Regression of endothelial dysfunction in patients with endometriosis after surgical treatment: a 2-year follow-up study

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STUDY QUESTION: How does endothelial function change in women with endometriosis after surgical treatment?

SUMMARY ANSWER: Surgical treatment of endometriosis leads to endothelial function improvement, resulting in reduction of cardiovascular risk.

WHAT IS KNOWN ALREADY: Some recent studies have demonstrated that in young women with endometriosis, even if structural alterations are absent, endothelial dysfunction, expressed as flow-mediated dilation (FMD) impairment, can nevertheless occur. However, there are no data about changes of endothelial function in women with endometriosis after surgical treatment of endometriosis.

STUDY DESIGN, SIZE, DURATION: This is a follow-up study carried out in 68 women enrolled in a previous study. Endothelial function was evaluated 2 years after surgical procedure and compared with baseline values.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Twenty-two patients who had undergone surgical treatment of endometriosis (named as patients with STE) and 10 control subjects without endometriosis, from the original study sample participated in this follow-up study. Assessment of endothelial function by FMD evaluation and measurements of serum markers of endothelial activation and inflammation were done in all these subjects.

MAIN RESULTS AND THE ROLE OF CHANCE: After a 2-year follow-up period, FMD increased significantly with respect to baseline values among patients with STE [average pre- to post-difference: 5.07%, 95% confidence intervals (CI) 3.50, 6.63%; P < 0.001] but not among controls (average pre- to post-difference: 1.56%, 95% CI −0.55, 3.67%; P = 0.13). Follow-up FMD values were not significantly different between patients with STE and controls (average difference 1.50%, 95% CI −1.24, 4.23%; P = 0.27). Follow-up markers of inflammation and endothelial cells activation were similar among patients with STE and controls.

LIMITATIONS, REASONS FOR CAUTION: Although this study represents the first in the literature assessing endothelial function after surgical treatment of endometriosis, further longitudinal studies are desirable to define better the real risk that women with a history of endometriosis will develop cardiovascular events.

WIDER IMPLICATIONS OF THE FINDINGS: Endothelial dysfunction may be a better predictor of future cardiovascular events than traditional risk factors and the improvement in endothelial function we observed in patients after STE may have significant implications for their future cardiovascular risk.

STUDY FUNDING/COMPETING INTEREST(S): No external funding has been either sought or obtained for this study. There are no conflicts of interest to declare.

Key words: atherosclerosis / endometriosis / endothelial dysfunction / laparoscopy / surgical treatment
**Introduction**

Endometriosis is a common gynecological disorder characterized by the presence of endometrial-like tissue outside the uterine cavity (Burney and Giudice, 2012). In the last few years, interest about the possible relationship of this condition with several diseases has grown quickly (Gemmill et al., 2010; Montalto et al., 2010). In particular, some recent studies have reported its potential association with atherosclerosis, underlining the role of chronic inflammation and oxidative stress as key factors (Pretta et al., 2007; Kinugasa et al., 2011; Santoro et al., 2012).

In a recent study, we found that women with endometriosis, although not already presenting structural atherosclerotic changes of arterial wall, have endothelial dysfunction, expressed as impaired flow-mediated dilation (FMD), configuring a condition of subclinical atherosclerosis (Santoro et al., 2012). This finding is very relevant because endothelial dysfunction, one of the earliest measurable markers of vessel wall deterioration in atherosclerosis, has a prognostic relevance even in the absence of traditional cardiovascular risk factors (Ross, 1993; Pore dos, 2002). Moreover, the identification of endothelial dysfunction (by FMD) provides, especially in young people, the opportunity to offer treatment to reverse the condition (Tomasoni et al., 2010).

There are no studies in the literature about changes in markers of subclinical atherosclerosis in women with endometriosis after surgical treatment of endometriosis.

The aim of the present study is to evaluate endothelial function changes after surgical treatment of endometriosis by assessing FMD and measuring serological markers of endothelial activation and inflammation.

**Materials and Methods**

**Patients and controls**

We asked all 37 patients with endometriosis and 31 control subjects enrolled in our previous study (Santoro et al., 2012) to participate in this follow-up study. Briefly, all these women had a history of laparoscopy or laparotomy for a suspected benign gynecological disorder (i.e. endometriosis, infertility, ovarian cysts, uterine myomas, etc.). The exclusion criteria were age <18 years, body mass index (BMI) >30 kg/m², use of vasoactive drugs, hormonal therapy within the previous 3 month or presence of diseases impairing endothelial function (i.e. diabetes, arterial hypertension, metabolic syndrome, hyperlipidemia, chronic inflammatory disorders, hepatic cirrhosis, etc.). On the day planned for the surgical procedure, all the subjects undergo instrumental evaluations and blood sampling to evaluate markers of subclinical atherosclerosis, as previously described (Santoro et al., 2012). They were classified as patients with endometriosis and controls without endometriosis, based on surgical and histological examinations.

After a 2-year follow-up period, we have attempted to contact all 68 women previously enrolled. Women with an ongoing or recent pregnancy (within the previous 3 month) were excluded; all other available women, whether patients who had had surgical treatment of endometriosis (named as patients with STE) or controls, were enrolled in this follow-up study. Blood sampling and instrumental evaluations for vascular and gynecologic assessment were repeated in these women, as mentioned below.

**Physical and laboratory examinations**

All patients with STE and controls were submitted to thorough examinations, including weight, height and blood pressure, BMI was calculated as weight (kg) divided by the square of height (m²). The mean arterial pressure (MAP) was calculated as diastolic blood pressure + 1/3 (systolic blood pressure — diastolic blood pressure). All women enrolled into this study were asked to come at 8:00 a.m. after overnight fasting. Blood samples were taken for the assessment of serum glucose, creatinine, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), full blood count, Ca-125, von Willebrand factor antigen levels (vWF) and ristocetin cofactor. Estimation of renal function was done using the CKD-EPI equation, which is considered the gold standard for glomerular filtration rate estimation (Levey et al., 2009). Blood was centrifuged at 3500 rpm for 10 min, and serum samples were separated, aliquoted and kept frozen at −80°C. Serum levels of vascular endothelial growth factor (VEGF), inter-cellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin were determined by enzyme-linked immunosorbent assays, according to the manufacturers’ instructions (Thermo Scientific, Rockford, IL, USA for VEGF, and R&D Systems, Minneapolis, MN, USA for ICAM-1, VCAM-1 and E-selectin). All assays were done in duplicate and laboratory staff were blinded to the clinical data. All subjects were also asked to complete a questionnaire where they recorded life habits (e.g. smoking and alcohol consumption), presence of cardiovascular diseases (CVD) and family history of CVD, as well as the possible presence of pelvic pain or other symptoms suggestive for endometriosis.

**Vascular ultrasound imaging**

A non-invasive vascular ultrasound evaluations for common carotid intima-media thickness (ccIMT) measurement and endothelial function assessment were done on the same morning, soon after the blood sampling, using a high-resolution Philips iU22 sonograph (Philips Medical Systems, Monza, Italy) and a linear 17–5 MHz transducer.

For the study of ccIMT, the B-mode ultrasound imaging technique was used. Briefly, patients were placed in the supine position, with the head rotated to one side. Longitudinal two-dimensional ultrasound images were obtained, focusing on the posterior (far) wall of the carotid arteries on each side; ccIMT was defined as the distance from the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface of the far wall. A minimum of three measurements of the IMT on the common carotid far wall were taken to be $5$. 10 and 15 mm proximal to the bifurcation on each side to derive the mean ccIMT. Results were expressed in millimeters, and the values $\geq 0.9$ mm were taken to correspond to increased ccIMT.

For the study of endothelial function, we have evaluated brachial artery reactivity, which is the best-established technique used in adults. The technique assesses FMD, which measures the nitric oxide-mediated vasodilation produced by increased flow after a period of ischemia (endothelium-dependent vasodilation). This evaluation has been conducted according to published guidelines (Corretti et al., 2002; Deanfield et al., 2005). Briefly, after a 15- to 20-min supine rest period, the right brachial artery was scanned over a longitudinal section of 5–7 cm above the antecubital fossa and its diameter was measured from the tunica intima of both anterior and posterior walls; in addition, a pulse Doppler velocity signal was recorded. After the basal measurements, a blood pressure cuff around the forearm distal to the target area was inflated to a pressure of 250 mmHg for 5 min and then abruptly deflated, after which a second scan was performed continuously for 90 s, to measure diameter changes after reactive hyperemia. A pulse Doppler velocity signal was also obtained no more than 15 s after deflation to measure the maximal hyperemic velocity. FMD data were expressed as the percentage increases relative to baseline diameters.

All ultrasound scans were done by a single skilled examiner blinded to the subject’s clinical characteristics, in a quiet, temperature-controlled room at the same morning hour (8:00 a.m.), to avoid the reported circadian variation
of the endothelial function of premenopausal women (Walters et al., 2006). All subjects had refrained from exercise and from ingesting foods and any vasoactive substances (i.e. tobacco, coffee) for at least 12 h before the examination.

Gynecologic ultrasonography

Ultrasound examinations were done using an HDI 5000 (Philips, The Netherlands) connected to a 5–9 MHz transvaginal transducer. All the scans were done by a single skilled examiner, who was blinded to the subjects’ clinical data. Recurrence of endometrioma was defined as the detection of a persistent cyst with the typical sonographic features of endometrioma measuring 2 cm or more in diameter, within the ovarian parenchyma.

Statistical analysis

Continuous characteristics were reported as means ± standard deviations or as medians and interquartile range (IQR); categorical characteristics were reported as frequencies and percentages.

Within-group changes in FMD were analyzed by means of paired t-tests. Differences in follow-up FMD values between patients and controls were analyzed by means of ANCOVA with adjustment for baseline FMD values. Models were further adjusted for age.

VEGF values below the limit of detection were replaced by the square root of the detection limit.

All P-values have been two tailed and regarded as statistically significant at P < 0.05.

All analyses have been performed with Stata 12.1 (Statacorp LP, TX).

Ethical approval

A written informed consent was obtained from all the participants before entry into the study. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Catholic University of Rome (ethic committee reference number: A.1285/C.E./2010).

Results

We enrolled 22 (59%) patients with STE and 10 (32%) controls of the original study sample of 68 subjects. Enrolled patients with STE had all been subjected to laparoscopy and did not significantly differ from the original sample of patients with endometriosis in terms of average age and disease severity (data not shown).

The average age was 34.7 ± 6.0 years among patients with STE and 39.7 ± 4.3 years among controls (P = 0.02). According to published guidelines, all subjects (patients with STE and controls) were classified as having normal values of blood pressure (Mancia et al., 2007). Median (IQR) follow-up times were 23 (18, 27) months and 25 (23, 30) months for patients with STE and controls, respectively. Among patients with STE, eight (36%) exhibited ultrasonographic signs of endometrioma recurrence. None of the 22 patients with STE complained of pelvic pain or other symptoms suggestive for endometriosis.

Instrumental findings

Compared with baseline values, FMD increased significantly among patients with STE [average pre- to post-difference: 5.07%, 95% confidence interval (CI) 3.50, 6.63%; P < 0.001] but not among controls (average pre- to post-difference: 1.56%, 95% CI −0.55, 3.67%; P = 0.13). Follow-up FMD values were not significantly different between patients with STE and controls (average difference 1.50%, 95% CI −1.24, 4.23%; P = 0.27) (Fig. 1).

Among patients with STE, follow-up FMD values were not significantly different between those with and without ultrasonographic signs of endometrioma recurrence (P = 0.87).

As regards vascular morphological assessment, compared with baseline values, cccIMT did not change among patients with STE (average pre- to post-difference: 0.03 mm, 95% CI 0.00, 0.07 mm; P = 0.07), as well as among controls (average pre- to post-difference: 0.06 mm, 95% CI −0.01, 0.13 mm; P = 0.09). Follow-up cccIMT values were not significantly different between patients with STE and controls (average difference −0.01 mm, 95% CI −0.19, 0.17 mm, P = 0.91) (Fig. 2).

Statistical adjustment for age did not change the results.

Laboratory data

Follow-up values of serum creatinine, glucose, total cholesterol, HDL-C, LDL-C, triglycerides, ESR, CRP, Ca-125, as well as estimated renal function, were similar among patients with STE and controls, except for LDL-C (Table I). Follow-up of serological markers of endothelial activation (ICAM-1, VCAM-1, E-selectin, VEGF, vWF and ristocetin cofactor) revealed no significant differences between patients with STE and controls, as opposed to what we observed for the baseline comparison (Table II).

Statistical adjustment for age did not change the results.

Discussion

This study demonstrates, for the first time, that laparoscopic surgical treatment of endometriosis leads to improvement of endothelial function, with a consequent reduction of cardiovascular risk of women with endometriosis.
has also been recently reported that women affected by endometriosis absent, endothelial dysfunction can nevertheless occur (Pretta et al., 2010). Young women with endometriosis, even if structural alterations are lacking, show increased serum levels of VCA-M-1, ICAM-1, E-selectin, ristocetin cofactor and von Willebrand factor, suggestive of systemic inflammation and endothelial cell activation (Santoro et al., 2012).

It is well known that endothelial dysfunction, assessed as FMD impairment, and endothelial cell activation and inflammation represent an early step of the atherosclerotic process preceding structural changes of arterial wall and clinical symptoms of atherosclerosis (Sprague and Khalil, 2009). According to some studies, FMD has an independent prognostic value to predict future cardiovascular events that may be even higher than that associated with traditional risk factors (Shimbo et al., 2007; Yeboah et al., 2007; Rossi et al., 2008; Shechter et al., 2009). In particular, a recent study reported that FMD is more predictive of cardiovascular risk in younger subjects (Yeboah et al., 2009). Moreover, as FMD reflects active vascular homeostasis it may be modified by a number of interventions, which include drugs, dietary intake and exercise (Rudolph et al., 2007; Tinken et al., 2010). This dynamic nature of FMD supports the possibility of choosing a treat-to-target approach, where FMD can be intermittently monitored as a functional marker, with the goal of normalizing or enhancing vascular health. It has been found that an improvement in FMD identifies those patients with a more favorable prognosis, whereas a persistent impairment, despite therapeutic interventions, is a significant independent predictor of adverse events. Moreover, some studies have demonstrated that changes in FMD, rather than a single FMD measurement, can predict more accurately future cardiovascular events. A recent meta-analysis provides clear evidence for a prognostic relevance of FMD, showing a 13% (95% CI: 9% to 17%) decrease in the future risk of cardiovascular events for every 1% increase in FMD (Inaba et al., 2010). All these findings lead us to hypothesize that the FMD improvement we have found in patients with STE may have a prognostic relevance for variations of their cardiovascular risk.

We can speculate that the mechanisms by which FMD improves in our patients with STE are related to inflammation reduction after surgery,

In previous years, the association between endometriosis and atherosclerosis has been a matter under active investigation, focusing on the possible common characteristic features concerning systemic chronic low-grade inflammation, oxidative stress and pro-atherogenic lipid profile. By evaluating both structural (i.e. cIMT) and functional (i.e. FMD) parameters of subclinical atherosclerosis, it turns out that in young women with endometriosis, even if structural alterations are absent, endothelial dysfunction can nevertheless occur (Pretta et al., 2007; Kinugasa et al., 2011; Santoro et al., 2012). Moreover, our group has also been recently reported that women affected by endometriosis

**Table I** Follow-up clinical and serum parameters of patients with surgical treatment of endometriosis (STE) and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients with STE, n = 22</th>
<th>Controls, n = 10</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>91 ± 4</td>
<td>90 ± 4</td>
<td>0.42</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 ± 3</td>
<td>22 ± 2</td>
<td>0.37</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.69 ± 0.08</td>
<td>0.70 ± 0.13</td>
<td>0.79</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>110 ± 10</td>
<td>103 ± 15</td>
<td>0.12</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>87 ± 9</td>
<td>89 ± 10</td>
<td>0.29</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>189 ± 32</td>
<td>178 ± 33</td>
<td>0.20</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>63 ± 14</td>
<td>59 ± 12</td>
<td>0.31</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>98 ± 27</td>
<td>116 ± 24</td>
<td>0.02</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>79 ± 32</td>
<td>77 ± 21</td>
<td>0.76</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>14 ± 7</td>
<td>12 ± 7</td>
<td>0.53</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>1.3 ± 1.5</td>
<td>0.91 ± 0.93</td>
<td>0.50</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. Data are presented as means ± standard deviation.

**Table II** Baseline and follow-up serum values of endothelial activation markers of patients with surgical treatment of endometriosis (STE) and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients with STE</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ICAM-1 (ng/ml)</td>
<td>227 ± 33</td>
<td>174 ± 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline VCAM-1 (ng/ml)</td>
<td>445 ± 55</td>
<td>393 ± 55</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline E-selectin (ng/ml)</td>
<td>51 ± 15</td>
<td>44 ± 13</td>
<td>0.22</td>
</tr>
<tr>
<td>Baseline VEGF (pg/ml)</td>
<td>150 ± 96</td>
<td>132 ± 71</td>
<td>0.59</td>
</tr>
<tr>
<td>Baseline vWF (%)</td>
<td>111 ± 20</td>
<td>87 ± 10</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline ristocetin cofactor (%)</td>
<td>102 ± 21</td>
<td>84 ± 11</td>
<td>0.002</td>
</tr>
<tr>
<td>Follow-up ICAM-1 (ng/ml)</td>
<td>385 ± 72</td>
<td>439 ± 136</td>
<td>0.15</td>
</tr>
<tr>
<td>Follow-up VCAM-1 (ng/ml)</td>
<td>677 ± 135</td>
<td>641 ± 144</td>
<td>0.51</td>
</tr>
<tr>
<td>Follow-up E-selectin (ng/ml)</td>
<td>9.4 ± 2.9</td>
<td>9.3 ± 2.5</td>
<td>0.95</td>
</tr>
<tr>
<td>Follow-up VEGF (pg/ml)</td>
<td>62 ± 48</td>
<td>32 ± 16</td>
<td>0.07</td>
</tr>
<tr>
<td>Follow-up vWF (%)</td>
<td>87 ± 11</td>
<td>87 ± 7</td>
<td>0.89</td>
</tr>
<tr>
<td>Follow-up ristocetin cofactor (%)</td>
<td>83 ± 10</td>
<td>86 ± 9</td>
<td>0.52</td>
</tr>
</tbody>
</table>

ICAM-1, inter-cellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor antigen. Data are presented as means ± standard deviation.
since both inflammation and endothelial activation serological markers reverted to values similar to controls ones. In particular, we can hypothesize that surgical excision of endometriosis lesions entails removal of the main source of inflammation; with regard to the observation that, in endometriosis, inflammatory processes are also linked to pro-inflammatory cytokine production by ectopic endometrial cells themselves (Tsudo et al., 2000; Akoum et al., 2001). On account of this, it is easy to infer that the more debulking is complete, the more inflammation is reduced. Thus, more advanced stages of endometriosis, in terms of extent and invasiveness, could represent an important determinant of enhanced inflammatory status persistence. Although, no conclusive studies about this topic are reported in the literature, both our previous results (Santoro et al., 2012) and the findings of the present study (data not shown) indicated no linear association between endothelial dysfunction and severity of endometriosis, maybe also due to the small sample of the considered patients.

Interestingly, FMD improvement also has been detected in 36% of patients with STE with ultrasonographic signs of endometrioma recurrence, a percentage consistent with literature reports (Campo et al., 2014). It is noteworthy that none of these subjects exhibited any clinical symptoms; this is consistent with the absence of peritoneal and systemic inflammation, as evidenced by the similarity of the pattern of cytokines and serum inflammatory markers in these patients, controls and patients with STE without ultrasonographic signs of endometrioma recurrence. It would be of interest to evaluate in further longitudinal studies if recurrence of symptoms of endometriosis, suggestive of relapse of chronic peritoneal and systemic inflammation, will be associated with further FMD impairment.

An additional proof about vascular health of our patients with STE ensues from cIMT evaluations, which were also similar between patients with STE and controls after a 2-year follow-up period. These findings demonstrate that patients with endometriosis after surgical treatment of disease, according to FMD improvement, have not developed structural atherosclerotic changes of arterial wall.

A limitation of our study was that we could not compare the follow-up values of serum markers of endothelial activation with baseline ones within each group, due to the different laboratories used in this follow-up study compared with the one used for previously published findings (Santoro et al., 2012). On the other hand, we think that the more important finding was that, after surgical treatment, serum values of these markers in patients with STE became similar to controls ones.

In conclusion, our study shows for the first time that surgical treatment of endometriosis can lead to endothelial function improvement. These findings are very interesting just considering that, it is well known that, endothelial dysfunction possesses an independent negative prognostic value to predict future cardiovascular events that may exceed that associated with traditional risk factor assessment. For this reason, our results lead us to hypothesize that the endothelial function improvement we have found in patients with STE may have a prognostic relevance for variations of their cardiovascular risk. Finally, further longitudinal studies are desirable to better define the real risk to develop cardiovascular events in these women.

Authors’ roles
L.S. has planned and executed the study; L.S. and F.D’O. have written the manuscript. E.N., F.A. and F.F. have given their contribution in the execution of the study; S.C., V.C. and F.M. in study design; P.M.F. in the analysis; P.T. and A.F. in manuscript drafting; R.L. and A.S. in critical discussion.

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Conflict of interest
None declared.

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