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IVF in women with severe endometriosis: should elective single embryo transfer be the first-line option?

Only a minority of women with advanced endometriosis seeking pregnancy achieves a conception spontaneously, and many of them eventually resort to IVF. It has been suggested that the success rate of IVF in women with endometriosis is significantly lower than in those without the disease (1), although the evidence is not consistent. Based on this tenet, many fertility doctors continue to transfer two or three embryos when the apparent cause of infertility is endometriosis.

It has been demonstrated that the results of elective single embryo transfer (eSET) are similar to those obtained with double embryo transfer (DET), when use of frozen and thawed embryos is taken into account (2). In other words, the conception rate is related to the absolute number of embryos transferred, independently of the number of transfers. Indeed, it appears that transfer of cryopreserved embryos is associated with a better outcome compared with fresh embryos, owing to decreased endometrial receptivity during ovarian hyperstimulation cycles (3, 4).

Implementation of systematic eSET is associated with a dramatic reduction in the rate of multiple pregnancies to almost "physiologic" figures (5, 6). Definition of the well known risks of IVF-related multiple pregnancies, including neonatal morbidity and mortality associated with preterm birth, is not among the objectives of this editorial, and the interested reader is referred to several excellent articles recently published on this issue (7, 8).

Inside this eJournal

A/Professor Paolo Vercellini
WES President

Sufficient here is to recall the wise words that our former President, Hans Evers, wrote already ten years ago:

> **"... it is becoming increasingly more evident, to patients and doctors alike, that the only way to contain risks and complications of IVF and its potential long-term health effects, will consist of elective transfer of a single, high quality, chromosomally normal embryo. The most appropriate outcome variable of all assisted reproduction procedures (IVF and non-IVF), therefore, is not pregnancy rate, but singleton pregnancy rate per cycle started" (9).**

With regard to the issue of non-IVF procedures, it has been reported that super-ovulation with intrauterine insemination (COH-IUI) is followed by modest improvement in the likelihood of conception in women with endometriosis (10). Dmowski et al (11) observed a pregnancy rate of 11% and 47% after, respectively, COH-IUI or IVF in infertile women with the disease. When the data were stratified according to the stage of endometriosis and women's age, the benefit of IVF over COH-IUI was even more pronounced. Moreover, D'Hooghe et al (12) reported that the cumulative recurrence rate in women operated for stage III-IV endometriosis 21 months after ART was 7% in patients treated with IVF only, and 70% in those treated with IUI only. The limited impact of IVF on the risk of endometrioma recurrence has been confirmed by

Benaglia et al (13). This group has also demonstrated that the dimensions of existing endometriomas are not substantially modified by IVF cycles, and that de-novo formation of ovarian endometriotic cysts is rare in spite of super-ovulation (14).

The above findings have been interpreted in terms of interference with the pathogenesis of ovarian endometriotic cysts. There is a growing body of evidence supporting the crucial role of ovulation in the development of endometriomas. The main difference between IUI and IVF is represented by the aspiration of the follicles prior to spontaneous dehiscence, and this practice may explain why COH is associated with increased risk of endometrioma formation if super-ovulation precedes IUI, but not if it precedes IVF (13, 14). Based on the available data on reproductive success and both disease progression and recurrence, IVF should be considered the first-line approach in the management of infertility associated with advanced endometriosis when ART is considered.

However, pregnancies in women with endometriosis, whether obtained spontaneously or by means of IVF, are at increased obstetrical risk (15, 16). In particular, the risk of preterm birth, intra-uterine growth restriction, and placenta previa appears to be influenced. A placenta previa was observed in 12/419 (3.7%) patients with endometriosis who achieved a first spontaneous singleton conception (17). The incidence was unevenly distributed, being 7.6% in 150 women with recto-vaginal lesions (ie, 1 in every 13 deliveries). An increase in the risk of placenta previa in the presence of endometriosis has been reported also in infertile women achieving pregnancy with IVF (18), with an OR of 1.7 compared with women without endometriosis. More recently, also Takemura et al (19) observed a greatly increased risk of placenta previa in pregnancies obtained with ART in women with endometriosis. Therefore, performance of IVF in women with severe disease may lead to a synergistic effect (endometriosis plus infertility plus ART per se) with a major increase in risk of placenta previa (17, 18, 20). Indeed, even with eSET, the risk of placenta previa is already six-fold (6.02; 95% CI, 2.79 to 13.01) compared with spontaneously conceived singletons (21). The combination of placenta previa with a twin gestation constitutes a very dangerous obstetric condition for both the mother and foetuses and such risk should not be iatrogenically increased.

There is a further clinical consideration strongly favouring eSET in women with advanced deep endometriosis. These patients generally show a severely altered abdomino-pelvic anatomy, with extensive and dense adhesions involving the uterus, adnexa, bladder, and bowel. Thus, a spontaneous pregnancy would be little probable, and IVF allows conceptions, which would have been otherwise impossible. However, in case a caesarean section is required, it may reveal a major technical challenge. In fact, great difficulties may be encountered as a result of the anatomical consequences of the disease itself as well as of previous surgery. This is of even graver concern if a post-partum hysterectomy is to be performed owing to uncontrollable haemorrhage. In these circumstances, elective caesarean sections should be centralised in tertiary-care obstetric centres with a blood bank and availability of expert abdominal surgeons and urologists. Performing double or multiple embryo transfers means that around one out of three pregnancies would be multi-foetal, necessitating an abdominal delivery in the vast majority of cases. This would be prevented by performing eSET.

> "According to Allan Templeton (5), the main problem when choosing eSET vs DET, is that "**in a commercially competitive environment, clinicians have been distracted by success rates and do not see the more important healthy outcomes. Most fertility doctors no longer practice obstetrics, so others look after the consequences of multiple embryo replacement**".

Infertile women with advanced endometriosis requesting ART may constitute a high-risk group who could benefit from accurate counselling. They must be informed with the aid of crude absolute percentages, and helped to understand that trying to increase the immediate pregnancy rate via multiple embryo transfer may entail severe risks, not only for the babies to come, but also for the mother herself. Is it worthwhile?

Indeed, the use of eSET in women with endometriosis was already suggested by David Healy in his article in our eJournal in 2010:

> "**If ART is required, perhaps we should always undertake only single embryo transfer**" (22).

Remembering the sage suggestions of David, gives me the opportunity to announce that the board of our society has decided to establish a "David Healy Award" starting from the next World Congress on Endometriosis in São Paulo. The prize will be awarded to the first

author and presenter of the best scientific presentation or poster at each world congress. The recipient must be under the age of 40 at the time of the congress. We are proud to honour his memory supporting young researchers. We believe that he would agree on this initiative, and that he is happy to see his name used to support young scientists.

Dear followers of the eJournal, let me wish you the best for the forthcoming year, and encourage you to strive through the rough journey in search for the best possible management for our infertile patients.

Paolo Vercellini
President
World Endometriosis Society

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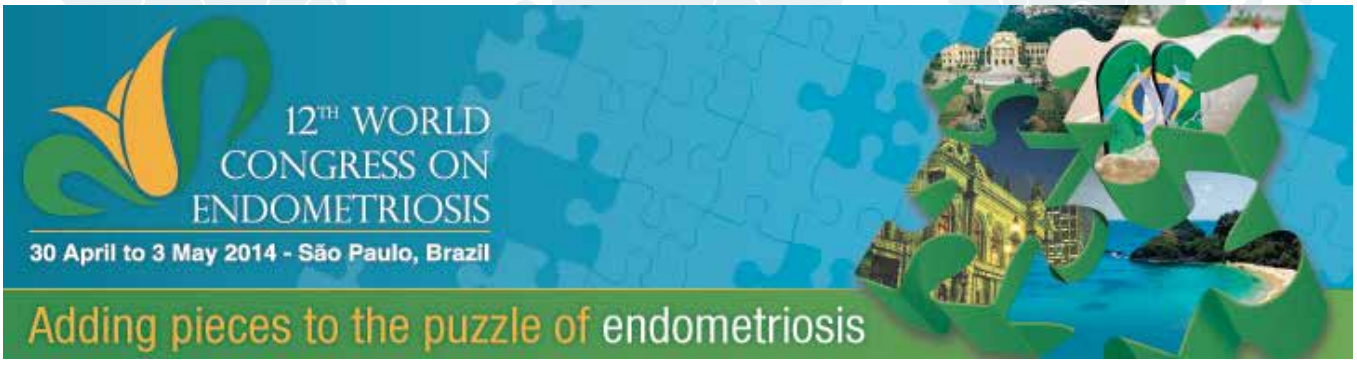
Upcoming meetings

Focus on Endometriosis	9 – 11 January 2013 Jeddah, Saudi Arabia
The Best of ESHRE and ASRM	6 – 10 March 2013 Paradise Island, Bahamas
AGES Annual Scientific Meeting XXIII 2013: The Pelvis in Pain: Endometriosis and Beyond	7 – 9 March 2013 Brisbane, Australia
4th Annual EFA Scientific and Surgical Symposium	9 – 11 March 2013 New York, USA
SGI 2013 60th Annual Scientific Meeting	20 – 23 March 2013 Orlando, USA
Deutscher Endometriose Kongress	25 – 27 April 2013 Linz, Austria
4th Nordic Congress on Endometriosis	23 – 25 May 2013 Turku, Finland
1st World Congress in Pelvic Pain	30 May – 1 June 2013 Amsterdam, The Netherlands
ESHRE Pre-Congress Course: Impact of pelvic pain and uterine bleeding on quality of life	7 July 2013 London, United Kingdom



Wishing you a Happy New Year!

A/Professor Luk Rombauts
WES eJournal Editor

I am writing this editorial for the last issue of 2012 on the second Wednesday of December. I will remember this for many years to come, because the date has a very special numerical significance: 12.12.12. Clearly, such an unusual alignment won't happen again in my lifetime and by that I don't suggest that the world will come to an end on 21.12.12 as some have predicted based on a controversial interpretation of the Mayan calendar.

In our **last issue** I celebrated the international collaboration at CERN that led to the discovery of the Higgs boson as a guiding example for us to move our field forward and I still hold that view. But sometimes individual excellence is so mind-blowing that it deserves a mention in this eJournal even if it is not related to achievements in the field of science. I am referring to Lionel Messi's recent record-beating tally of 86 goals in a single season. For a 10 minute compilation of all 86 goals **click here**. I am obviously a tragic fan of football (or soccer as it is known by those who favour the egg-shaped ball), but anyone can appreciate the other-worldly skills Messi displays in his handling of the round ball. He is a master of the set piece, a poker-faced and dead-accurate penalty kicker, but above all it is his dribbling technique that can make grown men cry. It is said that he runs faster with the ball than without and his deceptive weaving and winding is so refined that it often makes fools of his immediate rivals (for another amazing video-compilation **click here**. Jeré Longman wrote a beautiful essay on Messi's achievement in the New York Times for those that are interested **click here.**

At an individual level I am sure we have all scored some nice 'goals' this year and that's why we are winding down for are a well-deserved festive season. You should know (because you are a loyal reader of the eJournal) that, as a society, our scoreboard for 2012 also looks very good. My personal favourite is the President's initiative to 'crowd-source' the next WCE meeting. The Sao Paolo meeting in 2014 will be the first one where the WES membership has had substantial input into the programme following online voting earlier this year. How cool is that?

In this issue our President makes an impassioned plea for IVF with single embryo transfer as the first line infertility treatment in women with advanced endometriosis. He also announces the new David Healy Award, a beautiful initiative to commemorate David's contributions to the field of endometriosis. We also have a very interesting contribution from Hilary Critchley's team on pain. A scientific meeting was held to celebrate the long career of Professor Jacques Donnez, a co-founder of this society, and we have a 'local reporter' who was there to bring us the news. And last but not least Mauricio Abrao makes some very convincing arguments why Sao Paolo should be in your travel diary in 2014.

Managing women with chronic pelvic pain in the 21st century – are we missing the wood for the trees?

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The scale of the problem

Chronic pelvic pain (CPP) has a huge impact on women of reproductive age. It has a prevalence ranging from 2.1% to 24% of the female population worldwide and in the United Kingdom (UK) alone it affects over 1 million women (Latthe et al, 2006) and in the USA approximately 15% of women aged 18-50 (Mathias et al, 1996). It has a significant influence on quality of life, and represents a considerable financial burden due to lost productivity from sickness (Nnoaham et al, 2011; Simoens et al, 2012).

Chronic pelvic pain encompasses a 'syndrome' of symptoms including dysmenorrhoea, dyspareunia, dyschezia and dysuria, as well as pelvic visceral or muscle pain. The recent publication of the revised 'Green-top' publication by the Royal College of Obstetricians and Gynaecologists (UK) for the management of CPP has emphasised the need for a cultural mind shift on how we approach these patients, and the need for a holistic approach to the woman as an individual rather undue pre-occupation of the underlying pathology – the analagous 'wood and trees'.

Up to 55% of women with chronic pelvic pain have no associated pathology

Painful pelvic symptoms are associated with specific pathological processes, such as endometriosis or adenomyosis, affecting approximately 40%. They are also associated with non-gynaecological causes such as irritable bowel syndrome (IBS), interstitial cystitis or musculoskeletal problems. However, up to 55% of women with CPP have no obvious underlying pathology (Daniels et al, 2009). Furthermore, the impact of psychosocial elements on symptoms, is being increasingly recognised (Daniels and Khan, 2010). This may be particularly evident in those women with dyspareunia, irrespective of organic findings at laparoscopy.

'Endometriosis-associated pain' or 'pain associated with endometriosis'?

The prevalence of endometriosis ranges hugely depending on the patient population, from a background of 10% to 30-50% in those women with pain or undergoing infertility investigations (Rogers et al, 2009). It is this latter group that suggests that the relationship between endometriosis and pain is not clear-cut; compare the not infrequent finding of stage IV endometriosis during the course of infertility investigation in asymptomatic women with the finding of mild or minimal endometriosis in women with considerable pelvic pain symptoms. Part of this is due to use of the American Society for Reproductive Medicine revised classification of endometriosis – whilst well validated with regard to fertility it correlates less well to pain, particularly in those with endometriosis confined to the ovary (Chapron et al, 2003). This is particularly evident in those with deep infiltrating endometriosis (DIE), supported by animal models suggesting that the location and innervation of deposits have a greater impact on the degree of nociceptive pain that the macroscopic appearance (Berkley et al, 2004).

Consider endometriosis-associated pain in the context of chronic pain in general

Endometriosis-associated pain is best considered in the context of chronic pain in general. Incoming pelvic nerves convey painful messages that are likely to be altered by both inflammatory and non-inflammatory

responses to the lesion (nociceptive pain) and nerve damage (neuropathic pain). Enhanced neuronal activity at spinal and higher levels is key to the generation of chronic pain states, a concept known as central sensitisation (Latremoliere and Woolf, 2009). Central sensitisation probably plays an important part in determining the level of pain perceived. Experiments in animals and humans suggest that persistent painful stimuli generated by endometriotic tissue results over time in heightened pain awareness even from regions removed from the tissue itself (Stratton and Berkley, 2011). In addition, the limbic system doubtless plays a significant role. Although sensory and psychological aspects of pain are separable in terms of pathways within the central nervous system, there is interplay between the neural pathways that contribute to these components.

The neuropathic component

Actual nerve invasion has previously been demonstrated in the stroma of an endometriosis lesion, and it is postulated that this may lead to neuropathic pain (Anaf et al, 2002). Furthermore up-regulation of sensory C and Aδ, cholinergic and adrenergic fibres along with increased levels of nerve growth factor and tyrosine kinase receptor-A have also been demonstrated in DIE, and this may lead to hyperalgesia (Wang et al, 2009). In addition, endometriotic deposits require a blood supply and there is increasing suggestion at a molecular level that it is a paired 'neuroangiogenic' proliferation that may contribute to pain (Asante and Taylor, 2011).

Central sensitisation

Visceral hyperalgesia, and its place in the central sensitisation model remains a complex incompletely understood area. Chronic inflammation states, through the release of pro-inflammatory substrates such as bradykinnin, prostaglandins, TNF-α and IL-1 result in peripheral sensitisation of afferent neurons, there is also recruitment of so called 'silent' nocioceptors culminating in increased stimulus to second order neurons in the dorsal horn (Malykhina, 2007). Mast cell recruitment and growth factor release can alter sodium channel expression thereby further altering pain signalling (Aslam et al, 2009).

Furthermore there can be development of nocioceptive memory so that pain signalling following the initial insult can be disproportionately prolonged, and initiated by low potency stimuli. As a result of increased stimulus, compounded by external factors such as sleep fragmentation and depression (with associated alteration in the hypothalamic-pituitary-adrenal axis) there is central nervous remodelling. There is NMDA receptor dysregulation, alteration in substance P and an overall reduction in descending inhibitory pain messaging. The exact molecular mechanism behind central sensitisation remains elusive. Whilst research into the central sensitisation model has predominantly been in other modalities, it is increasingly accepted that recurrent nocioceptive stimulation from endometriotic inflammation, combined with the previously described up-regulation of sensory fibre numbers can explain results in chronic pain states inconsistent with the findings at laparoscopy seen in so many women. Equally the central model explains the increased prevalence of other clinical entities such as regional pain syndromes, fibromyalgia and chronic fatigue syndrome.

Evidence-based management of chronic pelvic pain

The American college of Obstetricians (ACOG) and the Royal College of Obstetricians and Gynaecologists (RCOG) have both published guidelines in the last two years regarding the management of endometriosis (ACOG, 2010; RCOG, 2012) (the latter under the umbrella of CPP). These two guidelines, along with the European Society of Human Reproductive Embryology (ESHRE) guideline (Kennedy et al, 2005) (last updated in 2007 and being updated again at present) represent the most frequently used body of evidence. As both the ACOG and ESHRE are specifically endometriosis management guidelines they are unsurprisingly more focused on the specific features of this to the exclusion of other aetiologies. However for the individual presenting with CPP the RCOG approach is more holistic and focused on patient outcome, rather than underlying pathology.

Diagnosis of underlying pathology in women with chronic pelvic pain

Whilst clinical assessment remains an imperfect correlator with positive findings at laparoscopy, even in those with significant cyclical symptoms (Eskenazi et al, 2001), the multitude of alternate positive pathologies and the incomplete understanding of the overall aetiology of CPP means that a thorough assessment of each patient as an individual is crucial to amelioration of symptoms and reduction in unnecessary laparoscopy.

The importance of a careful history

Red flags for endometriosis include 'cyclicity' of symptoms. IBS can be diagnosed with confidence from symptoms with a positive predictive value of up to 98% (Fass et al, 2001; Spiller et al, 2007). Equally a urological cause such as interstitial cystitis can also be elicited to a degree from the history. Nerve entrapment may result in a neuropathic picture but equally such symptoms may be from visceral hyperalgesia resulting from endometriosis. Specific enquiry into psychological and social factors in an appropriate setting may be helpful. The RCOG guideline in particular recognises their impact on the experience of pain, and their role in the development of abnormal central interpretation of painful stimuli. There is evidence, whilst not robust due to the inability to conduct randomised trials and difficulty in interpreting data in such a patient cohort, that sexual and physical abuse, can predispose to development of CPP. This is more marked in those who suffered abuse as a child that continued into adulthood (Jamieson and Steege, 1997).

Fundamentally, the RCOG guideline also underlines the critical importance of listening to the woman tell her story and eliciting her concerns, ideas and expectations regarding her pain. Clearly in those women in whom infertility rather than pain is the presenting complaint, the problem will be managed in a slightly different way to those in whom pain is the predominant feature. However, the woman's perception of her story being 'heard' and that her concerns are addressed appropriately has an impact on her eventual pain outcome (Selfe et al, 1998). Unfortunately the time required for this remains impractical in most health services, to the detriment of the patient.

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Is clinical examination helpful?

With all aetiologies, clinical examination may prove unremarkable, but may also reveal tethering, nodularity and adnexal masses. ESHRE specifically recognises that when examination is conducted during menstruation, the nodules of DIE are most reliably detected (Koninckx et al, 1996).

What basic examinations should we perform in women with chronic pelvic pain?

- **Swabs for gonococcus and Chlamydia**

The RCOG guideline (RCOG, 2012) has recommended that all women with chronic pelvic pain should be offered screening for these sexually transmitted infections (STI). The ACOG guideline recommends that screening should be offered to those in whom 'signs and symptoms warrant it'. The ESHRE guideline makes no comment on STI screening in their guideline.

- **Imaging**

Imaging remains a poor predictor of peritoneal endometriosis, even with the use of soft markers (Okaro et al, 2006) but still has an important role to play in the management of chronic pelvic pain. All three guidelines recognise the high accuracy of transvaginal ultrasound (TVS) for identification of endometriomas, and TVS remains the recommended imaging modality for the diagnosis of recto-vaginal disease. However, with regard to pelvic MRI, the guidelines diverge; the ESHRE guideline states that it does not have a role to play in diagnosis at present and the ACOG guideline recommends its use only in equivocal findings on USS for recto-vaginal and bladder disease. In contrast, the RCOG guideline states that pelvic MRI may be of use for assessment of palpable nodules or symptoms suggestive of rectovaginal disease.

- **Serum CA-125 measurement**

The elevation of serum CA-125 has been well documented in a number of inflammatory conditions, and both the ESHRE and ACOG guidelines presently view that it has limited utility in diagnosis. However, in the UK, the NICE guidelines advocate increased testing to try and improve earlier diagnosis of ovarian malignancy in women presenting with chronic pelvic pain. One of the recommended features that the NICE guideline states should prompt a CA-125 measurement is 'pelvic pain present on more that 12 times in one month'; this is also reflected in the RCOG guideline. The ESHRE guideline advises use only in those women with ovarian masses.

- **Diagnostic laparoscopy**

Laparoscopy remains the gold standard for the diagnosis of endometriosis. There remain limitations with grading of disease and the issue of visual inspection without biopsy potentially missing the full extent of disease, particularly in those with DIE. Equally, pathology such as dense adhesions may be found, division of which may improve symptoms (Swank et al, 2003). If endometriosis is found, notwithstanding the variable correlation between symptoms and degree of disease, surgical therapy may be carried out concurrently. This remains an efficacious intervention with regard to pain reduction, even when the placebo effect of laparoscopy is taken into account (Abbott et al, 2004).

To laparoscope or not?

There is definitely a place for empirical medical therapy prior to laparoscopy, given the well-documented risks of laparoscopy, a reasonably high rate of negative findings, and the fact that a negative laparoscopy can lead to disappointment and disengagement in medical services (McGowan et al, 2007). Indeed the RCOG guideline goes so far as to postulate that laparoscopy for CPP, including its use as a diagnostic tool, should be seen as 'a second-line investigation if other therapeutic interventions fail'. This draws on a study randomising patients to laparoscopy or to an 'integrated approach' (with attention to organic, psychological, dietary and environmental causes) where the latter group had significantly greater pain relief (Peters et al, 1991).

The ACOG guideline also agrees that the need for laparoscopy for a diagnosis is a subject for debate in women without infertility. Moreover, if improvements in imaging lead to greater confidence in the diagnosis of endometriosis, such as pelvic MRI (currently being assessed in the MEDAL trial: **http://www.hta.ac.uk/2400**) then laparoscopy might be reserved for treatment of known organic pathology. The exception to this will be those women with endometriomas on imaging when laparoscopy is still recommended for histological confirmation of benign pathology in women without a previous diagnosis of endometriosis.

What is the optimum therapy for pelvic pain following diagnosis of endometriosis?

All three guidelines (RCOG, ACOG, ESHRE) draw on the Cochrane Reviews (Stones and Mountfield, 2000), which state that the combined oral contraceptive pill, progestins (including the levonorgestrel intra-uterine system), danazol, and GnRH analogues are equally effective at managing pelvic pain symptoms, though their differing side effect profile may limit their acceptability to patients. There is also evidence that surgical excision is useful (Abbott et al, 2003), although even despite complete surgical excision re-operation rates for recurrent symptoms are over 50% (Vercellini et al, 2009).

Opinion regarding the role of post-laparoscopy hormonal suppression differs between the guidelines, with the ACOG guideline supporting therapies that extend the disease free interval and suppression of residual disease whereas the ESHRE guideline does not. The Cochrane review supports the ACOG guideline that insertion of an IUS following surgery improves dysmenorrhoea but agrees with the ESHRE guideline that there is a lack of evidence for long-term benefit. For the management of extra pelvic disease, the ACOG guideline recommend a medical approach with the exception of bowel or ureteric obstruction whereas the ESHRE guideline currently recommends excision if clear margins are possible. In those whom future fertility is no longer desired hysterectomy is regarded as a definitive treatment but it is acknowledged that this may not fully alleviate pain and the evidence to support concurrent bilateral oophorectomy to reduce recurrence is mixed, irrespective of HRT use (Redwine, 1994).

What is the best way to manage neuropathic pain?

The true incidence of neuropathic pain in women with endometriosis is unknown, partly due to difficulties in assessment. In the absence of a perfectly validated assessment tool, the gold standard for diagnosing neuropathic remains 'expert opinion' and access to this is difficult given the prevalence of endometriosis. Questionnaires have been used as a surrogate in other specialities but as yet these have not been validated for CPP or endometriosis in particular.

When identified, treatment of neuropathic pain should typically start with either the tricyclic antidepressant, amitriptyline, or the anticonvulsant, gabapentin, before progressing to the newer Norepinephrine Serotonin Reuptake Inhibitors (NSRIs), such as duloxetine. These can be highly effective in selected patients but are not without side effects (e.g. sedation) leading to issues with

compliance despite improvement of pain symptoms. However, the neuropathic model should be seen as a 'spectrum' rather than a 'pigeon hole'. In women in whom a 'central sensitisation' picture predominates, pain specialists strongly advocate the critical importance of a multidisciplinary approach. Frequently these patients have had poly-pharmacy including inappropriate opioids, and require optimalisation of medication by a pain specialist, but often also require input from psychology, a dietician, and physiotherapy.

Concluding remarks

The assessment and management of chronic pelvic pain, including those with endometriosis, is no longer simply a combination of ovarian suppression and laparoscopy. Communication is of crucial importance, not only in the assessment of these women, but also of managing on-going pain, particularly when symptoms are not explained and not treated by laparoscopy. Equally the place and timing of laparoscopy remains challenging. Further research is needed, at both a molecular level in pain mediators and signalling and also on clinical level for the holistic approach to these patients in a multidisciplinary setting. In the future it may be that with improved knowledge, imaging, appropriate multidisciplinary team input, and more rigorous assessment for non-gynaecological causes of pain, that the place of the 'diagnostic laparoscopy' is superseded by laparoscopy in only a carefully selected patient cohort in whom an operation is likely to improve their pain. Until then, we must encourage the management of every patient as an individual and address all aspects of their pain without undue fixation on the underlying pathology.

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See you in Brazil in 2014

(see page 14)

Pictures courtesy of RC&VB

Professor Jacques Donnez, co-founder of WES, retires

by Anne van Langendonckt MD, WES Ambassador

On 20-21 September 2012, an international symposium entitled "Fertility preservation: from endometriosis to ovarian tissue cryopreservation" was held in Brussels, Belgium, to celebrate the outstanding career of Professor Jacques Donnez upon his retirement.

On this great occasion, many of his friends from all over the world, renowned specialists in their own right, gathered to share their expertise and honor his phenomenal contribution to reproductive medicine.

This resulted in a congress of the highest scientific level and quality, which covered Professor Donnez's two favorite subjects, endometriosis and ovarian tissue cryopreservation, work which he pioneered. It was the best send-off he could have been given, and a standing ovation at the end of the meeting was the icing on the cake.

Professor Jacquez Donnez with professors Ernest Lourmay, Bart Fauser, David Barlow, and Philippe Bouchard

A career devoted to reproductive medicine

Jacques Donnez (born in 1947) studied medicine and did his internship in gynaecology and obstetrics at the Université Catholique de Louvain (UCL). He started his research activities in the very active Research Laboratory of Physiology of Human Reproduction under the supervision of Professors Jacques Ferin and Karl Thomas. Ever since, he has devoted his career to identifying and understanding the molecular and pathophysiological mechanisms underlying female infertility and developing new therapeutic options to restore or preserve women's health and fertility.
He defended his PhD thesis entitled: "The fallopian tube: normal and pathological histophysiology" in 1984 and became Head of the Department of Gynaecology in 1986. He founded the Infertility Research Unit of the UCL. He has focused his research activities on three main topics: 1) tubal infertility, 2) endometriosis and, more recently, 3) ovarian cryopreservation and transplantation. He has made a major contribution to these fields.

Professor Donnez has also been instrumental in spreading and sharing knowledge in reproductive medicine by promoting PhD theses, organising international meetings to bring together clinicians and scientists, writing and regularly updating books and publishing over 500 original articles in peer-reviewed journals. Each year, he organises an international congress on Gynaecological Endoscopy and Laparoscopy. He was president and founding Member of the:

- European Society of Gynecological Endoscopy (ESGE) (1994-1996)
- World Endometriosis Society (WES) (1998-2000)
- International Society of Gynecological Endoscopy (ISGE) (2002-2005)
- International Society for Fertility Preservation (2008-2010).

Summary of research activities

Normal and pathological histophysiology of the fallopian tube

Jacques Donnez conducted a scrupulous and comprehensive investigation of the fallopian tubes at the macroscopic, microscopic and molecular levels, correlating his findings with clinical data. His PhD work highlighted the importance of cyclical changes in epithelial ciliation, cell height and mitotic activity in human tubal physiology and pathologies.

Towards a better understanding and clinical management of endometriosis

The UCL gynaecology unit is recognised worldwide as a reference center in the field of endometriosis. Professor Donnez has made a major contribution to continued progress in laparoscopic surgical management of endometriosis, as well as the development of new therapies. He was the first president of the WES (World Endometriosis Society) and a member of the Committee for Endometriosis Classification of the American Society of Reproductive Medicine.

Studies on endometriotic lesions performed in his research laboratory have led to essential findings and made groundbreaking contribution to the field. These include:

1. Providing the first evidence that pelvic endometriosis, ovarian endometriosis, and nodules of the rectovaginal septum are three distinct entities with different pathophysiological mechanisms.
2. Classifying pelvic endometriotic lesions into red, black, and white lesions, according to their activity and vascularization.
3. Demonstrating overexpression of proteins in endometriotic lesions, which are currently being investigated as potential targets for the development of new therapeutic modalities: MMPS (extracellular matrix degradation), VEGF, heme oxygenase, transferrin, cyclooxygenase.
4. Developing a model of endometriosis in nude mice, allowing study and quantification of the early stages of lesion formation.
5. Designing a new medical device for local endometriosis treatment based on innovative research on inflammatory and angiogenic processes.
6. Clarifying hormonal responses and demonstrating the absence of aromatase in endometriotic lesions.

Pioneer in the field of ovarian cryopreservation and transplantation

In 1995, Jacques Donnez started his project on ovarian cryopreservation and transplantation. His team was one of the first to propose cryopreservation of ovarian tissue to patients treated by chemo- and/or radiotherapy (as part of an experimental program approved as early as 1995 by the Ethics Committee of the UCL). Professor Donnez published the first articles outlining the indications for ovarian cryopreservation. A model of human ovarian tissue heterografting in nude mice was developed in his laboratory in order to study factors affecting ovarian tissue survival after grafting.

In 2004, Professor Jacques Donnez achieved the first live birth after transplantation of cryopreserved ovarian tissue in humans. The scientific data, published in the Lancet, describe restoration of endocrine and reproductive function in a patient who had become infertile as a result of chemotherapy. This monumental achievement has brought hope to thousands of women faced with the prospect of infertility after undergoing gonadotoxic treatment for life-threatening conditions.

Professor Donnez with his wife Francoise and son Olivier – also a gynaecologist!

The adventures of Brazil are waiting for you!

The WCE2014 Team is working hard on an innovative scientific programme, bringing in experts from all over the world, as well as creating a social programme that will let you feel how and what it is to be Brazilian.

Professor Maurício Simões Abrão
WCE2014 President

Brazil is a huge country, with unique cultural diversity and the largest bio-diversity of the planet co-existing with a strong and competitive industry. The country has tourism options for all tastes, extremely beautiful beaches, sports, culture, nature, adventures, and so much more. Therefore we invite you not only to enjoy the conference, but to bring your family along for a vacation of a lifetime. You will certainly love it!

São Paulo is one of the most cosmopolitan and interesting capitals of the world.

It is difficult to define it in one word: beautiful, rich, intellectual, democratic, alive, sportive, cultural, sentimental, romantic, modern, serious, sociable, professional. After all, how can São Paulo be defined? There is absolutely no adjective that can precisely describe one of the world's megacities.

Embracing multi-nationalities, cultures, beliefs, and ideals, this great metropolis is truly cosmopolitan by vocation and adoption. These and many other features are present in the architecture of the buildings, in the streets, in the refined taste of its culinary suggestions, and in its people who never stop and who write the city´s history day by day.

The São Paulo state capital is one of the few places where modernity and history merge harmoniously. It offers hundreds of movie theatres, museums, theatres, historic and cultural heritage, parks, entertainment centres, theme parks, restaurants, bars, hotels, event spaces, fairs, malls, and specialised commerce streets.

Each year, about 10 million people visit the city to increase their businesses or professional contacts, to go shopping, or to enjoy a cultural calendar that levels with that of the main cities in the rest of the world. Every day in São Paulo is a full 24-hour experience of a lifestyle that combines work and pleasure, as if they were two sides of the same coin. São Paulo - capital of a state the size of the UK, with a population similar to that of Spain and accountable for almost 50% of the Brazilian economy - has also become the first tourist destination in the country.

Therefore, with our chests full of pride, we invite you to: Come to São Paulo! – A pleasant and unforgettable experience!

Mauricio Abrao
WCE2014 President

Pictures courtesy of RC&VB

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