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The Sleep Of Reason Produces Monsters

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WES President

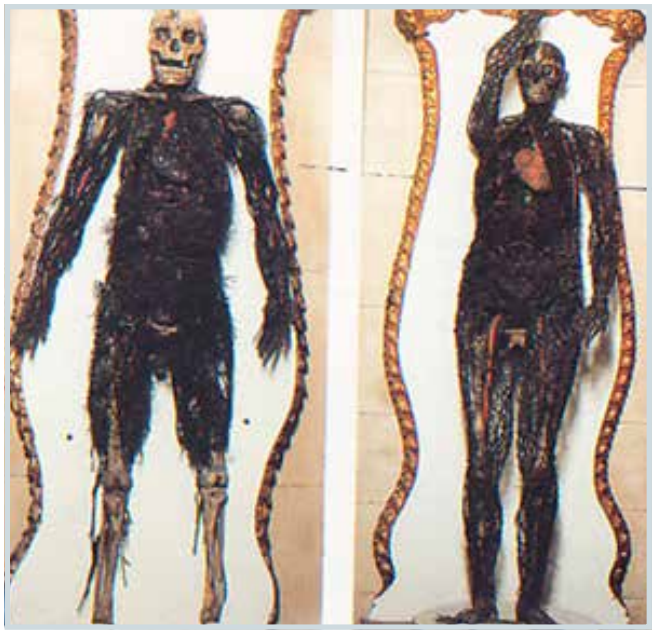
"Fantasy abandoned by reason produces impossible monsters: united with her, she is the mother of the arts and the origin of their marvels."

Francisco de Goya, epigraph for capriccio No. 43, 1799

Dear friends,

Once upon a time physicians could obtain major research achievements thanks to their intuition often helped by mere chance. There are plenty of examples in the history of medicine. For most disorders, treatments were very naive, if not even non-existent. Anything was sometimes better that nothing. There were almost no limits to the creativity of distinguished early academicians in a time when pharmacotherapy was practiced by the alchemists and surgery by the cerusicus (he could be a barber or even a butcher).

In that period there were apparently only minor requirements regarding ethics committee approval for trials conducted on human beings. In the historic centre of Naples, Italy, inside the Cappella Sansevero, a chapel north of the church of San Domenico Maggiore, two early examples of what would be a form of plastination are displayed (macchine anatomiche). These anatomical models are thought to be the result of the process of "human metallization" obtained by injecting a mercury-based hardening substance directly into the veins of living subjects. According to a popular legend, in 1760 the anatomist Giuseppe Salerno conducted this experiment on two servants of Prince Raimondo di Sangro. Their skeletons are encased in the hardened circulatory system constituted by very detailed arteries and veins.



Inside this eJournal

In 2008, researchers from the University College of London were authorized by the current owners of the chapel to conduct a scientific examination on the two "anatomical machines". As I don't want to spoil the atmosphere, I will let you discover by yourselves the results of that study by clicking on the following **link**.

However, beware of too simplistic explanations. As an example, for innumerable years international "experts" maintain that liquefaction of what is claimed to be a sample of the blood of San Gennaro (patron saint of Naples) kept in a sealed glass ampoule, is a fake. However, evidence-based medicine also here does not seem to be easily applicable!

The first known comparative trial was conducted in 1753 by James Lind, a Scottish surgeon in the Royal Navy. In his book, "A Treatise of the Scurvy" he says:

> "I took twelve patients in the scurvy on board the Salisbury at sea. The cases were as similar as I could have them… they lay together in one place… and had one diet common to them all. Two of these were ordered a quart of cider a day. Two others took twenty-five guts of elixir vitriol… Two others took two spoonfuls of vinegar… Two were put under a course of sea water… Two others had each two oranges and one lemon given them each day… Two others took the bigness of a nutmeg. The most sudden and visible good effects were perceived from the use of oranges and lemons, one of those who had taken them being at the end of six days fit for duty… The other… was appointed nurse to the rest of the sick."

However, the Royal Navy did not implement his advice for almost half a century (1). Archibald Cochrane was not yet around at that time.

In the centuries that followed, both surgery and pharmacology made tremendous progresses, research methodology gradually improved, evidence-based medicine finally became our karma, and the CONSORT guidelines (Consolidated Standards of Reporting Trials) are now considered as the tables of the law for any smart investigator. Have we reached the Nirvana of clinical research? Unfortunately not, partly because in the meantime medicine turned into a huge market, the grassland of some pharmaceutical companies and device producers. The clinical trial, the paradigm of good research practice, the approach that should guarantee those findings that are closest to the truth, is being used as the knife to cut the largest possible piece of cake. How was this made possible? There is more than one way to skin a cat (also in the endometriosis field) from both a qualitative and quantitative point of view.

For some years, several researchers such as Garattini and Chalmers (2) warn us about the risks potentially hidden behind the surface of an apparently faultless methodology, pointing out the issues of *"research agendas distorted by priorities that are important to industry but not to patients; inappropriately restricted study populations […]; uninformative trial designs that fail to assess whether new drugs are better than existing treatment options; outcome measure that ignore the effects of treatments on morbidity and mortality or on the quality of life; biased under-reporting and over-reporting, not only of whole studies, but also of outcomes within published reports of research; and specious promotion of drugs, including disease mongering"* (2).

It took some time before full awareness of the potential distortion of the apparently best quality available evidence pervaded our specialty (3), but now the curtain of fog is dissipating also over the field of endometriosis (4). Sun-Wei Guo and Hans Evers have reported the results of their recent review on the patterns of publication of interventional clinical trials on endometriosis that were registered at **ClinicalTrials.gov** and updated as having been completed by October 2012 (5). A total of 71 interventional trials testing various drugs and biologicals were identified. Among them, 49.3% (35/71) were completed, 21.1% were either stopped or inactive in the past 2 years, and the remaining 29.6% were ongoing. Among the 35 completed trials, 25 (71.4%) were sponsored by industry and results were published for only 11 (31.4%; 5 industry-sponsored, and 6 non-industry-sponsored). Trials sponsored by industry were nearly four times less likely to publish their results compared with non-industry-sponsored trials, despite these studies had larger sample sizes and were completed faster.

Why should pharmaceutical companies not publish the results of exceedingly costly, hard to conduct, but already completed trials? One possibility is that something went wrong with safety, efficacy, or both (4). Thus, one way to "steer" the evidence is to tailor trial methodology

customizing it on the experimental drug, another way is cherry picking of findings, choosing only the favourable ones that will see the light, and putting in the closet the unfavourable or negative ones (selective reporting). This may have major effects also on secondary research (systematic reviews and meta-analyses), which is based on data in the public domain.

Novel drugs for endometriosis, potentially acting on the very pathogenic mechanisms of the disease, are essential. Much of the pharmacologic research in our field is currently supported by industries, and we badly need their commitment in this regard: it would be a disaster if companies would withdraw from developing new compounds. At the same time, in order to respect those who participate in clinical trials, all suffering patients, and the scientific community at large, it is of paramount importance that the entire information resulting from human experimentation is fully reported. The first step toward greater transparency and better science is recognition of the possibility of evidence distortion. To achieve this goal, we need to improve our scientific culture. In this regard, the aid of freethinkers such as Guo and Evers (4, 5) is of utmost value. Moreover, we should look constantly behind the hedge of our garden, avoiding the creation of a close community investigating under a sort of bell jar. The prospective offered by "external observers", not necessarily involved in our area of research, can greatly help widening our usual horizon on global medical issues that may apply also to the field of endometriosis.

This is why it is with great enthusiasm that the WES board announces that Fiona Godlee, the Editor-in-Chief of the British Medical Journal, will honour our society by opening the 12th World Congress on Endometriosis on 30 April 30 2014, giving a lecture entitled "Overdiagnosis, overtreatment, and responsible management of finite healthcare resources".

This unique opportunity will leave a sign in our congress, confronting us with some of the main, current, hazards of medicine. The BMJ is currently conducting some campaigns of major impact on patients, physicians, and the way we practice medicine and research. One of the most important initiatives undertaken by the journal is the "Too Much Medicine" campaign, which "aims to highlight the threat to human health posed by overdiagnosis and the waste of resources on unnecessary care. There is growing evidence that many people are overdiagnosed and overtreated for a wide range of conditions." (**http://www.bmj.com/too-much-medicine**).

Even if Fiona Godlee will address general ethical concepts and practice aspects, there is much to discuss in this regard within our scientific community. In the interest of our patients, we must keep a close scrutiny over behaviours at risk of overdiagnosis and overtreatment.

Hence, our world congress is taking its definitive shape, and we should be proud of the results.

You, our members and delegates from WCE2011, have selected the topics to be addressed through an online vote. In addition, the vast majority of presentations will be dedicated to those of you willing to bring in brand new data. We have made our best to offer you the most transparent event possible. Now it's time to do your part: register for WCE2014, you're your flights and your accommodation and help us make our 12th World Congress a unique "open meeting on endometriosis".

There will be fresh air in San Paulo next year, and together we can impact on the health of our patients.

Paolo Vercellini
President
World Endometriosis Society

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Brazil, here we come!

A/Professor Luk Rombauts
WES eJournal Editor

The count-down is on again! It is only six months away and we will be exposed again to the tri-annual smorgasbord of endometriosis research updates.

This world event on endometriosis is a meeting like none other, heavily and purposefully biased towards free communications. Whereas outstanding science and breakthroughs in clinical practice are always at the forefront, the meeting is also a wonderful opportunity to brainstorm, germinate collaborative projects, or just socialise and have fun. And what better to place to do this than in Brazil?

I was looking forward to it when the successful bid of Mauricio Abrao was first announced, but I am now even more excited with my first visit to Brazil after reading about the feedback of my parents' travels in Brazil last month. They are both well into their 70s and have seen most of the world and they have simply called it a fantastic journey: friendly welcoming people and sights that should be on anyone's bucket list. Sadly I won't have enough time to do everything, but on my "must do list" is definitely the Isuagu waterfalls. Make sure you see them from both the Brazilian and Argentinian side! One of them is called the Garganta do Diabo or "Throat of the Devil". I have included one of the many iPad snaps my parents took. Mauricio invites us in this eJournal to come and join the Brazilians who have in recent years been a real endometriosis research powerhouse!

Also in this edition another very interesting and thought provoking contribution from Paolo, our WES president. There is always something new or a fresh perspective in his editorials. Make sure you read it because he makes a really exciting announcement for WCE2014.

From the team of Professor Bernard Hedon in Montpellier (our hosts for WCE2011) we have a review by Drs Hamamaha and Haouzi of the work being done in the field "omics in endometriosis", focusing on mRNA and miRNA profiling; as well as a review of recurrences in deep infiltrating endometriosis by Drs Rafii and Borghese. Both are excellent reads and a treasure trove of useful references!

Enjoy your read and start booking those flights!

Pain recurrence after surgery of deeply infiltrating endometriosis, from cause to management

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Endometriosis is a public health issue. Its high prevalence (10%) and the consequences of the symptoms (pain, infertility) directly impacts the quality of life of the patients. It is calculated that endometriosis carries an average annual total cost per woman of 9579 euros (Simoens et al, 2012).

Deep endometriosis the most severe form of endometriosis is arbitrarily defined as a peritoneal invasion over 5mm (Koninckx et al, 1991). Recently it was proposed that deep endometriosis should be defined by the involvement of the muscular layer of the organs around the uterus (Chapron et al, 2010),

Deep endometriosis is not a disease of a specific organ but rather represents a multifocal and heterogeneous disease requiring a multidisciplinary approach.

While the place for surgery in treating the pain related symptoms such as dysmenorrhea, dyspareunia and chronic cyclic pelvic pain has been clearly established in many clinical studies (Vercellini et al, 2009), recurrence after first surgery remains a major issue in the treatment of deep endometriosis.

In this short review we will discuss the possible cause and management of deep endometriosis recurrences.

How frequent are recurrences?

Analysis of the literature shows great heterogeneity in the recurrence rates reported. It is estimated that 40 to 50 % of the patients will recur within the first five years (Garry , 2004; Guo SW, 2009). The recurrence rate at 2 years is estimated to be around 20 % ranging from 6 to 67% (Busacca, 1999; Morgante, 1999). Late recurrences above 5 years are not well documented.

This heterogeneity in assessing recurrence rates is due to several factors:

- Recurrence of symptoms or lesions: different studies have different way to assess the recurrences: clinical examination, imaging, histology. Vignali et al reported in a retrospective study that the rate of recurrence of pain is significantly higher than the rate of clinical recurrence (Vignali et al, 2005). This pointed out the absence of correlation between the symptoms gravity and the clinical recurrence (recurrence rate for pain was 20.5 and 43.5 % at 3 and 5 years respectively, but only 9 and 28 % for clinical recurrence).
- Other factors such as duration of follow-up, type of endometriosis (deep, superficial, endometrioma), type of surgery (radical versus conservative), surgical and center expertise and finally post-operative medical treatment might play a major role in the occurrence of recurrences.

What are the causes of recurrences?

There are no precise data on the mechanisms of endometriosis recurrences and several hypotheses have been suggested.

Incomplete resection

Vignali et al demonstrated that an incomplete surgery was the main risk factor for a re-intervention (OR, 21.9, (3.2-146.5, p<0.001)). In the patients with a second operation the recurrence was observed most frequently at the same location than the initial surgery (Vignali et al, 2005).

These results are concordant with Taylor study (Taylor et al, 2010) that showed in a prospective study of 39 patients undergoing a second intervention for pain that recurrences would mostly occur in the initially treated

location (RR 2.54). Similarly 90% of endometrioma recurrence occurs on the original ovary.

The risk of recurrence is significantly correlated to the radicality of the surgery, which is correlated to the surgeon expertise. Hence studies with low number of patients have a higher rate of recurrence reflecting the surgeon/center expertise (Guo, 2009).

Development of de novo lesions

Bulleti et al demonstrated that radical excision of deep endometriosis associated to the endometrium abrasion prevented recurrence within the two first years (Bulletti et al 2001). While the number of patients in this study was low (14), similar findings for patients undergoing continuous postoperative medical treatment might indicate a role for de novo lesions (Seracchioli et al. 2010; Sesti F et al, 2007).

Finally an altered endometrium as well as the presence of adenomyosis has also been associated to increased recurrence (Landi et al, 2008).

Management of a recurrence

Medical treatment

There is obviously an increased risk of complications in patients who have usually gone multiples surgeries. Moreover the procedures might be quite important (digestive resections, segmental ureterectomy, ureteroneocystotomy, partial cystectomy, nephrectomy).

Therefore there is a strong incentive to try medical treatment first aiming at analgesic control and ovarian function suppression. Only Danzol and Norethindrone acetate have been used in deep endometriosis recurrence context and can be proposed as an alternative to surgery (Razzi et al, 2007;Vercellini et al, 2005).

Surgical treatment

There is little evidence about benefits of iterative surgery in particular regarding pain related symptoms. Vercellini et al. report a recurrence rate between 20 to 40% for pain after a second surgery and the requirement for another surgery in 15 to 20 % of the cases (Vercellini et al, 2009).

However good functional results with an acceptable complication rate have also been reported (Dousset B et al , 2010). Such findings could advocate referring the patients with recurrences to expert referral centers allowing a global management of the patients.

One option in recurrent situation is non-conservative surgery including hysterectomy and bilateral salpingo-oophrectomy. Ovarian preservation has been associated to a 6-fold increase in symptomatic recurrences (Namnoum et al, 1995). Concordantly Fedele et al (2005) reported that complete resection of the endometriotic lesions associated to non conservative hysterectomy was associated to the absence of recurrence

The benefits of such surgical attitude have obviously to be considered in the context of hormone deprivation and a global approach considering fertility, other associated uterine pathologies such as adenomyosis is mandatory.

Preventing recurrences

In order to prevent recurrences different approaches have to be used.

Detecting patients as soon as possible

Many studies demonstrate that there is an important delay between the occurrence of symptoms and the diagnosis of deep endometriosis (around 10 years) (Matsuzaki et al, 2006). Early diagnosis will allow better management including less invasive surgeries with lower recurrence rate as well as complications. One approach is to investigate potential biomarkers and combine them with the classical risk factors such as family history, primary severe dysmenorrhea….

Perform the most complete primary surgery

This single factor seems to be the most important one in reducing the risk of recurrence. Expert team are now proposing an approach close to carcinologic surgeries: removal of all microscopic lesions associated to rectal involvement, complete resection of the mesorectum, en

bloc resection of rectal nodules with the Douglas pouch, vaginal posterior wall and utero-sacral ligaments, rectal margins of 2 cm. Such approaches allows very low rate of recurrence (6%) (Chapron et al, 2010).

Post-operative medical treatment

A recent meta-analysis has shown a benefit for such treatment (Vecellini et al, 2009). In such context a combined oestro-progestative treatment seems as efficient as an analog with lower side effects.

Conclusion

Recurrences of deep endometriosis after surgical treatment are heterogenous and not always clearly identified.

There is a requirement to prevent as much as possible by treating the patients as early as possible and in the most optimal way. This can be achieved by having expert surgeons in referral centers where a global approach combining multiple stakeholders can be proposed. Indeed comprehensive treatment will optimally associate experts in pain management, surgical procedures and fertility.

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Upcoming meetings

42nd Annual Meeting of the AAGL	10 – 14 November 2013 Washington DC, USA
Ovarian Club III	15 – 16 November 2013 Paris, France
The female patient with pelvic pain – an event for general practitioners	22 November 2013 Chester, England
2nd European Congress on Endometriosis 2013	28 – 30 November 2013 Berlin, Germany
1st ISSA Focused Course on Laparoscopic Surgery for Deep Endometriosis and Benign Gynecological Diseases	19 – 21 December 2013 Paris, France
The 11th International Symposium on GnRH	9 – 11 February 2014 Salzburg, Austria
61st Annual Scientific Meeting of the SGI	26 – 29 March 2014 Florence, Italy
RCOG World Congress 2014	28 – 30 March 2014 Hyderabad, India

To view the full congress schedule go to **http://endometriosis.org/congress-schedule**

Omics and endometriosis: lessons from transcriptomic and miRNA approaches

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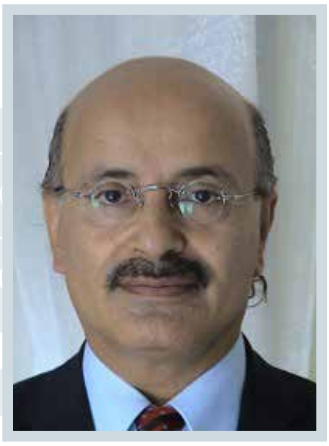

Samir Hamamah, MD

Introduction

Obtaining true and correct non-invasive diagnostic tests for endometriosis remains an important medical stake. The difficulty in diagnosis is probably inherent to the absence of a precise and reliable molecular characterisation of this pathology. Indeed, although endometriosis is one of the oldest gynecological diseases, this pathology is still molecularly poorly characterized. Various high-output technologies, including transcriptomics and micro-RNAs (miRNAs) profiling, are tolls of choice to see real and sustained progress in this field that could represent new options in the diagnosis of endometriosis. However, studies in this field with global approaches are few and the microarray or miRNA comparisons performed were often not addressed in an adequate manner (absence of a control study population group, small number of samples, miss of defined clinical populations…). The aims of this present review is to discuss new considerations with the light of transcriptomic and miRNA profiling studies in endometriosis.

Endometriosis and mRNA profiling

Using PubMed, we searched for English language articles with the following terms: 'mRNA' and 'endometriosis', 605 references were identified. However, only thirteen (less than 3%) concerned the human and used large scale profiling methods to screen transcripts. Among them, ten studies compared the gene expressions of endometriotic lesions and endometrium from patients with endometriosis (Table I) but three of them were excluded from our analysis for incompatible language (Japanese language).

Three studies compared gene expression in ovarian endometrial with that of eutopic endometrium in the same patients and identified more than one thousand four hundred genes differentially expressed, unspecified and more than five thousand genes differentially

Study	Type of endometriosis (number of patients)	Endometriosis's classification	Grade	Microdissection	Comparisons	Ages (min-max)	Cycle phase	Number of mRNAs differentially expressed
Arimoto *et al.*, 2003	Ovarian (n=23)	?	?	No	Ectopic vs eutopic (paired samples)	?	proliferative and secretory	1413
Hever *et al.*, 2007	ovarian (n=10)	unspecified	unspecified	No	Ectopic vs eutopic (paired samples)	unspecified	proliferative (n=2), secretory (n=8)	unspecified
Borghese *et al.*, 2008	ovarian (n=12)	unspecified	IV	No	Ectopic vs eutopic (paired samples)	unspecified	secretory	5600
Eyster *et al.*, 2002	Abdominal (n=3)	unspecified	unspecified	No	Ectopic vs eutopic (paired samples)	unspecified	proliferative	8
Eyster *et al.*, 2007	Peritoneal and ovarian (n=11)	ASRM	severe (n=6), mild-moderate (n=5)	No	Ectopic *vs* eutopic (paired samples)	28-45	proliferative (n=9) and secretory (n=1)	701
Wu *et al.*, 2006	peritoneal (n=5), ovarian (n=6), adnexa (n=1)	ASRM	II to IV	Yes	Epithelial cells from ectopic vs eutopic (paired samples)	25-44	early proliferative (n=2), proliferative (n=6), secretory (n=3), late secretory (n=1)	904
					proliferative			21
					secretory			25
Matsuzaki *et al.*, 2004	Deep rectovaginal (n=6)	ASRM	I to IV	Yes	Ectopic vs eutopic (paired samples)	27-37	proliferative (n=3), secretory (n=3)	0
					Glandular epithelial cells from ectopic vs eutopic			25
					Stromal cells from ectopic vs eutopic			11

Table I:
Transcriptomic studies comparing endometriotic lesions and endometrium from patients with endometriosis

expressed, respectively (Arimoto et al, 2003; Hever et al, 2007; Borghese et al, 2008). Similarly, Eyster et al (2002) compared gene expression in abdominal wall endometriomas with that of eutopic in the same patients and identified only 8 genes differentially expressed between the two compartments. While Eyster et al (2007) compared gene expression profile in peritoneal and ovarian endometriosis and reported approximately seven hundred genes differentially expressed between ectopic and eutopic endometrium. On the other hand, two studies used the laser microdissection to obtain either epithelial cells from endometriotic lesions and compared gene expression with epithelial cells from eutopic endometrium (Wu et al, 2006), or epithelial and stromal cells from deep endometriosis and compared them with eutopic endometrium in the same patients (Matsuzaki et al, 2004) (Table I).

Interestingly, regardless of the moment in which have been performed biopsies during menstrual cycle and the location of the lesions, Wu et al (2006) identified more than nine hundred genes differentially expressed between ectopic and eutopic endometrium. In contrast, taking into account of the menstrual phase, they identified only 21 and 25 genes differentially expressed between ectopic and eutopic endometrium during the proliferative and secretory phase respectively. These data raise the necessity for taking into account of the cycle phase in performed analyses. They also identified specific genes clusters that are location-specific allowing the classification of ovarian and non-ovarian endometriosis, suggesting that there is probably a specific molecular endometrial signature according the location of endometriotic lesions. More investigations are required to confirm this finding, suggesting also that further studies in this field should taking into account of this consideration. In the same way, Matsuzaki et al (2004) reported no genes differentially expressed in whole tissues between ectopic and eutopic endometrium from patients with endometriosis, while laser microdissection of glandular or stromal cells reported significant differences. Several explanations can be at the origin of these disparities such as, the number of patients, selection criteria to analyse microarray data and as a consequence, the cross-intersection of published results in only five of the seven articles (because two don't give any information on the identified genes) revealed that there was no gene in common between these studies (Figure 1).

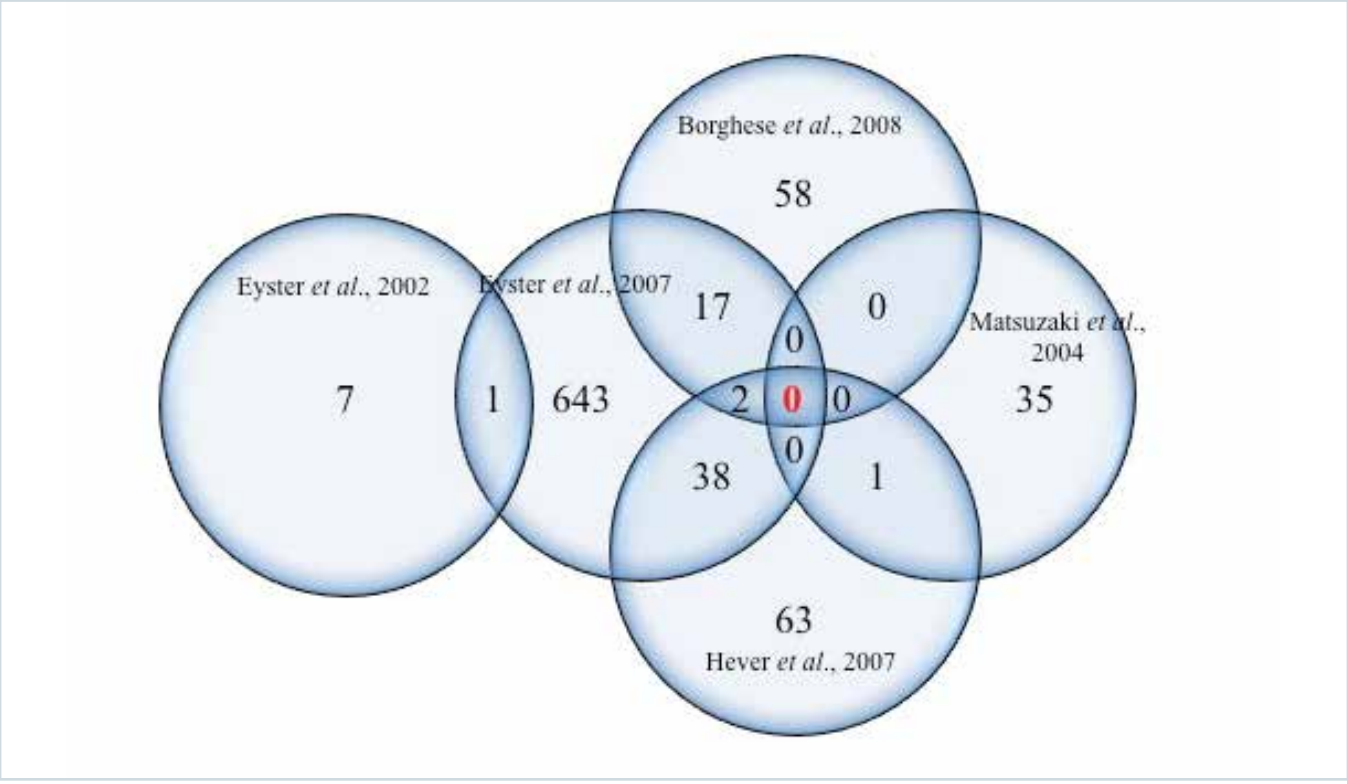

Figure 1:
Venn diagram of overlap of differentially expressed mRNAs in multiple studies comparing endometriotic lesions and endometrium from patients with endometriosis

On the other hand, two studies (Kao et al, 2003; Matsuzaki et al, 2005) examined differential gene expression in eutopic endometrium from women with endometriosis and that of eutopic endometrium from women without endometriosis (Table II).

Study	Type of endometriosis (number of patients)	Endometriosis's classification	Grade	Samples (number of samples)	Control group (number of patients)	microdissection of tissues	Comparisons	Ages (min-max)	Cycle phase	Number of mRNAs differentially expressed
Kao *et al*., 2003	unspecified (n=8)	unspecified	mild/moderate	Eutopic (n=8)	without endometriosis (n=7)	No	eutopic with *vs*. without endometriosis	28-39	mid-secretory	206
Matsuzaki *et al*., 2005	Deep rectovaginal (n=12)	unspecified	unspecified	eutopic (n=12)	endometrium from fertile women (n=12) who underwent laparoscopic tubal ligation	Yes	eutopic with *vs*. without endometriosis	?	late proliferative (n=3), early (n=3), mid (n=3), late (n=3) secretory	0
						Glandular epithelial cells	late proliferative			4
							early secretory			39
							mid-secretory			14
							late secretory			25
						Stromal cells	late proliferative			8
							early secretory			51
							mid-secretory			12
							late secretory			3

Table II:
Transcriptomic studies comparing eutopic endometrium from women with versus without endometriosis

The first one gives no information concerning the control study population, which is however a crucial point to really appreciate the data obtained in their analyses. The second joins in the continuity of the study already published by Matsuzaki et al (2004) by screening more phases of the menstrual cycle. They reported no significant differences between eutopic endometrium from patients with versus without endometriosis when they analyse whole tissue and without taking account of the cycle phase. In contrast, laser microdissection of specific tissular compartments (glandular epithelial cells and stromal cells) and taking into account of the cycle phase, they identified genes differentially expressed between eutopic endometrium from patients with versus without endometriosis. A recent study compared endometrial gene expression profiles according to both the severity of the pathology and the cycle phase in a large cohort of patients (Aghajanova and Giudice, 2011). Indeed, they reported 380, 817 and more than 1200 genes were differentially expressed in eutopic endometrium from severe compared with mild endometriosis in proliferative, early secretory and mid-secretory phase respectively. Principal component analysis (PCA) between all samples revealed that mild and severe endometriosis samples cluster according to their cycle phase rather than the disease stage, reinforcing the necessity to perform adequate analyses.

Endometriosis and miRNA profiling

However, despite accumulating data validating the important role of mRNA expression, the post-transcriptional events that also influence cellular behavior remain to be completely delineated. MicroRNAs (miRNAs) are small non-coding RNA transcripts that influence cell function via modulation of post-transcriptional activity of multiple target genes by repression of translation or regulation of mRNA degradation. Evidence indicates that the genes for many of miRNAs are important in cellular processes that are known to occur during cyclic changes in endometrium such as cell proliferation and differentiation (Bueno and Malumbres, 2011). In addition, aberrant miRNA expression has been associated with human endometrial disorders such as endometriosis, endometrial hyperplasia and carnicoma (Pan et al, 2007; Boren et al, 2008; Ohlsson Teague et al, 2009). The expression profiling of mRNAs and miRNAs in the same samples allowed to identify specific mRNAs that may be post-transcriptionally repressed by miRNAs in human endometrial epithelium and to determine some cellular functions and molecular pathways targeted by these differentially expressed miRNAs in both physiological and pathological conditions. To date, six studies have investigated endometriosis-associated miRNAs (Table III).

Study	location of endometriosis (number of patients)	Endometriosis' s classification	Grade	Samples (number of samples)	Control group (number of patients)	Comparisons	Ages (min-max)	Cycle phase	Nombre of miRNAs differentially expressed
Ohlsson Teague *et al*., 2009	peritoneal (n=7)	ASRM	II–IV	Eutopic (n=7) , Ectopic (n=7) (paired samples)		Ectopic vs eutopic	unspecified	proliferative (n=4), secretory (n=3)	22
Filigheddu *et al*., 2010	ovarian (n=3)	ASRM	III-IV	Eutopic (n=3) Ectopic (n=3) (paired samples)		Ectopic vs eutopic	24-48	proliferative	50
Pan *et al*., 2007	unspecified (n=8)	ASRM	III	Eutopic (n=4), Ectopic (n=8)	uterine leiomyomas (n=4)	Eutopic endometriosis vs ectopic endometriosis vs eutopic without endometriosis	27-39	early to mid secretory	48
Burney *et al*., 2009	peritoneal , rectovaginal and ovarian (n=4)	ASRM	III-IV	Eutopic (n=4)	uterine intramural leiomyomas (n=3)	Eutopic with vs without endometriosis	23-50	early secretory	6
Laudanski *et al*., 2013	ovarian (n=10)	AFS	III-IV	Eutopic (n=10)	ovarian cysts or infertility	Eutopic with vs without endometriosis	20-35	proliferative (n=20)	15
Hawkins *et al*., 2011	ovarian (n=10)	unspecified	unspecified	Ectopic (n=10)	uterine leiomyomas (n=9)	Ectopic vs eutopic without endometriosis	20-48	proliferative (n=12), secretory (n=2), interval (n=3) or indetermined (n=2)	22

Table III:
miRNA profiling studies in endometriosis

Two compared miRNAs expression in peritoneal and ovarian endometrial with that of eutopic endometrium in the same patients and identified twenty two and fifty miRNAs, respectively, as differentially expressed (Ohlsson Teague et al, 2009; Filigheddu et al, 2010). Three studies compared miRNAs expression profiles between endometrium from patients with versus without endometriosis, and the last one, between ovarian endometrial versus endometrium from control groups. However, in these studies, control groups were not appropriated consisting of patients with uterine leiomyomas. Indeed, recent results provided evidence that aberrant miRNAs were expressed in leiomyomas (Pan et al, 2008). As a not surprising observation and according to disparities (number of samples, location….), the cross-intersection of published miRNA results revealed only two miRNAs in common between all these studies: miR-29c and miR-100. Functionnal annotations with both mRNAs and miRNAs have been performed and generated hypotheses for miRNA regulated processes involved in endometriotic lesion development. As example, the over-expression of miR-29c has been associated to down regulation of several components of the extracellular matrix (Teague et al, 2010). However, potential application of miRNAs as biomarkers of endometriosis is limited by our absence of knowledge on miRNAs regulated cyclic normal endometrial changes. Only one study analysed miRNA expression profiles during the late proliferative and secretory phase in primary epithelial endometrial cells isolated from normal endometrium (Kuokkanen et al, 2010). The identification of miRNAs as biomarkers of endometriosis requires at first to improve our knowledge on miRNA expression throughout the menstrual cycle.

Conclusion

Progress in the molecular characterization of endometriosis is taking place and cover many major/ crucial points to better understand the physiopathology of endometriosis. However, the necessity to better define clinical populations as well as to perform adequate comparisons/analyses (cycle phase, location, sub-cellular compartment, control group) will be the key to successful translational research that could lead to the development of new diagnostic tools of endometriosis and targeted new therapeutic approaches. Such diagnosis is important for both patient care management and for the preservation of fertility in these patients.

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Expectations for WCE2014

At the 11th World Congress on Endometriosis (WCE2011) in Montpellier, delegates were asked for feedback on their experiences at the congress – and to convey to the WES board topics they would like to see addressed in 2014. I am going to address these here!

Topics
WCE2011 delegates were asked to state which of the 2011 topics they found to be the most interesting and which they would like to see covered at WCE2014 in São Paulo; the topics that received the most mentions concerned pain, fertility, and pregnancy. The organisers have taken note and it has been ensured that these topics will be well covered at WCE2014.

Here are just a few highlights of what you can expect:
An entire pre-congress course dedicated to "The complexities of endometriosis-related infertility".

- Dr Sylvia Mechsner, winner of the 2012 Friedmund Neumann Prize for her outstanding work on the pathogenesis of endometriosis, will present her findings on the mechanisms of endometriosis generation and development, and with possible mechanisms of pain generation through endometriotic lesions.
- Dr Henrik Falconer of the Karolinska Institutet in Sweden will present a keynote lecture on endometriosis and pregnancy outcome, which assesses the association between adverse pregnancy outcome, ART, and a previous diagnosis of endometriosis.
- Professor Horace Roman of the Department of Gynaecology and Obstetrics at Rouen University Hospital in France will address the management of pain and infertility in deep disease.

What could we have done better in 2011?
The suggestions for improvements were generally minor concerns regarding facilities and catering.

WCE2014 will be hosted at the WTC Complex in São Paolo, which boasts to be "the most comprehensive business complex in Latin America, bringing together in one place the best in services, hospitality, events, and business". Delegates can be confident that their experiences from start to finish will be nothing less than outstanding.

Professor Maurício Simões Abrão
WCE2014 President

Safety and security concerns

The view that São Paulo is less safe than other large European or North American cities is on the whole, an urban legend. In fact, crimes of a violent nature against visitors coming into the city are extremely rare and when they do occur they make newspaper headlines.

São Paulo is a large city with a population of over 11 million people, and as with most large cities anywhere in the world, problems occur in the less affluent neighbourhoods on the outskirts of the city. In the areas where the recommended hotels are situated, and the areas around where WCE2014 will take place, problems are minimal.

São Paulo is recognised as a respected hub for national and international business; a large event takes place every 6 minutes and 75% of the Brazilian trade fair market is concentrated within the city which generates R$2.4 billion annually.

I cannot wait to welcome you to my home city, and look forward to seeing you at WCE2014 – the largest world event ever in endometriosis!

For the full programme and to register, please go to **www.endometriosis.ca/wce2014**

Mauricio Abrao
WCE2014 President

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