonadotrophin preparations. The time between the first discovery of gonadotrophic hormones (Zondek and Aschheim, 1927) to the clinical availability of recombinant (r)FSH spans just over six decades. These 60 years have seen the development of the use of exogenous gonadotrophins which were initially extracted from animals, then from the human pituitary and finally from human menopausal urine.

The advent of rFSH has made urinary (u)HMG redundant, or so it seems. Before we bid farewell to HMG let us remember that the therapeutic availability of HMG revolutionized treatment options for ovulatory dysfunction and was an essential component in the development of assisted reproductive techniques. The demand for the latter increased towards the end of the last century to such a degree, that in several developed countries $>1\%$ of live births are directly attributed to this technology (ESHRE, 2001). This rising demand on a limited resource (human menopausal urine) was one, if not *the* driving motive for the development of rFSH. In the article 'Gonadotropic preparations – lessons learned', (Lunenfeld and Lunenfeld, 1997) it was calculated that $>100\times10^6$ litres of urine would be required to facilitate the treatment of infertile women in the developed world between 1996 and 2000. Interestingly, no reference is made to possible requirements in the developing world.

To date two rFSH preparations are available (Gonal-F®, Serono International and Puregon®, NV Organon). The most significant advantage attributed to this technology is the constant availability of a biochemically highly pure product which is independent of urine collection (Frydman *et. al.,* 2000). Careful consideration of this statement and other reports in the literature (Coelingh Bennink *et al.,* 1998; Daya and Gunby, 1999) allows the conclusion that there are indeed two main advantages of this new technology. Firstly, it provides a more convenient source for exogenous gonadotrophins, an advantage which accrues first and foremost to the pharmaceutical industry although clinicians and patients benefit if an otherwise world-wide shortage of the product can be avoided. Secondly, greater purity of the product is attained ($>99\%$ pure FSH with a specific activity of $>10\ 000$ IU FSH/mg) which, unlike HMG, does not contain LH or other urinary protein contaminants.

It has been suggested that rFSH is associated with better treatment results in assisted reproduction when compared with urinary (u)FSH or HMG, although the demonstration of statistically increased pregnancy rates (PR) is based on meta-analyses. According to these meta-analyses this increase in PR is in the order of 5%. In the meta-analysis by Daya and Gunby twelve trials including a total of 2875 cases demonstrated a 3.7% risk difference in clinical PR per cycle started in favour of rFSH when compared with uFSH (95%CI, 0.5–6.9%) (Daya and Gunby, 1999). Out *et al*. analysed three randomized controlled trials, which compared the efficacy of rFSH with uFSH and HMG (Out *et al.*, 1997). The result was a 5% difference in the ongoing PR (95%CI, 0.2–9.7) in favour of rFSH. However, these findings were not confirmed in a meta-analysis by Agrawal *et al*. (Agrawal *et al.*, 2000). Following the evaluation of 11 randomized controlled trials on the use of FSH versus HMG in assisted reproductive technologies the authors concluded that both preparations yielded similar PR in cycles utilizing GnRH agonists for pituitary desensitization (both long and short protocol). FSH was associated with a higher PR only in the absence of pituitary desensitization (95%CI, 1.01–7.72). A number of subsequent studies addressed the question of treatment benefits

secondary to the use of rFSH when compared with HMG but failed to demonstrate an effect on oocyte quality, embryo quality and pregnancy rates(Ng *et al.*, 2001; Strehler *et al.*, 2001; Westergaard *et al.*, 2001).

Recombinant FSH may carry other treatment benefits including both a reduction in the number of ampoules required per treatment cycle as well as the number of days of FSH treatment, although statistical significance may be based on as little a difference as 1.7 ampoules and 0.8 days (Schats *et al.,* 2000). The notion that rFSH is associated with a lower risk of ovarian hyperstimulation syndrome still needs further investigation. The absence of contaminating urinary, non-hormonal proteins reduces the (albeit rare) complication of local reactions to exogenous gonadotrophins at the injection site (Albano *et al.*, 1996). Most recently the concern has been raised that the urine of humans affected with transmissible spongiform encephalopathies (prion diseases) may contain infective prion proteins. Although the clinical relevance of this finding with regard to disease transmission is currently unclear it has been recommended in this debate on urinary gonadotrophins that their use be discouraged (Matorras and Rodriguez-Escudero, 2002).

However, this new technology comes at a cost. In South Africa the difference in cost between rFSH (75 IU) and HMG (75IU) is nearly 100%. Trying to establish the overall increase in cost per assisted reproductive treatment cycle is difficult as the reported requirements for rFSH (dosage and duration treatment) vary considerably. Furthermore, the relative contribution of the cost of medication to the overall cost of assisted reproduction is likely to vary not only between countries but between individual centres. Suffice it to say that the increased cost associated with rFSH is significant and from the perspective of the developing world a cause for grave concern—a concern which tempers the enthusiasm surrounding this new technology. In order to appreciate this concern it is perhaps necessary to reflect briefly on the status of, and the need for, infertility care in Africa.

Infertility in Africa is a major reproductive health problem. Prevalence rates are high (20–40% in certain regions) and the associated burden of disease is significant. The commonest cause of infertility is tubal disease secondary to pelvic sepsis, which in turn is probably the commonest gynaecological disease amongst African women (Muir and Belsey, 1980). It is arguably the psycho-social consequences which have the greatest negative impact on the well-being of infertile men and women. In a continent where marriage is almost universal, and the purpose of marriage is children, infertility is often a major tragedy. Women in particular are affected, as their social status and security usually depends directly on their fertility. Those who cannot reproduce are at a substantial risk of divorce, stigmatization, socio-economic deprivation and abuse (Bergström, 1992; Gerrits, 1997; Sundby, 1997). Until recently the problem of infertility in Africa received scant attention as national and international health strategies focused almost exclusively on reducing population growth (Van Balen and Gerrits, 2001). Although the reproductive health needs of patients with involuntary childlessness are gradually being recognized they are, generally speaking, still far from being respected.

The recommendation that infertility care in Africa has to focus on prevention is both logical and relevant, but it has two shortcomings. It does not address the needs of those who are already infertile (Van Balen and Gerrits, 2001). In addition it requires a change of human behaviour which depends on many variables and if this can indeed be achieved, will take several generations for the benefits to be felt. In terms of infertility treatment, cognisance has to be taken of the high prevalence of tubal disease and the fact that most women with a tubal factor present with severe disease (Kasia *et al.,* 1997; Dyer and Tregoning, 2000). In this setting assisted reproductive technologies (and therefore exogenous gonadotrophins) play a central role as probably the most effective treatment option for the majority of infertile couples. Not surprisingly, availability of this technology in Africa is rare. Where available, access is often difficult for the majority of patients who would ultimately benefit most.

Assuming that cost is the only limiting factor would unduly simplify the matter, as there are many barriers to treatment. The assumption that modern, evidence-based medicine works equally well everywhere in the world has been proven wrong many times (Foster, 1987). It has to be clearly stated, however, that cost is a particularly prominent barrier. It is a fair assumption that the cost of assisted reproduction in most African countries, with the rarest of exceptions, is not covered by public health care or private insurance companies. In this context, cost becomes a critical factor and any further increase in cost may further limit access to treatment. The argument that the more expensive treatment may be more effective, perhaps even more cost-effective, does not really resolve the problem. Whatever the pregnancy rates may be, if the treatment becomes too expensive, fewer and fewer patients will be able to access it and despite higher pregnancy rates the number of children born as a result of assisted reproduction may be lower than before. It is difficult to dismiss the notion that the ‘rich’ will get better and more effective treatment whilst the ‘poor’ may be left with less than they had before.

According to the declaration of the 18th Conference of the Council for International Organisations of Medical Sciences (CIOMS), ‘health services should be effective, efficient, accessible and affordable’ (Bankowski and Bryant, 1994). How do we resolve the conflict where a health service becomes so effective and efficient due to better but more expensive technology that it is no longer accessible and affordable? Although the answer to this question occupies governments, insurers, unions and health planners all over the world, it serves to highlight the vast differences between the developing and developed world.

The real crux of the matter is not the introduction of new technology, it is the concern that old, ‘cheaper’ technology will be withdrawn. With the advent of rFSH the pharmaceutical companies appear to plan the discontinuation of uHMG. Urinary gonadotrophins have been good enough and, all in all, safe enough to be used on a very large scale in the industrialized world for over 40 years. It could be argued, that this product is still suitable for use in poorer

resource settings where costs need to be kept to a minimum in order to deliver or even expand infertility care. If both products (HMG and rFSH) continued to be available, patients and doctors could make an informed choice and it would be interesting to see what these choices would be around the world. Unless a pharmaceutical company continues the product or other companies try and register new urinary products (neither option being guaranteed in South Africa at the moment) there will be no choice and the decision as to which gonadotrophin to use is pre-empted by the market.

Perhaps South Africa—a developing country which, however, has certain private and public health care structures in place to offer tertiary level infertility care at least in certain regions—stands alone in this matter. It is possible that the rising cost associated with the advent of rFSH in reproductive medicine is not a concern in the developed world where resources are more abundant. And perhaps it is not a concern for other developing countries where infertility treatment is both out of the reach and out of the focus of national health priorities. But if the latter is true and if, at the same time, we are trying to improve reproductive health in the developing world, then any significant rise in the cost of assisted reproduction may be just a further step in the wrong direction.

From the perspective of a health care worker trying to provide effective and affordable infertility care to economically disadvantaged couples in South Africa, there are many questions and no easy answers. The ongoing availability of uHMG which would give doctors and patients a choice of different exogenous gonadotrophins would be welcomed. Does the pharmaceutical industry, with its high profit margins and extraordinary resources spent on advertising and marketing, carry some responsibility towards producing affordable drugs? Is the cost of rFSH justified or is it inflated due to the absence of a therapeutic alternative that could challenge it? Is it in order or indeed indicated to discontinue somewhat less effective albeit 'cheaper' (for the consumer, that is) drugs in favour of newer, better and safer products (which, incidentally, may also carry a higher profit margin)? What other options are available to develop truly low cost assisted reproductive technologies? The harvesting of immature oocytes and subsequent in-vitro maturation for as little as 24–48hrs is a particularly promising development. This technique may obviate the costly and potentially risky process of controlled ovarian stimulation (Mikkelsen, 2002). On a much larger ethical and political scale the question may be asked what, if any, is the national and international responsibility of the 'haves' towards the 'have-nots'? Health for some and not for others creates an inherently unstable situation and, given the overall dimension of the problem, requires global strategies (Bankowski and Bryant, 1994).

In the absence of any answers to these questions I would like to conclude with a quote from the Conference on 'Poverty, Vulnerability, the Value of Human Life and the Emergence of Bioethics' held by the Council for International Organisations of Medical Sciences CIOMS (Bankowski and Bryant, 1994): 'The twentieth century will go down in history characterized by the quest for knowledge. The twenty-first century, it is hoped, will be characterized in history by the wisdom with which the acquired knowledge was applied with equity'.

References

Agrawal, R., Holmes, J. and Howard, S.J. (2000) Follicle-stimulating hormone or human menopausal gonadotropin for ovarian stimulation in in vitro fertilization cycles: a meta-analysis. *Fertil. Steril.*, **73**, 338–343.

Albano, C., Smitz, J., Camus, M., Coelingh Bennink, H., Van Steirteghem, A.C. and Devroey, P. (1996) Pregnancy and birth in an in-vitro fertilization cycle after ovarian stimulation in a woman with a history of allergic reactions to human menopausal gonadotrophin. *Hum. Reprod.*, **11**, 1632–1634.

Anonymous (2001) Making medicines affordable: the prize factor (position paper). *Am. J. Public Health*, **91**, 486–490.

Bankowski, Z. and Bryant, J.H. (1994) *Poverty, vulnerability, and the value of human life – a global agenda for bioethics.* Council for International Organisations of Medical Sciences (CIOMS), Geneva.

Bergström, S. (1992) Reproductive Failure as a Health Priority in the Third World: A Review. *East Afr. Med. J.*, **69**, 174–180.

Coelingh Bennink, H.J.T., Fauser, B.C.J.M. and Out, H.J. (1998) Recombinant follicle-stimulating hormone (FSH; Puregon) is more efficient than urinary FSH (Metrodin) in women with clomiphene citrate-resistant, normogonadotropic chronic anovulation: a prospective, multicenter, assessor-blind, randomised, clinical trial. *Fertil. Steril.*, **69**, 19–25.

Daya, S. and Gunby, J. (1999) Recombinant versus urinary follicle stimulating hormone for ovarian stimulation in assisted reproduction. *Hum. Reprod.*, **14**, 2207–2215.

Dyer, S.J. and Tregoning, S. (2000) Laparoscopic reconstructive tubal surgery in a tertiary referral centre – a review of 177 cases. *S.A. Med. J.*, **90**, 1015–1019.

ESHRE (2001) The European IVF-monitoring programme (EIM), for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 1998. Results generated from European registers by ESHRE. *Hum. Reprod.*, **16**, 2459–2467.

Foster, G.M. (1987) World Health Organization behavioural science research: problems and prospects. *Soc. Sci. Med.*, **24**, 709–717.

Frydman, R., Howles, C.M. and Truong, F. for the French Multicentre Trialists. (2000) A double-blind, randomized study to compare recombinant human follicle stimulating hormone (FSH; Gonal-F) with highly purified urinary FSH (Metrodin HP) in women undergoing assisted reproductive techniques including intracytoplasmic sperm injection. *Hum. Reprod.*, **15**, 520–525.

Gerrits, T. (1997) Social and Cultural Aspects of Infertility in Mozambique. *Patient Educ. Couns.*, **31**, 39–48.

Kasia. J.M., Raiga, J., Doh, A.S., Biouele, J.M., Pouly, J.L., Kwiatkowski, F., Edzoa, T. and Bruhat, M.A. (1997) Laparoscopic fimbrioplasty and neosalpingostomy: Experience of the Yaounde General Hospital, Cameroon. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **73**, 71–77.

Lunenfeld, B. and Lunenfeld, E. (1997) Gonadotropic preparations – lessons learned. *Fertil. Steril.*, **67**, 812–814.

Matorras, R. and Rodriguez-Escudero, F.J. (2002) Bye bye urinary gonadotropins. *Hum. Reprod.*,**17**, 1675.

Mikkelsen, A.L. (2002) Oocyte maturation in vivo and in vitro. In Healy, D.L., Kovacs, G.T., McLachlan, R. and Rodriguez-Armas, O. (eds), *Reproductive Medicine in the twenty-first century.* Parthenon Publishing Group, UK, pp346–355.

Muir, D.G. and Belsey, M.A. (1980) Pelvic inflammatory disease and its consequences in the developing world. *Am. J. Obstet. Gynecol.*, **138**, 913–928.

Ng, E.H.Y., Lau, E.Y.L., Yeung, W.S.B. and Ho, P.C. (2001) HMG is as good as recombinant human FSH in terms of oocyte and embryo quality: a prospective randomised trial. *Hum. Reprod.*, **16**, 319–325.

Out, H.J., Driessen, S.G.A.J., Mannaerts, B.M.J.L. and Coelingh Bennink, H.J.T. (1997) Recombinant follicle-stimulating hormone (follitropin beta, Puregon) yields higher pregnancy rates in in vitro fertilization than urinary gonadotropins. *Fertil. Steril.*, **68**, 138–142.

Schats, R., De Sutter, P., Bassil, S., Kremer, J.A.M., Tournaye, H. and Donnez, J. on behalf of the Feronia and Apis study group (2000) Ovarian stimulation during assisted reproductive treatment: a comparison of recombinant and highly purified urinary human FSH. *Hum. Reprod.*, **15**, 1691–1697.

Strehler, E., Abt, M., El-Danasouri, I., De Santo, M. and Sterzik, K. (2001) Impact of recombinant follicle-stimulating hormone and human menopausal gonadotropins on in vitro fertilization outcome. *Fertil. Steril.*, **75**, 332–336.

Sundby, J. (1997) Infertility in the Gambia: Traditional and Modern Health Care. *Patient Educ. Couns.*, **31**, 29–37.

Van Balen, F. and Gerrits, G. (2001) Quality of infertility care in poor-resource areas and the introduction of new reproductive technologies. *Hum. Reprod.*, **16**, 215–219.

Westergaard, L.G., Erb, K., Laursen, S.B., Rex, S. and Rasmussen, P.E. (2001) Human menopausal gonadotropin versus recombinant follicle-stimulating hormone in normogonadotropic women down-regulated with a gonadotropin-releasing hormone agonist who were undergoing in vitro fertilization and intracytoplasmic sperm injection: a prospective randomised study. *Fertil. Steril.*, **76**, 543–549.

Zondek, B. and Ascheim, S. (1927) Das Hormone der Hypophysenvoderlappens; Testobject zum Nachweis des Hormons. *Klin. Wochenschr.*, **6**, 248–265.