

Endometriosis management in the time of economic crisis

The current economic crisis is putting a strain on both governments and individual people. Health care is by far the top spending item for most developed countries and, as an example, it absorbs almost 70% of the entire yearly Italian government budget.

According to a recent report of the Nuffield Trust (Roberts et al, 2012), the current squeeze on the National Health Service (NHS) in the UK is likely to be sustained for many years and, without unprecedented gains in productivity or an economic turnaround leading to greater spending, the total costs incurred in running the health service in the UK are likely to exceed the cash available by a cumulative total of as much as £54bn (€66bn; \$86bn). In fact, for several reasons, including demographical changes and the rising incidence of chronic disease, the demand for health care funding is increasing at a rate of 4% a year. Therefore, the NHS will face a decade of extreme financial pressure (Hawkes, 2012).

Italy's prime minister, Mario Monti, has claimed that the tax funded NHS is unsustainable in its current form, and new ways to finance and reorganise the services and working practices must be found within two years. Although Italy has consistently figured near the top of the World Health Organization rankings for its health



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services, chronic problems and funding shortfalls are becoming more and more apparent, and hospitals around the country are steeling themselves for massive bed closures (Day, 2012).

We as physicians have great responsibilities regarding the overall expenditure for health care, and any time we take our pen out to request a test, prescribe a therapy, or indicate a surgical procedure, we must always keep in mind that we are spending the citizens' taxes or the individual's money.

This means that, in countries with a NHS, someone else, somewhere else, will have to wait for health assistance, as funds are limited. As a matter of fact, we are acting as managers of the resources of governments and/or of families, and our decisions will have an impact also on the general or individual financial budget(s). In these times of constraints, our medical approach has something to do with the respect and dignity of our patients also from an economical point of view: we must never waste someone's money, and today this is even more important than ever.

We take care of our patients affected by a chronic and sometimes debilitating disease, who may need treatments for years. The potential for suboptimal allocation of resources is thus inflated. In order to avoid what has been defined as "bad medicine" (Spence, 2012), each of us must strictly adhere to the principles

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of evidence-based medicine, which implies deepening our methodological knowledge and keeping up to date with the best quality clinical research findings. Before suggesting screening campaigns, we must be well aware of drawbacks and risks of unsound strategies (see also Professor Guo's article on page 6). Screening (ie. investigating asymptomatic subjects) must follow defined epidemiological rules, which may not be fulfilled in the case of endometriosis (Somigliana et al, 2010).

Diagnosis should be achieved through the least costly, but equally accurate modalities. As an example, use of magnetic resonance imaging (MRI) must be limited to selected patients, as there is no robust evidence demonstrating that ultrasonography is inferior to MRI even for deep lesions (Chapron et al, 2004; Abrao et al, 2007). When suggesting laparoscopy in a woman with unexplained infertility with the aim of treating minimal-mild endometriosis, if present, let's consider that the number-needed-to-treat is about 25: can the health system as well as our patients afford this, independently of risks/benefits balances?

In symptomatic patients with suspected endometriosis, should surgery be systematically the first-line choice or should medical therapies be tried instead? And when choosing pharmacological treatments, should we propose the most recent and costly drugs or the probably less fashionable but often equally effective and certainly less expensive progestins? Is there any available and definitive evidence demonstrating that small ovarian endometriotic cysts in young women not seeking pregnancy must always be removed? In addition, implementing long-term adjuvant medical therapy with oral contraceptives would reduce the risk of postoperative endometrioma recurrence enormously (Vercellini et al, 2013), thus decreasing also the overall



economic burden related to serial ultrasonography to detect cyst reformation and to manage disease relapse. These are but a few examples of how health care expenditure for women with endometriosis can be reduced without worsening the quality of disease management. However, rationalisation of costs should not be limited to the clinical setting. In the future, research itself should be focused on the outcomes that really matter to our patients and address questions of relevance to them (Krumholz and Selby, 2012). Applied medical research should be transformed by more fully integrating into the research process those that will use the research outcomes. This could also lead to better allocation of funding with reduction of the dispersion of efforts and final cost savings.

Last but not least: do we really need all the medical conferences on endometriosis that are held so frequently all over the world (Ioannidis, 2012)? Will patients benefit from their caring gynaecologist's systematic attendance? Is our field so rich of truly innovative findings to justify the costs of so many congresses, or could part of those resources be dedicated to rational applied medical research in the interest of women with endometriosis? The answer might be a bit hard to swallow.

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Upcoming meetings

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

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

Thinking outside the box

A defining feature of us, humans, is that we are supremely adaptable. Of course, it can be argued that this very feature, that has made us such an evolutionary success, is turning the world we inhabit into a depleted home of rapidly dwindling resources. Whether in the end we will be adaptable enough to ensure a safe future for generations to come is uncertain.

Adaptability in a creative sense, not an evolutionary one, means the ability to think outside the box. It is to see patterns where conventional wisdom only sees noise. It means coming up with solutions where established theory arrives at a dead end.

In the field of medicine, there are plenty of examples where lateral thinking has led to pivotal changes in our understanding and management of certain diseases. **Barry Marshall** and **Robin Warren**, two Australian academics, were awarded the Nobel Prize for their work on the link between *Helicobacter Pylori* and peptic ulcers. Their hypothesis was derided by the scientific community for a long time and the seminal paper, now the highest cited paper in the Medical Journal of Australia, was rejected by one of the top medical journals. Famously, Barry infected himself by ingesting a culture of *Helicobacter Pylori* to prove their hypothesis.

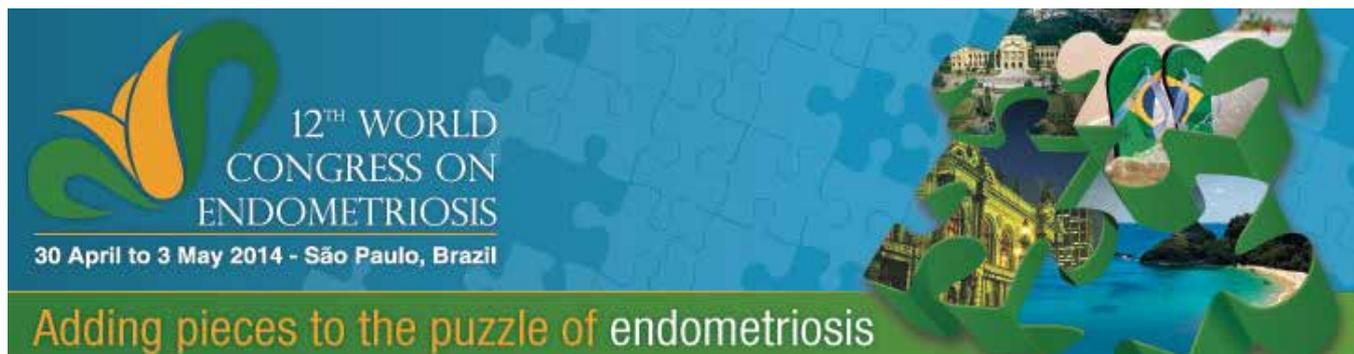
Understanding endometriosis is another challenge where an unconventional approach and creative lateral thinking may lead to a sudden breakthrough that could fill in the blanks. It feels a bit as we have identified almost all the dots of a connect-the-dots cartoon, but we are missing the order in which to connect them. Coming back to our impact on the environment, America

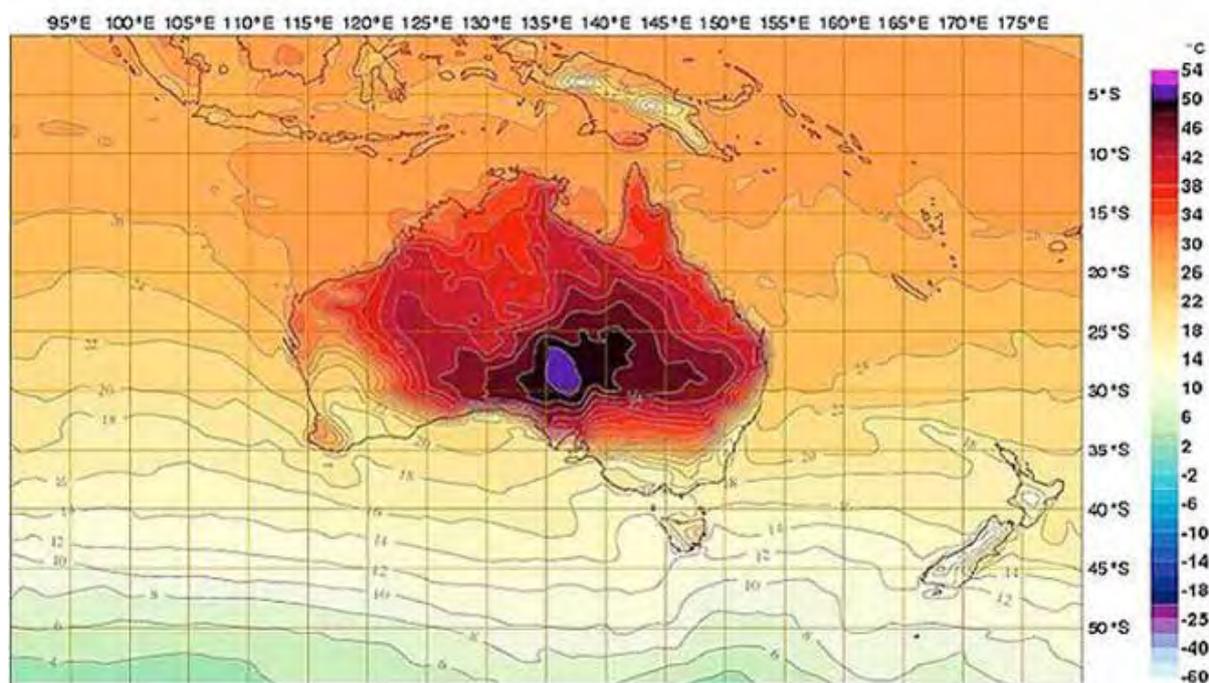


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has been affected by one of the worst droughts in the last 100 years. Australia has also been hit with some extreme weather events, again. Queensland has experienced a series of tornados and at the time of writing torrential rain is threatening major flooding in its capital, Brisbane, for the second time in two years. The event that probably made world news in early January was the massive bubble of extremely hot air that was hovering over most of central Australia, leading to record heat waves in Melbourne and Sydney.

The forecast temperatures in central Australia were so high that meteorologists had to start thinking outside the box. The scales on their charts simply didn't allow for such high temperatures to be plotted. So, they simply added deep purple and purple to get the scale up to 54°C (129.2°F), for all clarity I will repeat this: fifty-four degrees Celsius (see figure on the next page).





In the presidential editorial for this issue of the eJournal, Paolo Vercellini makes an impassioned plea to think outside the box when managing endometriosis patients. The theme of his editorial is for us all to be money-wise in our use of health resources, especially now that in many countries, including Australia, governments are tightening the expenditure on health.

We also have an exciting review of the link between endometriosis and ovarian cancer by Sun-Wei Guo. To learn whether the link is a causal one or just an association, read on and get a master class in epidemiology for free!

Finally, Mauricio Abrao introduces us to the members of his local organising committee for the 2014 World Congress of Endometriosis.

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Hans Evers becomes editor of Human Reproduction

Congratulations to Professor JLH Evers, immediate past president of WES and a former chairman of ESHRE, who started a six-year term as Editor-in-Chief of Human Reproduction in January.

In a recent interview Professor Evers declared his ambition of raising the impact factor of Human Reproduction from a respectable 4.475 to 5 by improving a system, which has to be better at identifying and weeding out poor papers. This is an increasing challenge in an electronic world where anyone can publish anything. Professor Evers has thus stressed that the peer reviewed journal – whether published on paper or electronically – becomes even more important and will remain one of the mainstays of journal publishing.

We wish Hans Ever all the best of luck in his new position!



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Is endometriosis a precursor of ovarian cancer?

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“When the populace all detests something, be watchful; when the populace all favours something, be watchful.”

Confucius (551-479 BC)

Although endometriosis is well recognised as a benign gynaecologic condition, its association with ovarian cancer has often been reported and mentioned in the literature. A PubMed search with the keyword, endometriosis, yielded a total of 19,204 papers. Using the combination of “endometriosis” and “ovarian cancer”, it turned up 2,490 papers, or 13.0% of the total literature on endometriosis. In contrast, 3,625 (18.9%), 3,426 (17.8%), and 497 (2.6%) papers were on endometriosis and infertility, endometriosis and pain, and endometriosis and inflammation, respectively (Accessed on 17 January 2013).

Many review papers on this topic have been published, yet there is no consensus on whether or not endometriosis is a precursor of ovarian cancer (Sayasneh et al, 2011). While many scientists sit on the fence, some investigators think that ovarian endometriomas “could be viewed as a neoplastic process”, and consider the malignant transformation of endometriosis as rather obvious (Kobayashi et al, 2009). Other investigators are more cautious, arguing that, among the nine criteria of causality, proposed by Hill (Hill 1965), many are still unfulfilled (Vigano et al, 2007).

However, a Lancet Oncology paper, published early last year, seemed to tip the balance of this debate towards the conclusion that endometriosis is a precursor of ovarian cancer. From a pooled analysis with primary data from 13 case-control studies, Pearce et al reported that women with self-reported endometriosis were at a significantly increased risk of clear-cell (odds ratio (OR)=3.05), low-grade serous (OR=2.11), and



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endometrioid invasive (OR=2.04), but not high-grade serous invasive ovarian cancer (Pearce et al, 2012).

The authors of that paper concluded that “we will develop a risk stratification model that combines genetic and epidemiological risk to better stratify women into high-risk, intermediate-risk, and low-risk categories, allowing better individualisation of prevention and early detection approaches such as risk-reduction surgery and screening.” The lead author, Dr Celeste Leigh Pearce, was even more optimistic, stating in a journal news release that “[t]his breakthrough could lead to better identification of women at increased risk of ovarian cancer and could provide a basis for increased cancer surveillance of the relevant population, allowing better individualization of prevention and early detection approaches such as risk-reduction surgery and screening” (<http://health.usnews.com/health-news/news/articles/2012/02/22/endometriosis-could-raise-risk-of-3-ovarian-cancers>, accessed on January 15, 2013). In other words, endometriosis is indeed a precursor of ovarian cancer and, as such, certain measures should be taken accordingly.

Ovarian cancer is by far the deadliest cancer among all gynaecological cancers. Despite advances in radical surgery and chemotherapy, the overall survival has changed very little in the last thirty years (Vaughan et al, 2011). With the advent of molecular biology, a great

deal of efforts have been focused on early detection yet this attempt often brings with it a roller-coaster experience and consequently it has so far not resulted in any tangible survival benefit to the patients. Faced with such an abject failure, it is important to identify the precursor(s) of ovarian cancer, even for some specific histotypes.

With this in perspective, it is perhaps understandable why there has been so much attention on the endometriosis-ovarian cancer link. However, how solid is the evidence for this link? Would the evidence, gathered so far, warrant any actionable measures such as those suggested by Dr Pearce? These are simple yet weighty issues that are worth careful examination.

In this article, I shall provide a balanced yet critical review of the evidence in support of the link in a narrative manner, point out the challenges in proving the causal link, and, in the end, sketch a way to solve this problem. Due to space limitation, I shall restrict my attention to epidemiological and clinical data. While there is a growing body of literature documenting various shared molecular aberrations between endometriosis and ovarian cancer, suffice to say that, due to the nature of these studies, many such aberrations are indicative of association, only suggestive for a causal link, simply because the temporality of the link is difficult to prove. It should be noted that this review is by no means to discredit published studies. On the contrary, by exposing uncertainties and deficiencies in some studies, and also areas in need of further investigation, it is hoped that we can have better studies in the future, and perhaps think of innovative ways to delineate the endometriosis-ovarian cancer link.

Evidence from clinical series

Early criteria

As early as 1925, Sampson proposed histopathological criteria for inferring that the malignancy arose from endometriosis, or the causal relationship between endometriosis and malignancy:

1. clear evidence of endometriosis close to the tumour (“proximity”);
2. the carcinoma must be seen to arise in endometriosis, and not to be invading it from other

- sources (“arising from endometriosis”); and
3. presence of tissue resembling endometrial stroma surrounding characteristic glands (“endometrial stroma plus glands”) (Sampson, 1925).

Scott later added one more criterion: the demonstration of a histology-proven transition from benign endometriosis to cancer (“transition”) (Scott, 1953).

Clearly, these criteria are all based on histological evidence, which, in turn, are based on tissue samples taken from patients. While the “proximity” and “endometrial stroma plus glands” criteria may be relatively easy to establish, the inference of “arising from endometriosis” and “transition” has, by necessity, to be based on a single snap shot, in contrast to serial observations, of the histological images or morphologic features during a presumably long period of tumorigenesis and, as such, can be challenging to establish. It is no wonder that these criteria, considered to be stringent, are rarely fulfilled (Somigliana et al, 2006; Sayasneh et al, 2011).

The morphologic data can tell us something, but only to a certain extent. For example, ovarian cancer was once regarded as a single disease since by morphology the tumour seemingly originated from ovary but now a dualistic model of carcinogenesis of ovarian cancer based on distinctive clinico-pathologic and molecular genetic features seems to have replaced the older view (Kurman and Shih 1e, 2011; Vaughan et al, 2011). Also, just by morphology or histological data, it would be very difficult to find that there are 4 main subtypes of breast cancer caused by different subsets of genetic and epigenetic abnormalities (Cancer Genome Atlas Network, 2012). In addition, since the choice of tissue sections entails a certain degree of selection, it may be susceptible to attribution error, especially when the pathologists are inexperienced.

Prevalence data: The intimate connection with the odds ratio

About a dozen reports on the prevalence of endometriosis in women with ovarian cancer have been published. If we denote the prevalence of endometriosis (E) as P(E), the prevalence of women with both

endometriosis and ovarian cancer (O) (often called endometriosis-associated ovarian cancer or EAOC) as $P(E,O)$, and the proportion of E among women with O as the conditional probability $P(E|O)$, then we can denote the relative risk of having O in women with E vs. women without E (E_c) as $RR=P(O|E)/P(O|E_c)$, that is, the relative risk of having O when a woman has E vs. a woman who does not. This is the quantity that most, if not all, epidemiological studies attempt to estimate. Here, the age-dependency is ignored for ease of exposition.

Since both $P(O|E)$ and $P(O|E_c)$ are small (because the life-time risk of developing O is about 1% or 0.01 and even lower for some specific histotypes of ovarian cancers), $1-P(O|E) \approx 1-P(O|E_c) \approx 1$,

$$RR = P(O|E)/P(O|E_c) \approx P(O|E)[1 - P(O|E)]/P(O|E_c)/[1 - P(O|E_c)] = OR,$$

That is, when ovarian cancer is rare (and indeed it is), the OR obtained from case control studies is merely an approximation of the RR.

By Bayes theorem and after some simple algebra, it is easy to see that $RR=P(E|O)[1-P(E)]/(P(E)[1-P(E|O)])$.

That is, the true RR depends only on the prevalence of endometriosis (of which we have a fairly good idea) and the prevalence of endometriosis among women with ovarian cancer (which can be estimated from data, at least in theory). Note that this RR does not depend on the prevalence of O. Hence we can calculate RR even for some specific histotypes of ovarian cancer, such as clear cell or endometrioid ovarian cancers. It is noted that RR can be expressed in a more revealing form, as $RR=rO/r$, where $rO=P(E|O)/[1-P(E|O)]$, the odds of having endometriosis given that the woman has O, and $r=P(E)/[1-P(E)]$, the odds of having endometriosis in the general population.

Prevalence data from published studies

The prevalence data extracted from 13 studies reporting the prevalence of endometriosis in women with ovarian cancers, along with the estimated RR using either the 10% prevalence for endometriosis or the 5% for ovarian endometriomas, are listed in Table 1. It can be seen that there are enormous variations in the reported prevalence, and, consequently, the RR estimates also vary greatly from study to study. It should be noted that the reported prevalence of endometriosis in women with ovarian cancer is likely to be an underestimate of $P(E|O)$, since some endometriotic lesions may have been missed by the surgeon who performed the operation, or pathologists, who performed the histologic examination, may not have found any lesion which might still exist.

Anyhow, it can be seen from Table 1 that, even though $P(E|O)$ may be underestimated, some RR estimates based on the reported prevalence still deviate greatly from the OR estimates reported from case-control studies, especially for clear cell and endometrioid histotypes. It is unclear whether some seemingly high prevalence estimates are genuine or a result of ascertainment bias, population idiosyncrasy, or chance events.

Based on all published prevalence estimates listed in Table 1, one can get that a pooled estimate of prevalence for all histotypes of ovarian cancer weighted by the sample size, which is 12.9%, yielding an RR estimate of 1.33 if a 10% prevalence is assumed, or 2.81 if a 5% prevalence is assumed. For clear cell and endometrioid

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ID	Author	Year of Publication	Overall			Clear cell and Endometrioid			Remark
			Prevalence	RR (P=10%)	RR (P=5%)	Prevalence	RR	RR	
A71	Aure et al.	1971	4.2% (35/831)	0.39	0.83	12.5% (34/271)	1.29	2.71	
K72	Kurman and Craig	1972	NR	-	-	10.2% (5/49)	1.02	2.16	
R79	Russell	1979	11.3% (46/407)	1.15	2.42	34.3% (36/105)	4.70	9.92	
B89	Brescia et al.	1989	NR	-	-	18.4% (14/76)	2.03	4.28	
V93	Vercellini et al.	1993	11.1% (52/466)	1.12	2.37	25.0% (38/152)	3.00	6.33	
C96	De La Cuesta et al.	1996	NR	-	-	40.0% (16/40)	6.00	12.67	
J97	Jimbo et al.	1997	14.5% (25/172)	1.53	3.22	35.6% (16/45)	4.96	10.50	
F97	Fukunaga et al.	1997	24.1% (54/224)	2.86	6.03	49.4% (40/81)	8.79	18.55	
O00	Ogawa et al.	2000	29.1% (37/127)	3.69	7.80	66.0% (33/50)	17.47	36.88	
V00	Vercellini et al.	2000	43.5% (91/209)	6.93	14.63	60.7% (54/89)	13.90	29.35	Only unilateral cancer and left-sided lesions were considered
O03	Oral et al.	2003	7.7% (14/182)	0.75	1.59	26.3% (5/19)	3.21	6.79	
D11	Dzatic-Smiljkovic et al.	2011	11.0% (23/210)	1.11	2.35	33.3% (19/57)	4.49	9.49	
K12	Kondi-Pafiti et al.	2012	5.9% (1/17)	0.56	1.19	0.0% (0/16)	0.00	0.00	

Table 1. Prevalence of endometriosis in women with ovarian cancers and the estimated relative risk of developing ovarian cancer in women with endometriosis vs. women without.

ovarian cancers, the pooled estimate of prevalence is 28.0% and the corresponding RR estimates are 3.51 and 7.40, respectively, depending on the endometriosis prevalence.

Epidemiological evidence

Cohort studies

In a typical cohort study, two cohorts or two groups of people, one with and one without a particular attribute (in our case, women with or without endometriosis) are identified and followed up longitudinally. The incidence of a particular event in the two groups -quite often, disease (ovarian cancer, in our case)- is evaluated and compared. In this way, whether having the particular attribute (exposure) would increase or decrease the incidence can be investigated.

Due to constraint in time and resources, cohort studies are seldom conducted concurrently or truly

prospectively. Instead, many cohort studies are conducted retrospectively. In the latter case, the cohorts are identified and assembled in the past based on archived records. In this case, the occurrence of the event of interest is often retrieved from the records as well. While retrospective cohort studies require much less resources and time, their major disadvantage is their exclusive reliance on available information, sometimes the subjects' own memory. Consequently, the quality of exposure or disease data can be compromised (for example, recall bias).

In epidemiology, the outcome is frequently a disease. One common outcome measure in cohort studies is incidence, or the risk of developing certain disease within a specified period of time given no occurrence prior to that time period. It can be expressed either in cumulative incidence (incidence proportion) or incidence rate with a denominator (called incidence

density rate or person-time incidence rate). In analytical epidemiology, one measure that is used very frequently is the standardised incidence ratio (SIR), which is a ratio or percentage quantifying the increase or decrease in incidence of a study cohort with reference to the general population.

While the SIR provides a succinct measure of the change from the incidence from the reference population or cohort, it becomes a bit cumbersome when there are some confounding factors that need to be controlled for, especially in retrospective cohort studies. In these circumstances, the rate ratio (RR, also called ratio of incidence densities) or hazard rate (HR) would be more convenient, and their use would render the use of some sophisticated statistical models such as the Cox regression model possible, facilitating elaborate statistical analysis. The RR gives the ratio of the event rate in the cohort of interest (say, women with

endometriosis) vs. that in the reference group after adjustment for other known confounders. Both SIR and RR provide a measure of causality (or, rather, association, especially for retrospective cohort studies) between exposures and outcomes.

So far, seven cohort studies, with varying qualities, on endometriosis-ovarian cancer link can be identified (Table 2). Some of them were population-based and prospective studies, others were hospital-based or retrospective cohort studies. These studies yielded either SIR or RR estimates, along with 95% confidence intervals (CIs) (Table 2).

From these SIRs and their CIs, their standard errors (SEs) can be easily calculated. Since all the RRs were calculated based on logistic or Poisson regression models after adjusting for possible confounding factors, the SE of the log-transformed RR can be calculated based on RRs and their CIs.

<i>ID</i>	<i>Author</i>	<i>Year of Publication</i>	<i>Cohort size</i>	<i>Length of follow-up</i>	<i># of cases</i>	<i>SIR or RR</i>	<i>SE</i>	<i>95% CI</i>
B97	Brinton et al	1997	20686	11.4	29	1.92	0.38	1.3—2.8
O02	Olson et al.	2002	1392	13	13	0.78*	0.74	0.25—2.44
B04	Brinton et al.	2004	1919	18.8	13	1.26*	0.29	0.6—2.6
B05	Brinton et al.	2005	2491	NA	50	1.69*	0.09	1.27—2.25
M06	Melin et al.	2006	66187	12.7	122	1.43	0.133	1.19—1.71
M07	Melin et al.	2007	63630	13.4	134	1.37	0.12	1.14—1.62
K07	Kobayashi et al.	2007	6398	12.8	46	8.95	2.85	4.12—15.3
A10	Aris	2010	2854	10	333	1.6*	0.10	1.12—2.09
S12N	Stewart et al.	2012				3.11* (for nulliparous women)	0.52	1.13-8.57
S12P						1.52* (for parous women)	0.76	0.43-6.75

Table 2. Published cohort studies reporting ovarian cancer risk in women with endometriosis. Numbers with an asterisk in the “SIR or RR” column are RR estimates.

Abbreviations used: SIR: Standard incidence ratio; RR: Rate ratio; SE Standard error; CI: Confidence interval.

In evaluating risk estimates -be it SIR, RR, or OR if from case-control studies- from various studies, funnel plots are often employed (Sterne et al, 2001). In funnel plots, risk estimates, such as RRs or log RRs, are placed on the horizontal axis against some measure of study size or precision, such as their standard errors, on the vertical axis. The funnel plot is so named because its shape: in the absence of selection biases (such as publication bias and bias in inclusion criteria), true heterogeneity (ie. size of effect differs according to study size), and data irregularities (such as poor methodological design of small studies, inadequate analysis, and fraud), studies of large or small sample sizes should be more or less symmetrically scattered around the true log RR. Hence the plot should have the shape of a funnel with wide opening on the top (due to sampling variability), with the tip of the funnel pointing to the bottom and centering on the true log RR (Sterne et al, 2001). The choice of log OR instead of OR is due to the fact that the standard error of RR is related with the odds ratio, while the standard error of log OR is purely a function of sample sizes in different exposure-disease status combinations. The use of log OR also renders ORs that are greater than 1 or less than 1 symmetric about 1 (=0 on the log-scale). When plotting the 9 log-transformed SIRs/RRs against their SEs in a funnel plot (Figure 1), two features can be noted. First, the plot looks like an asymmetric funnel, with its tip gravitating towards somewhere near log SIR or log RR=0, i.e. SIR=1 or RR=1.

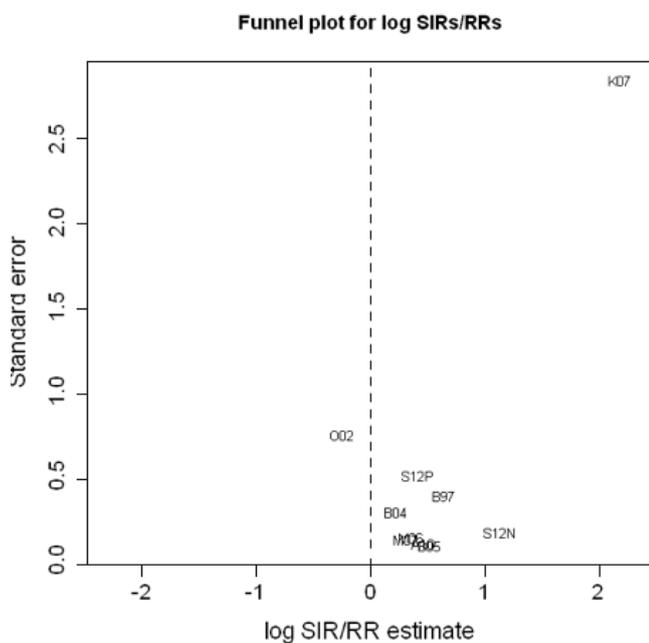


Figure 1.

Since there is no indication of bias in inclusion criteria or heterogeneity, this suggests that there may be a publication bias towards favouring positive studies and higher estimates of odds ratios may well be a chance variation. In addition, the plot seems to suggest that the true SIR or RR is near 1.

Second, the SIR estimate, K07 in the plot, provided by Kobayashi et al (Kobayashi et al, 2007) is situated at the rim of the funnel, suggesting that while it gave a larger SIR estimate, it is not a precise estimate.

The paper by Aris (Aris, 2010) gave $P(E)=0.107$, and $P(E|O)=0.14$, yielding $RR=1.36$ as discussed above. This is very close to the RR estimate of 1.6 reported by the paper.

An overview on case-control studies

Case-control studies are an alternative to cohort studies for investigating the association between exposure (in our case, having endometriosis) and disease (ovarian cancer). The basic questions for such studies are the degree of association between risk for disease and the factor(s) under investigation, the extent to which the observed association may result from bias, confounding, and/or chance, and the extent to which they may be described as causal (Breslow and Day, 1980). A case-control study compares cases (in our case, women with ovarian cancer) and controls (women without ovarian cancer, say) with respect to their exposure (or lack thereof) or levels of exposure to a suspecting risk factor (in our case, having endometriosis). When the risk factor at hand is a dichotomous variable, such as having endometriosis or not, the outcome measure is typically the odds of exposure in cases as compared with that in controls, or OR. When the occurrence of disease is rare, such as ovarian cancer, the OR estimated from case-control studies becomes an acceptable approximation to the relative risk. Case-control studies can be a powerful tool in the investigation of exposure-disease relationship when both the disease and the exposure are rare. A prime example is the uncovering of the relationship between in utero exposure to diethylstilbestrol (DES) and vaginal adenocarcinomas in the daughters (Herbst et al, 1971). This study was based on 8 cases, each with 4 matched controls. Seven out of 8 cases had been exposed to DES in utero but in contrast none of the 32 controls had.

As with SIR or RR used in cohort studies, the OR or relative risk (RR) used in case-control studies are measures of association between disease and exposure. However, the association could be causal, but also could be merely a correlation. For women with endometriosis (E), or with ovarian cancer (O), the association between E and O could be due to a variety of scenarios. Figure 2 shows several scenarios in which E and O can be found to be associated. Scenario A is the case where factor X has a causal relationship with both E and O. E and O are associated simply because of the presence of the common risk factor X, which may or may not be measured in a study. It should be noted that E and O share at least one common risk factor; that is the incessant ovulation/menstruation. Incessant ovulation or unopposed oestrogen exposure is a known major risk factor for ovarian cancer (Casagrande et al, 1979).

Similarly, incessant menstruation is a known, major and consistently identified risk factor for endometriosis (Vercellini et al, 2011). Figure 3 shows two numerical examples, perhaps somewhat extreme but nonetheless not unusual cases. In example A, failure to control for the confounding factor gives rise to spurious results. It is interesting to point out that, while the OR for the O-E association in each stratum of factor X is 1, the OR for the association with pooled levels of the factor is $1.35 > 1$. Of course, the failure to control for confounders can also go the other direction, in which the pooled OR can be smaller than ORs in each stratum (example B).

In figure 2, Scenario B shows the case in which both factor X and E represent the same underlying cause for O, such as the case when X and E represent different aspects of the same factor. Scenario C is the case where E leads to X, which, in turn, has a causal relationship with O.

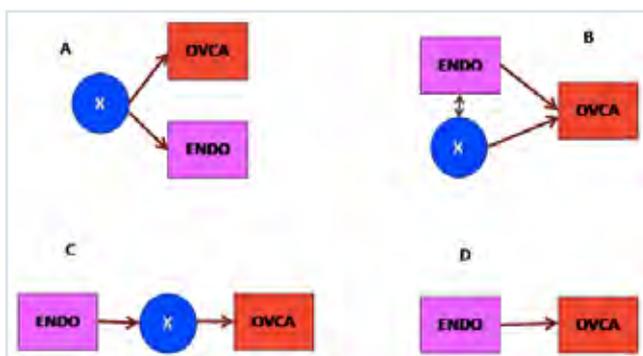


Figure 2.

A.	Factor X + Exposure E	Factor X - Exposure E	Pooled levels of Factor X Exposure E	
	+	-	+	-
Case	60	50	65	56
Control	6	5	56	65
OR	1	1	1.35	

B.	Factor X + Exposure E	Factor X - Exposure E	Pooled levels of Factor X Exposure E	
	+	-	+	-
Case	100	100	190	110
Control	10	90	110	190
OR	9.0	9.0	2.98	

Figure 3.

In the case of E-O association, it is possible that the diagnosis of endometriosis may result in the use of Danazol, an androgenic agent, which could increase the risk of O in light of the “androgen hypothesis” of ovarian cancer (Risch, 1998; Cottreau et al, 2003). In other words, it could be the exposure to an androgenic agent, once a popular therapeutic for endometriosis, that increases the risk of ovarian cancer not the endometriosis itself. Scenario D is the case in which E-O has a causal relationship.

It should be noted that factor X in scenario A is considered a confounding factor. Confounding is the distortion of a disease/exposure association brought about by the association of other factors with both disease (O) and exposure (E) (Breslow and Day, 1980).

The magnitude of OR is a measure of the strength of association, or the effect size. In general, when an OR is large, say greater than 10, the association is likely to be real, especially when the magnitude of OR varies with the level of exposure in a dose-dependent fashion. For example, the relative risk of having cervical cancer in women with HPV positivity vs. negativity is about 1000. Depending on the number of daily cigarettes consumed, the OR for smoking-lung cancer association ranges from 7 to about 27. The OR for the association between the DES exposure and vaginal cancer is about 40. In contrast, for an association with an OR < 2 , it is likely that the OR estimate could be a result of confounding or bias, and needs to be scrutinized rigorously even though the association could also be genuine (Rothman and Poole 1988).

Case-control studies: Guilty by association

Nine case-control studies can be identified (Table 3). As expected, these studies vary in the types of ovarian cancer and the selection of controls (women with endometriosis or endometriomas, or infertility). Regardless, the forest plot revealed that the pooled (raw) OR estimate is 1.52 (95% CI=1.41–1.64; Figure 4), suggesting that the overall OR value is moderate. In addition, there is little heterogeneity ($p=0.57$ for heterogeneity test).

As with the SIR/RR estimates, the funnel plot of the log ORs from the 9 studies indicates that the plot also looks like an asymmetric funnel, with its tip pointing towards somewhere near $\log OR=0$, i.e. $OR=1$ (Figure 5). Since there is no indication of bias in inclusion criteria or heterogeneity, this suggests that there may be a publication bias towards favouring positive studies and higher estimates of odds ratios may well be a chance variation. In addition, the plot seems to suggest that the true OR is quite moderate.

<i>ID</i>	<i>Author</i>	<i>Year of Publication</i>	<i># of cases</i>	<i># of controls</i>	<i># case w/ Endo</i>	<i># controls w/ Endo</i>	<i>Adjusted OR (95%CI)</i>	<i>Remark</i>
N00	Ness et al.	2000	764	1364	66	85	1.7 (1.2-2.4)	
N02	Ness et al.	2002	3678	5268	51	39	1.73 (1.10-2.71)	Originally considered infertility as a possible risk factor, but also looked at patients with infertility due to endometriosis
M04	Modugno et al.	2004	2089	2943	177	184	1.32 (1.06-1.65)	This study also included some data from Ness et al, 2000
B04	Borgfeld et al.	2004	27050	81254	81	181	1.34 (1.03-1.75)	
M08	Merritt et al.	2008	1555	1500	124	87	1.31 (0.97-1.78)	
N08	Nagle et al.	2008	87	1450	13	87	3.0 (1.5-5.9)	For endometrioid and clear cell ovarian cancers
R08	Rossing et al.	2008	585	1293	64	94	1.6 (1.1-2.3)	For invasive ovarian cancer
W09	Wu et al.	2009	604	679	51	37	1.66 (1.01-2.75)	
P12	Pearce et al.	2012	7911	13226	738	818	1.46 (1.31-1.63)	Invasive clear cell and endometrioid ovarian cancers

Table 3.
Published case-control studies reporting ovarian cancer risk in women with endometriosis.

Abbreviations used: OR: Odds ratio; SE Standard error; CI: Confidence interval; #: numbers; Endo: endometriosis; w/: with.

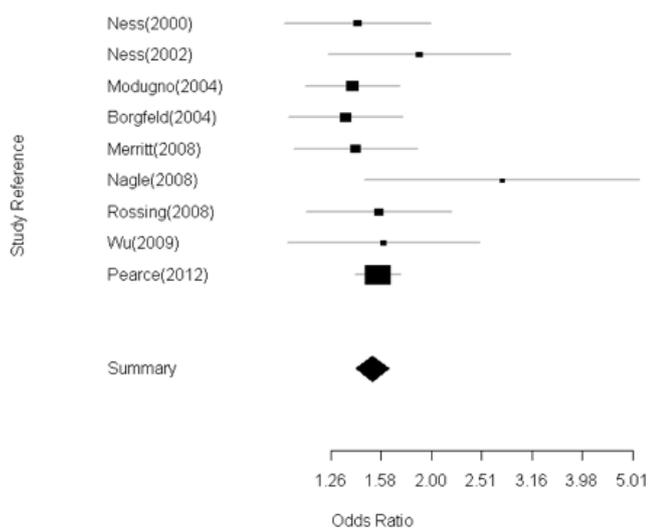


Figure 4.

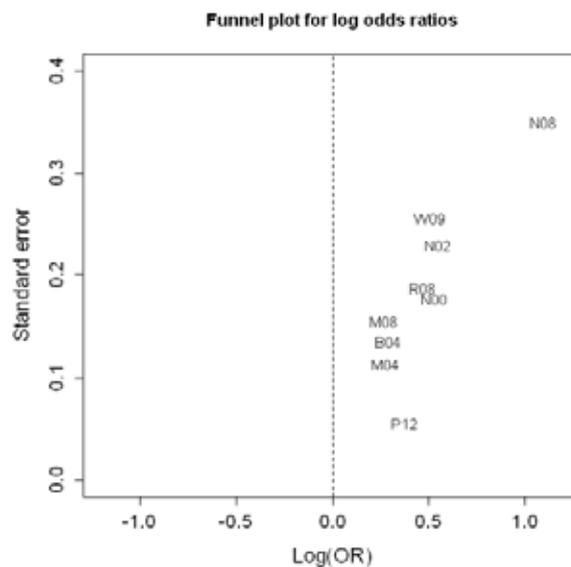


Figure 5.

Other considerations

The control for shared risk (and/or protective) factors between E and O appears to be a big challenge in sorting out the relationship between E-O association. Besides the scenario depicted in Figure 3A, it is known that E and O share some other common risk/protective factors. For example, the use of oral contraceptives (OC), age at menarche. These factors are very likely to be causally associated with both E and O, effectively making them confounding factors when assessing the E-O association in case-control studies. However, while some studies did control for OC use, few, if any, controlled for the number of ovulations/menstrual cycles.

While the mean age at onset of ovarian cancer is about 56 years (Vigano et al, 2007), the onset of endometriosis occurs mostly and typically during a woman’s reproductive age. This has been taken as support for the temporality requirement in Hill’s 9 criteria of causality (Vigano et al, 2007). Indeed, the reported mean age of EAO cases is often significantly younger than ovarian cancer patients without endometriosis but older than women with endometriosis alone (Aris, 2010).

However, the case-control studies published so far have not directly demonstrated a clear, graded temporal relationship between endometriosis and ovarian cancer.

Most epithelial tumours take a latent period of at least 15 years to develop (Vigano et al, 2007). If endometriosis is a precursor of certain types of ovarian cancer, then it should take a certain latent period, likely to be

shorter than 15 years, for ovarian cancer to develop. Consequently, one would expect that after excluding some cases with endometriosis, say, <=3 years of interval between the diagnosis of endometriosis and of ovarian cancer, the OR would be elevated since this would effectively remove many “noisy” cases which would dilute the association signal. Unfortunately, we actually see the opposite from the study by Pearce et al. (Pearce et al, 2012). Figure 6 is a graphical rendition of its sensitivity analysis (Table 4 in Pearce et al, 2012). One can see that once the cases who had at least 3, 5 or 10 years of interval between the diagnosis of endometriosis and of ovarian cancer were removed, the OR estimate goes down considerably.

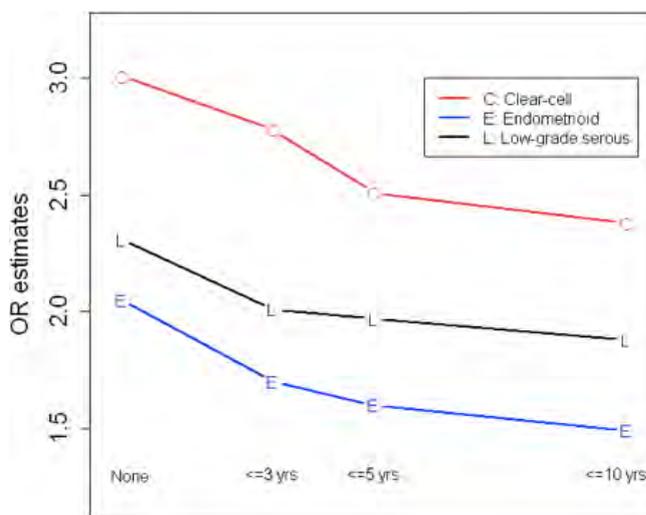


Figure 6.

Should any action be taken?

Given the somewhat consistent but rather moderate increase in OR, some investigators believe that ovarian cancer originates from endometriosis, at least for clear cell carcinoma and endometrioid adenocarcinoma (Kuhn et al, 2012), hence screening, laboratory and imaging evaluation should be “recommended for early detection of malignant disorders in women with endometriosis” (Baldi et al, 2008). Some even show that patients with EAOc actually had a more favourable prognosis (Erzen et al, 2001). However, two more recent studies do not seem to support this notion (Cuff and Longare, 2012; Noli et al, 2013).

Due to the low incidence of ovarian cancer and the rather moderate increase in risk, extreme caution needs to be exercised when conveying the message to the public and also in the context of screening. For clear-cell ovarian cancer, the prevalence is reported to be 13 per 100,000 women (Surveillance Epidemiology and End Results: <http://seer.cancer.gov/statfacts/html/ovary.html>, accessed on 17 January 2013). Let us assume, perhaps too optimistically, that a screening test exists that is 99% sensitive and 99% specific. Even with this rosy scenario, the corresponding positive predictive value is a disappointing 3.7%. In other words, out of 100 women who have tested positive, fully 96 would have a false positive result and be likely to be subjected to invasive procedures. Therefore, given the low incidence and also the moderate increase in OR, it is perhaps premature to talk about screening, let alone intervention.

Conclusion

From the funnel plots for the SIR/RRs reported from cohort studies and the ORs from case-control studies, it seems that there may be a publication bias towards favouring positive studies. In addition, the plots seem to suggest that the true effect size is very moderate. Yet the vast discrepancy between RRs estimated from the prevalence of endometriosis in women with ovarian cancer and ORs reported from published case-control studies is puzzling.

Since the prevalence is very likely an underestimate, the true RR is likely to be higher, which would highlight the discrepancy even more.

It is unclear what factors contributed to the discrepancy. Have all epidemiological studies published so far

underestimated the effect size due to a failure to control for some, yet to be identified, confounders or certain biases of unknown sources? Or have many studies reporting the prevalence of endometriosis in ovarian cancer somehow over-reported, perhaps unwittingly, because of ascertainment or selection bias, population idiosyncrasy, or simply fallen into the trap of attribution error? There is no answer as of now, and addressing these questions would warrant future studies.

While the presence of ovarian endometriomas may generate a pro-inflammatory micro-environment that may be conducive to the development of ovarian cancer, it is noted that most, if not all diseases, especially those associated with pain, more or less have signs of inflammation. Even obesity produces signs of inflammation.

What is unclear is how the pro-inflammatory milieu in endometriosis per se leads to ovarian cancer. It is also unclear whether the peritoneal or vagino-rectal deep-infiltrating endometriosis would also increase the risk of ovarian cancer more than that of other gynaecological cancers.

Moreover, the failure in providing or adjusting for information on treatment in many published epidemiological studies raises the question whether surgery or drug treatment can actually reduce or increase the risk of ovarian cancer. It also raises the question whether the use of Danazol, an androgenic agent, could increase the risk of ovarian cancer. Finally, due to the nature of case-control studies, it cannot be ruled out that both endometriosis and ovarian cancer (especially clear-cell or endometrioid type) may simply share some common risk and/or protective factors -such as the “incessant menstruation” and OC use, or others yet to be identified- so that an elevated OR is still an association but the relationship is by no means causal.

While younger age at diagnosis of endometriosis than that of ovarian cancer is often taken as a proof of temporality in the causal link, many epidemiological studies have not directly demonstrated a clear temporal relationship between endometriosis and ovarian cancer. Since it is now well documented that, similar to cancer, endometriotic lesions are monoclonal in origin (Wu et al, 2003), one way to prove the temporal relationship and to provide a convincing proof that some histotypes

of ovarian cancer originate from endometriosis is to reconstruct a phylogenetic tree delineating the genetic relationship between endometriotic lesions and ovarian cancer based on a molecular clock. A proof-of-concept study demonstrating the utility of the molecular clock in reconstructing the geographical relationship among pieces of endometrial fragments demonstrates that the phylogenetic approach is feasible using today's genetic technology (Wu and Guo, 2008).

In summary, while published clinical and epidemiological studies strongly implicated the risk, though moderate, of developing certain histotypes of ovarian cancer in women with endometriosis, many stones are still left unturned. It should be noted that the evaluation of the nature and strength of the association between the two diseases is intrinsically challenging: Both diseases have different histotypes/subtypes, variable age of onset, and the lack of means for early detection, making any study attempting to unravel the relationship prone to various biases such as misclassification. In addition, the two diseases share several important risk and protective factors. The utility of animal models is limited due to an apparent paucity of appropriate animal models.

Future studies need to determine whether the association is truly causal with a clear temporal relationship or merely an association due to exposure to shared risk factors. Given the moderate association, it is perhaps premature to institute any actionable measures as of now. Future studies also need to resolve an apparent discrepancy in estimated effect size between the clinical data and epidemiological data. Furthermore, they need to delineate the molecular pathways linking endometriosis and ovarian cancer. Care should be taken to avoid making "just-so" stories.

Acknowledgment

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Figure legend:

Figure 1. Funnel plot for the 9 log-transformed SIRs/RRs, using data extracted from Table 2. The dashed line represents SIR=1 or RR=1. The alphabet-numeric combinations are the IDs shown in Table 2, and each ID represents one study.

Figure 2. Diagrams showing 4 different scenarios in which E and O can be found to be associated.

Figure 3. Two hypothetical examples showing that failure to control for confounding can lead to spurious results. (A) Artificially inflated OR; (B) Underestimated OR.

Figure 4. Forest plot summarizing the results from 9 case-control studies using data from Table 3.

Figure 5. Funnel plot for the log ORs, using data extracted from Table 3. The dashed line represents OR=1. The alphabet-numeric combinations are the IDs shown in Table 3, and each ID represents one study.

Figure 6. A graphical rendition of the sensitivity analysis for the association of endometriosis and risk of invasive ovarian cancer based on timing (time interval) of diagnosis between the two diseases, as reported by Pearce et al. (Pearce, Templeman et al. 2012)(their Table 4). When patients with the time interval less than or equal to 3 years, 5 years, and 10 years are excluded, the increase in the OR estimate is seen.

Meet the local organising committee (LOC) of WCE2014

I am excited to be able to introduce the local organising committee. We pride ourselves in Brazil on having contributed significantly to research in endometriosis. In more recent WCE meetings, the largest number of abstracts in Maastricht in 2005 were from Brazil, and again in Montpellier with 16% of the total number of abstracts received. Brazilians were also the most numerous in Melbourne in 2008, where we carried off the Rodolphe Maheux Award. In short: we are serious about endometriosis in Brazil and we are working hard to make your experience at the 12th World Congress on Endometriosis the most special ever!



Mauricio Abrao
WCE2014 President

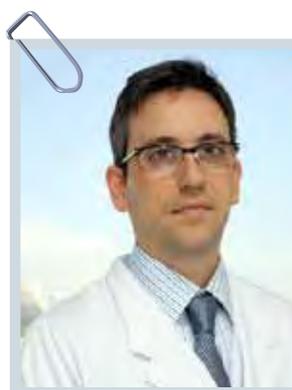


Professor Maurício Simões Abrão
WCE2014 President



Carlos Alberto Petta
(WCE2014 Vice President)

Dr Petta is the Medical Director of the Center for Human Reproduction of Campinas and of the Center for Human Reproduction of Sirio Libanês Hospital, as well as Professor of Obstetric and Gynaecology, State University of Campinas (UNICAMP) and the Head of the Endometriosis Clinic of the Center for Integrated Health Care of Women (CAISM/UNICAMP) in Campinas. Professor Petta is involved in numerous educational initiatives at both an international and national level and has written authoritatively for numerous medical publications and journals. His main research fields are endometriosis and benefits of hormonal contraceptives. Professor Petta is a Member of the Board of the International Society for Gynecological Endoscopy (ISGE), vice-president of the Brazilian Society of Endometriosis (SBE), on the board of trustees of the World Endometriosis Research Foundation (WERF).



Sergio Podgaec
(Treasurer)

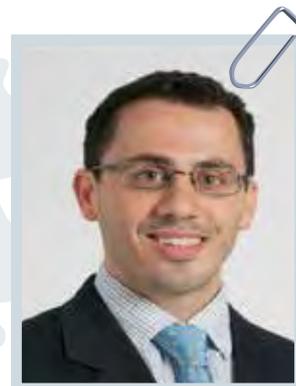
Dr Podgaec is the Assistant Professor of Gynaecology at the School of Medicine of the University of São Paulo, where he has a specific interest in the diagnosis and treatment of deep endometriosis. Dr Podgaec was the co-winner of the first Rodolphe Maheux Award for the best clinical presentation by an author under the age of 40 at the 2008 world congress in Melbourne, Australia. His and Dr Dias' winning paper showed that women with deep endometriosis affecting the rectum, bladder or ureter have symptoms for longer until they have a diagnosis and are treated, than those women, who do not have these types of lesions.



Rui Alberto Ferriani
(Scientific Programme Chair)

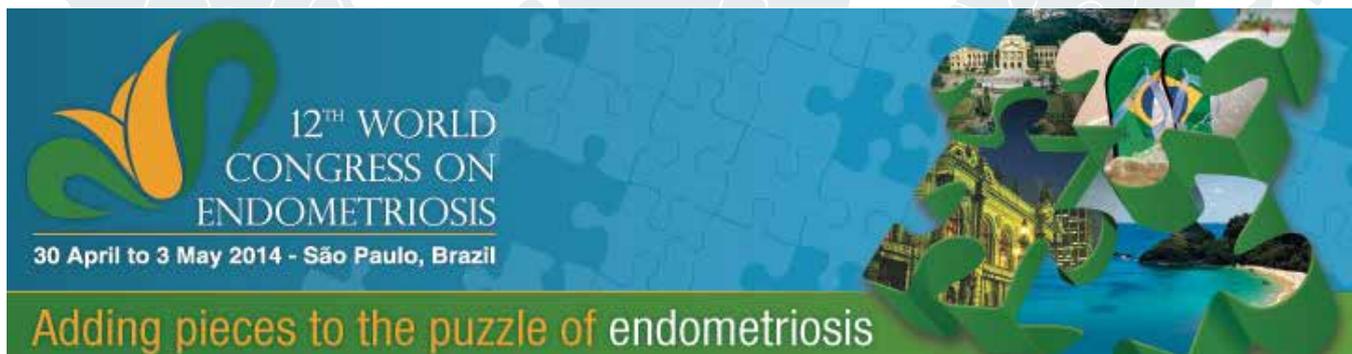
Dr Ferriani is a Professor at the Ribeirao Preto School of Medicine of the University of São Paulo and the Chief of the Human Reproduction Section of the Clinics Hospital of Ribeirão Preto, Sao Paulo University, Scientific Director of FAEPA, a foundation associated with the Clinics Hospital and member of the Evaluation Committee of CNP – the National Research Council of Brazil. He is the current Scientific Director of the Brazilian Society of Endometriosis (SBE), and an active member of the Brazilian Societies of Gynaecological Endocrinology, Assisted Reproduction, Human Reproduction and Obstetrics and Gynaecology. He is also a member of the American Society of Reproductive Medicine, of the European Society of Human Reproduction and Embryology, of the North American Menopause Society, and of the World Endometriosis Society.

Professor Ferriani has published numerous articles and participated as guest professor in many national and international congresses, and is currently Associated Editor of *Reproductive Science*.



Luiz Fernando Carvalho
(Technology & Innovation
Chair)

Dr Carvalho is a gynaecologist and obstetrician with eight years of clinical practice and research with strong emphasis on an academic career. He joined the OBGYN department of the University of São Paulo in 2008. Dr Carvalho joined the Center for Reproductive Medicine, and the Department of OBGYN at the Cleveland Clinic for his doctorate research entitled “Prospective Controlled Trial of Oxidative Cell Injury as a Predictor of Endometriosis Progression” in March 2010, and in August 2011, he joined as a Research Fellow in OBGYN at the Brigham and Women’s Hospital, Harvard Medical School with an additional research appointment at the Massachusetts Institute of Technology. He has authored 10 scientific articles, two books, and more than 15 book chapters, and has presented over 40 papers at both national (Brazil) and international scientific meetings. Dr Carvalho is on the editorial board of *Theriogenology Insight*, *In Vitro Fertilization*, and the *Asian Pacific Journal of Reproduction*. His current research interests include studies on: infertility and endometriosis; eutopic endometrium and IVF; oxidative stress; and female fertility preservation.





Eduardo Schor
(Secretary)

Dr Schor is an Affiliated Professor and Head of the Pelvic Pain and Endometriosis Unit of the Gynaecology Department of the Federal University of São Paulo. Dr Schor has been working with basic research and clinical treatment of endometriosis with his main research topics being progesterone resistance, cell cycle alterations, and stem cells in topic endometrium.



Nicolau D'Amico Filho
(Social Programme Chair)

Dr D'Amico Filho has been a gynaecologist and obstetrician since 1987 and has over ten years of clinical and surgical practice in treating advanced endometriosis in the Brazilian Public Health Service with emphasis in academic career (residents). He was also responsible for the Centre for Endometriosis in a private hospital (Samaritano, São Paulo) and is a board member of the Brazilian Society of Endometriosis (SBE).

Dr D'Amico Filho is initiating his doctorate in Stem Cells and Endometriosis at the Department of Obstetrics and Gynecology of the School of Medicine of the University of São Paulo. He has co-authored several articles on endometriosis, bowel disease, and quality of life. His current research interests and studies are focused on stem cells, TRegs, pelvic pain, and adolescents with endometriosis.



Luiz Flavio Fernandes
(Pre-Congress Programme
Chair)

A graduate of São Paulo University, Dr Flavio is now a Medical Assistant within the Endometriosis Division of São Paulo University and an advisor to the Brazilian Endometriosis Society (SBE). He is a former Preceptor of the Department of Obstetrics and Gynaecology at São Paulo University.



Claudio Peixoto Crispi
(1st Secretary)

Dr Peixoto Crispi is the president of SOBRACIL (Brazilian Society of Videosurgery) and the general coordinator of graduate studies in gynaecologic endoscopy – UNIFESO. He is a member of the Brazilian College of Surgeons, the Brazilian Society of Endometriosis (SBE), the Brazilian Society of Assisted Reproduction, and the American Association of Gynecologic Laparoscopists (AAGL).

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Endometriosis Awareness takes places globally in March

National endometriosis organisations traditionally arrange outreach and awareness events in March – some groups do this during “Endometriosis Awareness Week” (4 – 10 March 2013) and others throughout the month.

2013 **endometriosis**
AWARENESS”

Please back-up around these initiatives. Support your national endometriosis organisation in its endeavour to educate the general public about the disease and its symptoms, and the need for early diagnosis and improved treatments.

We continue to see relatively little investment in endometriosis – national endometriosis organisations are part of the solution to change this.

Full schedule of events by country



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