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THE PRESIDENT's MESSAGE

Not all laparoscopies are equal

Professor Hans Evers
WES President

Surgeons stem from barbers, they shave and they cut. The barber surgeon was one of the most common medical practitioners in medieval Europe. Until the 1750s, surgery was not generally conducted by physicians but by barbers. The traditional barber's pole, its red and white representing blood and bandages, is probably the last remnant of the link between barbers and the medical community.

Which is the best surgical technique in cases of deeply invasive rectovaginal endometriosis with involvement of the bowel? Simultaneously with the switch from open to laparoscopic surgery, more refinement of the type of surgery and more careful consideration of conserving healthy tissue has evolved. This has lead to two separate and ostensibly conflicting schools of surgeons: those advocating bowel resection and anastomosis, and those favouring the so-called "shaving technique". The latter consists of surgical separation of the anterior rectum from the posterior vagina and excision of the endometriotic nodules in the area. The advocates of this technique claim that shaving allows for preservation of the nerves by avoiding deep lateral rectal dissection as is inherent to rectosigmoid resection. The antagonists, believers in bowel resection, warn that shaving may leave residual endometriotic foci behind, which in turn inevitably will give rise to new manifestations of the disease, sooner or later after the laparoscope has left the pelvis. The shavers mention that leaving a few endometriotic foci behind will not give rise to pelvic pain persistence and that in 10% of bowel resections the margins are also not free from disease. It all boils down to the question: how can we be aggressive enough to remove all destructive endometriosis and prevent recurrence, but at the same time be not too aggressive that quality of life is affected by bladder dysfunction, digestive problems, intestinal complaints, and sexual pain?

Two recent papers have shed new light on this impossible conundrum from two different angles. First, our highly respected past president Jacques Donnez's report on complications (3%) and recurrence (<0.1%) in a prospective series of 500 patients undergoing the shaving technique in his skilled hands [1], and then Julie Harvey's poignant account of her "Patient's Journey" stringing together visits with many of our colleagues: "I had extensive excision of endometriosis and adhesions, but at the time it was presented to me as "*only keyhole surgery; you should be back at work in a couple of weeks*". I now know I had a major operation and that not all laparoscopies are equal in terms of recovery. When symptoms persisted, I felt that I was doing something wrong, complaining too much, or that my body wasn't reacting as it should. (…) From my surgeons' point of view, each of my operations has been successful – but from my point of view, surgery hasn't worked" [2].

If we consider the patient as a partner, we cannot close our eyes to patient perception and patient preferences. We are not all Jacques Donnezs. In my view we still have quite some work to do. Or am I being too preposterous?

Too bad the only people who know how to run the country are busy driving cabs and cutting hair *

1. Donnez J, Squifflet J. Complications, pregnancy and recurrence in a prospective series of 500 patients operated on by the shaving technique for deep rectovaginal endometriotic nodules. Hum Reprod 2010;25(8):1949-58.
2. Harvey J, Warwick I. A Patient's Journey. BMJ 2010;340:c2661
* George Burns

In this issue of the WES e-Journal

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A WORD FROM THE EDITOR

The round ball

Dr Luk Rombauts
WES e-Journal Editor

By the time you read this edition of the e-Journal the 2010 World Cup will be well and truly digested, better by some than others... Here, Down Under, the term World Cup doesn't necessarily refer to the event that captivates the attention of more than 700 million viewers. On the vast continent that Australia is, the inhabitants are enthralled with several other football codes, all of which involve the grabbing and throwing and occasional kicking of a leather implement that is more egg-shaped than round. In Melbourne the fascination is principally with Australian Rules, whereas in Sydney the dominant game is Rugby (and to make it even more complex Rugby comes in two flavours: Rugby Union and Rugby League).

There is no doubt that economies around the world always go into a lower gear while the big game is on (perhaps not what the doctor ordered right now…).

As usual the Cup coincided with the ESHRE meeting, this year in Rome. Many of my Australasian colleagues make it a tour of duty to pilgrimage to Europe when the ESHRE meeting is eclipsed by the World Cup. They say, and they would be right, that the atmosphere in the hosting city is like nothing you will experience anywhere else: nine thousand like-minded delegates congregating on a historical city to enjoy science and soccer.

ESHRE is over and so is the Cup. The Australian socceroos' second attempt at capturing the coveted cup ended prematurely in the Round of 16, just as it did in 2006 when the Italians were awarded a controversial penalty in the last minutes of the match. This year the socceroos were kicked out (excuse the pun) when they failed to score enough points in their last match against Serbia to qualify for the next round. But at least we can take comfort from the fact that Germany not only scored four goals against us, but also against England and Argentina. We are looking for a new coach. Anyone have the contact details of a good one? And, ahem... we are not interested in Maradonna...

In this edition, Professor David Healy, WES board member and president elect of IFFS, presents us with his take on recent developments in our field. Never shy to stir the pot, he brings us interesting new perspectives on the link between endometriosis and obstetric outcomes.

We are also getting closer and closer to the 2011 World Endometriosis Society meeting in Montpellier. When we start our countdown we will bring more regular contributions from the organising team led by Professor Bernard Hédon. We hope to bring you some advice on local wineries, gastronomical specialities, and cycling/walking tours. Stay tuned.

UPCOMING MEETINGS

13th World Congress on Pain
29 August - 2 September 2010
Montreal, Canada

IFFS 20th World Congress on Fertility & Sterility
11 - 16 September 2010
Munich, Germany

19th Annual Meeting of the European Society for Gynaecological Endoscopy
29 September - 2 October 2010
Barcelona, Spain

4th Hellenic Congress of Endometriosis
16 - 17 October 2010
Heraklion-Crete, Greece

19th SLS Annual Meeting and Endo Expo
01 - 04 September 2010
New York, USA

Advanced course in deep endometriosis
13 - 15 September 2010
Florence, Italy

Fertility Society of Australia's Annual Meeting 2010
10 - 13 October 2010
Adelaide, Australia

66th Annual Meeting of the ASRM
23 - 27 October 2010
Denver, USA

COMPLETE CONGRESS SCHEDULE

GUEST EDITOR's RESEARCH DIGEST

Obstetrics after endometriosis

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Introduction
Obstetric consequences of endometriosis seem rarely reported in medical journals. In this contribution, I have selected three recent manuscripts which address obstetric risks after endometriosis and suggest a new research direction.

Endometrioma and pregnancy
The first article I have selected is by Fernando and colleagues, reported in Fertility and Sterility in 2009. This paper investigated the perinatal and obstetric outcomes following assisted reproductive technologies (ART) in women with ovarian endometriosis. A retrospective cohort study was designed including 4,387 mothers of singleton babies. Such a study design overcame the obstetric consequences of twins and higher order multiple pregnancies. These authors found 95 ART patients who had ovarian endometriomata and who subsequently gave birth to a singleton child. Their study also included 535 mothers of singleton babies with other forms of endometriosis. In addition, there were 1,201 subjects who needed ART but had other aetiologies for their infertility, 156 sub-fertile couples who conceived without the aid of ART and the general fertile population of 2,400 mothers of singleton babies.

Ovarian endometriomata can be diagnosed by its characteristic appearance on vaginal ultrasound with experienced ultrasonographers. Differentiation of ovarian endometriomata from other adnexal masses has both high positive predictive values and negative predictive values and is comparable to magnetic resonance imagining for ovarian endometriomata.

Fernando and colleagues showed that there were obstetric problems with endometriosis patients. In particular, those pregnant women with previous ovarian endometriomata were at high obstetric risk. Mothers with ovarian endometriomata were twice as likely to deliver a baby of low birth weight, compared with pregnant women with other forms of endometriosis. Endometriomata patients were more likely to deliver a baby of low birth weight when compared with ART patients with other causes of their infertility. Pre-term delivery was also likely in the women with ovarian endometriomata, compared with the general population. These investigators also showed the risk of placenta praevia was increased in pregnancy patients with ovarian endometriomata.

Preterm birth, ovarian endometriomata, and assisted reproduction technologies
Fertil Steril 2009;91(2):325-30

Fernando S, Breheny S, Jaques AM, Halliday JL, Baker G, Healy D

OBJECTIVE: To report preterm birth and small for gestational age (SGA) rates from assisted reproduction technologies (ART) patients with ovarian endometriomata compared with control groups. DESIGN: Retrospective cohort study. SETTING: Tertiary university affiliated ART center and Perinatal Data Collection Unit (PDCU). PATIENT(S): Every woman who had an ART singleton baby born between 1991 and 2004 had her database record assessed (N = 4382). Control groups included 1201 singleton babies from ART patients without endometriosis and 2400 randomly selected women from the PDCU database of 850,000 births. INTERVENTION(S): There were 95 singleton ART babies from patients with ovarian endometriomata and 535 ART singleton babies from patients who had endometriosis but no ovarian endometriomata. MAIN OUTCOME MEASURE(S): Preterm birth rates and SGA birth rates. RESULT(S): Preterm birth rate increased only in the ovarian endometriomata group when compared with community birth records (n = 850,000). Furthermore, ART patients with ovarian endometriomata had a statistically significantly increased likelihood of having a SGA baby when compared with other forms of endometriosis. CONCLUSION(S): Rates of preterm birth and SGA babies doubled in infertility patients with ovarian endometriomata who required ART.

Swedish study

The second article I have selected is by Stephansson and associates, reported in Human Reproduction in 2009. This was the best article I have seen on the possible risk of adverse pregnancy outcome following endometriosis.

These authors undertook a nation-wide Swedish study. They included 1,442,675 singleton births. It was a linkage study with a linkage of data between 1992 and 2006 in the Swedish Medical Births Register: there was also an opportunity to study the influence of ART on preterm birth in this group of subjects. The authors studied 13,090 singleton births among 8,922 women diagnosed with endometriosis. Women with endometriosis of any type were at higher risks of pre-tem birth (adjusted odds ratio 1.33:95% CI 1.25-1.44), compared with women without endometriosis.

In this large cohort study the increased risk of pre-term delivery was also associated with a greater chance of pre-eclampsia and antepartum haemorrhage in the pregnant women who previously had endometriosis. Furthermore, delivery through Caesarean section was about twice as common as compared with women without endometriosis.

The authors of this large study also report, like Fernando and colleagues, that the endometrium from women with endometriosis differs from health controls.

Once again, the proposition is that abnormal placentation could provide the rationale for the increased risk of pre-term birth, pre-eclampsia and antepartum haemorrhage observed in these two studies.

For these authors, there were 113 patients who had endometriosis and required ART, compared with 1129 subjects without endometriosis who had ART. The endometriosis sufferers had a trend towards a greater risk of pre-term birth in this ART cluster.

Pre-term birth

Both the Fernando and Stephansson papers are important.

They are important because pre-term birth is the greatest problem in obstetrics, and, arguably, the greatest problem throughout obstetrics and gynaecology in any country.

There is not much doubt that, for governments and financial regulatory bodies, pre-term birth is the most significant single problem in modern obstetrics.

Any improvement or improved understanding of pre-term birth would have a major benefit to women's health. This view has been effectively promoted by organisations such as the USA March of Dimes.

Endometriosis, assisted reproduction technology, and risk of adverse pregnancy outcome

Hum Reprod 2009;24(9):2341-7

Stephansson O, Kieler H, Granath F, Falconer H

BACKGROUND: Endometriosis, a common gynaecological disease, is characterized by local and systemic inflammation, which may cause infertility and consequently, increased utilization of assisted reproduction technology (ART). We aimed to estimate the risk for preterm birth, small-for-gestational-age (SGA) birth, stillbirth, Caesarean section, pre-eclampsia and antepartal haemorrhage among women with a previous diagnosis of endometriosis compared with women with no
previous diagnosis of endometriosis. METHODS: In a nationwide Swedish study including 1,442,675 singleton births we assessed the association between adverse pregnancy outcome, ART and a previous diagnosis of endometriosis. Information was obtained by linkage of data between 1992 and 2006 in the Medical Birth Register with the Patient Register between 1964 and 2006. RESULTS: There were 13,090 singleton births among 8922 women diagnosed with endometriosis. Compared with women without endometriosis, women with endometriosis had higher risks of preterm birth [adjusted odds ratio 1.33, 95% confidence interval (CI), 1.23-1.44]. Among women with endometriosis 11.9% conceived after ART compared with 1.4% of women without endometriosis. The risk of preterm birth associated with endometriosis among women with ART was 1.24 (95% CI, 0.99-1.57), and among women without ART 1.37 (95% CI, 1.25-1.50). Women with endometriosis had higher risks of antepartal bleeding/placental complications, pre-eclampsia and Caesarean section. There was no association between endometriosis and risk of SGA-birth or stillbirth.
CONCLUSIONS: Endometriosis appears to be a risk factor for preterm birth, irrespective of ART. Women with endometriosis may be more likely to be delivered by Caesarean section and to suffer from antepartal haemorrhage/placental complications and pre-eclampsia.

The uterine junctional zone

The final article I have selected is by Ivo Brosens and co-workers, published in Human Reproduction this year. In the early 1980s Ivo Brosens and Robert Pijnenborg published a series of seminal papers on interstitial trophoblast invasion during early pregnancy (Pijnenborg et al, 1980) and they can therefore be considered experts on the placental bed, or the uterine junctional zone (JZ) as it is known in more recent literature.

Thirty years later these investigators focus once more on the JZ, which is the endometrial-myometrial part of the feto-maternal interface. The JZ represents the inner third of myometrium which, together with its overlying endometrium, is involved in placentation.

Normal placentation involves deep invasion of the JZ. There is conversion in both the endometrial-myometrial segments of approximately 100 spiral arteries into large, remodelled placental vessels.

Defective or superficial placentation, defined by absent or incomplete remodelling of the JZ segment of the spiral arteries, is associated with the obstetric complications of pre-term birth, intrauterine growth retardation (IUGR) and pre-eclampsia.

These are precisely the types of abnormalities which could be occurring in the populations studied by both Fernando and by Stephansson and their groups.

In ART subjects, the use of gonadotrophins for stimulated IVF cycles is necessary to produce multiple codominant folliculogenesis. Inevitably, the use of gonadotrophins for such stimulated cycles also leads to serum oestradiol concentrations much higher than in the spontaneous and natural cycles, and it is suggested that this would produce an abnormal JZ and defective placentation.

Clearly, there are mechanisms which can overcome these problems within the uterus so that many, many normal babies are born despite IVF or ART, even when these are singleton births. Nevertheless, the increased risk of abnormalities of pre-term labour, IUGR, pre-eclampsia and antepartum haemorrhage now has one unifying explanation – the enigmatic uterine JZ is defective.

The paper of Ivo Brosens and co-authors is important because the JZ is open to research. There are even suggestions from these workers that defective placentation is predominantly a disorder of the first ongoing pregnancy.

The enigmatic uterine junctional zone: the missing link between reproductive disorders and major obstetrical disorders?

Hum Reprod 2010;25(3):569-74

Brosens I, Derwig I, Brosens J, Fusi L, Benagiano G, Pijnenborg R

While there is a growing realization that the origins of major obstetrical complications associated with defective deep placentation, such as pre-term labour, fetal growth restriction and pre-eclampsia, may lie in the very early pregnancy events, the underlying mechanisms are not understood. Impaired deep placentation is foremost a vascular pathology, characterized by a lack of endovascular trophoblast invasion and remodelling of a segment of the spiral arteries embedded within the inner myometrium of the uterus. Outside pregnancy, the inner myometrium represents a highly specialized, hormone-dependent structure, termed the junctional zone (JZ), which plays an integral part in the implantation process. The JZ changes with age and is disrupted in several reproductive disorders, such as endometriosis and adenomyosis, which in turn may account for the increased risk of adverse pregnancy outcome. Unlike the endometrium, the myometrial JZ is not readily accessible to biochemical or molecular studies, yet its structure and function can be assessed using imaging techniques, such as high-resolution ultrasound and magnetic resonance imaging. Thus, non-invasive assessment of the JZ prior to conception may turn out to be useful in identifying those women at risk of major obstetrical complications.

Future directions

Putting these three manuscripts together, there are implications for all of us who care for infertile patients suffering from endometriosis.

If ART is required, perhaps we should always undertake only single embryo transfer. Any transfer of two embryos is associated with an increased risk of pre-term birth, even when only a singleton baby develops from the double embryo transfer.

Moreover, a second implication of these three papers is that the time may have come to abolish fresh embryo transfer in ART/IVF.

Perhaps what we should be doing now in the 21st century is to freeze all embryos of high quality, allow the woman to recover from her stimulated cycle, including recovery from her operation, and then transfer one thawed embryo each consecutive month until ongoing pregnancy starts.

A final implication of these three papers is that, when patients in developed countries attend for a nuchal translucency Down syndrome risk assessment ultrasound scan at 12-13 weeks gestation, the ovaries of these women should be looked at by ultrasound for ovarian endometriomata.

If found, such patients with endometriosis should be placed into those of high risk for pre-term birth and antepartum haemorrhage. If endometriosis in the 20th century was a gynaecologist's disease, perhaps endometriosis in our century might become an obstetric disorder?

REFERENCE

Pijnenborg R, Dixon G, Robertson WB, Brosens I. Trophoblast invasion of human decidua from 8 to 18 weeks of pregnancy. Placenta 1980;1:3-19.

NEWS ROUND-UP

First WERF study shows that endometriosis significantly impacts on women's productivity at work

GSWH coordinator Dr Nnoaham presenting at ESHRE, Rome, June 2010

The first ever worldwide study of the societal impact of endometriosis has found a significant loss of work productivity among those women who suffer from the condition.

Dr Kelechi Nnoaham, from the Department of Public Health and the Nuffield Department of Obstetrics & Gynaecology, University of Oxford, UK, presented this data, from the first study funded by the World Endometriosis Research Foundation (WERF), at the 26th annual meeting of the European Society of Human Reproduction and Embryology in Rome in June.

Endometriosis accounts for a significant loss of productivity of over 11 hours per woman per week - 38% more than those without endometriosis.

Dr Nnoaham said that the results of his team's study would help highlight the previously unrecognised plight of the estimated 176 million women around the world, whose lives are affected by endometriosis.

Dr Nnoaham and colleagues recruited 1418 women aged 18-45 from 16 participating centres in ten countries across five continents to the Global Study of Women's Health (GSWH). The women were all scheduled to undergo a laparoscopy because of symptoms suggestive of endometriosis. Women who had been previously diagnosed with endometriosis were excluded. The participants were asked to complete a 67 item questionnaire, in their own language, about their symptoms and the impact these had on their lives. After surgical diagnosis, recorded in a standardised manner, the questionnaires were analysed comparing the impact of symptoms between women diagnosed with and without endometriosis.

Key findings:

- Women with endometriosis experienced an average delay of 7 years from symptom onset until they were finally diagnosed;
- Two thirds of women presented with symptoms before they were 30 years old (1/5 under the age of 19);
- 65% of women with endometriosis presented with pain, and 1/3 of these patients also reported infertility;
- Infertility alone, without pain, was reported in 14% of patients with endometriosis and 29% of patients who did not have endometriosis.
- The severity of endometriosis (r-AFS disease stage) did not reflect the severity of a woman's symptoms;
- The pain symptoms of endometriosis reduce quality of life, with the impact being mainly on physical, rather than mental, health. As symptoms become more severe, quality of life is further reduced;
- Women with endometriosis suffer a 38% greater loss of work productivity than women without endometriosis – this difference was mainly explained by a greater severity of pain symptoms among women with endometriosis;
- Reduced effectiveness at work accounts for more loss of work productivity than time missed from work;
- Non-work related activities, such as housework, exercising, studying, shopping and childcare were also significantly impaired by the painful symptoms of endometriosis.

GSWH study coordinator Dr Kelechi Nnoaham, principal investigator Dr Krina Zondervan, and WERF trustee Stephen Kennedy

"Our research is the first ever prospective study to be undertaken in the field of endometriosis to assess the impact of the disease" said principal investigator, Dr Krina Zondervan, epidemiologist and senior scientist at the Wellcome Trust Centre for Human Genetics.

"We now have to explore why endometriosis affects different women in different ways. And, not only are we now able to build on these findings to look at how a woman's experience of the diagnostic and treatment process can be improved, but the data registries resulting from the GSWH will serve as a repository for ongoing and future studies."

Mr Stephen Kennedy, WERF trustee, added: "Endometriosis affects women during the prime years of their lives, a time when they should be finishing an education, starting and maintaining a career, building relationships and perhaps have a family. For these women to have their productivity affected, their quality of life compromised and their chances for starting a family reduced, is something society can no longer afford to ignore. It is time we see serious investment in preventing this debilitating condition in the next generation of women", said Mr Kennedy.

See also: **http://www.endometriosisfoundation.org/gswh.php**

MERGE sees the light of day

MERGE coordinator Mr Luciano Nardo

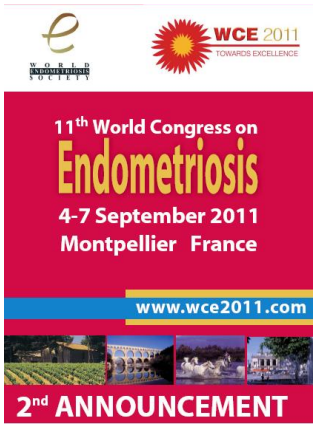
Mr Luciano Nardo and colleagues from Central Manchester University Hospitals NHS Foundation Trust and the University of Manchester have recently set up the **M**anchester **E**xpert **R**esearch **G**roup in **E**ndometriosis and Endometrium (**MERGE**).

The group is a multi-disciplinary collaboration between basic scientists and clinical colleagues including gynaecologists, colorectal surgeons, urologists, pain specialists, radiologists and pathologists based in the North West of England. The priority of the group is to collaborate in endometriosis research with a focus on detailing the pathophysiology of the condition, improving the classification system and identifying novel diagnostic indicators with an ultimate goal of generating innovative treatment strategies for endometriosis.

For more information please call +44 (0)161 701 6965
or email **merge@cmft.nhs.uk**

WORLD CONGRESS ON ENDOMETRIOSIS 2011

Preliminary WCE2011 programme now available



The 2nd announcement for the 11th World Congress on Endometriosis is now available to download at **www.wce2011.com**

The World Congresses are traditionally "abstract driven", which means that there are very few invited speakers – the idea (and the ideal!) is that everyone in the endometriosis community should have an opportunity to share their clinical and/or scientific progress with as many as possible.

The congress is therefore divided into a number of topics against which it is possible to submit an abstract as part of the main programme. The top five abstracts for each "topic", in either the clinical or the scientific stream, will be selected for the plenary lectures. The remainder abstracts will be selected for either "free communications" sessions or posters. Abstract submission starts on 30 September 2010.

What are you going to submit?