The impact of endometrioma on ovarian reserve: what is the evidence?

Johnny S. Younis, MD
Endometriosis

• A chronic gynecological condition that affects an estimated 1 in 10 women during their reproductive years; approximately 176 million women worldwide

(Zondervan et al., Nature Reviews 2018).
Endometriotic cyst

- The most pathognomonic feature of endometriosis.
- The most commonly diagnosed form of endometriosis, most likely related to the improvement and accuracy of contemporary ultrasound technology (Van Holsbeke et al., 2010; Guerriero et al., 2016).
Endometriotic cyst

• Affects 17–44% of women with endometriosis (Busacca & Vignali, 2003).

• Bilateral cysts complicate in 19-28% of cases (Vercellini et al., 1998; Busacca et al., 2006).
Endometriotic cyst – open questions

• Does an E. per se affect ovarian reserve?
• What is the impact of E. surgery on ovarian reserve?
• Is ovarian E. surgery impact reversible?
• Does an E. cystectomy improve IVF results?
• Does an intact E. adversely affect pregnancy achievement?
• Does conservative management increase the risk of E. complications?
• Surgery or IVF should come first?
Does an endometrioma per se affect ovarian reserve?

The concept that endometrioma per se could affect ovarian reserve was implied when histological studies reported a significant reduction in the primordial follicle cohort in affected ovaries.

Maneschi et al., 1993; Schubert et al., 2005; Kitajima et al., 2011
Does an endometrioma per se affect ovarian reserve?

- Some clinical studies have indicated that E. by itself could decrease AMH level (Hwu et al., 2011; Uncu et al., 2013; Chen et al., 2014).

- The adverse effect was explained via direct mass effect, local inflammatory reactions and by increased tissue oxidative stress leading to fibrosis or burnout effect (Sanchez et al., 2014; Kitajima et al., 2014).
The impact of endometrioma and laparoscopic cystectomy on serum anti-Müllerian hormone levels

Yuh-Ming Hwu1,2,3*, Frank Shao-Ying Wu1, Sheng-Hsiang Li1, Fang-Ju Sun1, Ming-Huei Lin1 and Robert Kuo-Kuang Lee1,3*

Prospective assessment of the impact of endometriomas and their removal on ovarian reserve and determinants of the rate of decline in ovarian reserve†

Gurkan Uncu1, Isil Kasapoglu1, Kemal Ozerkan1, Ayse Seyhan2, Arzu Oral Yilmaztepe1, and Baris Ata1,*
Does an endometrioma per se affect ovarian reserve?

• Conversely:

• In a population of operated patients, ovarian E. per se is not associated with an increased risk of presentation with infertility, while previous surgery for endometriosis was identified as a risk factor for infertility (Santulli et al, HR 2016).

• Low serum AMH level is encountered only in women with bilateral E. but not in cases with unilateral E. (Nieweglowska et al, RBE 2015).

• E. recurrence has no detrimental effect on AMH level (Ferrero et al, FS 2015).

• AMH level is decreased only in cases with previous E. surgery (Streuli et al, HR 2012).
Antimüllerian hormone is reduced in the presence of ovarian endometriomas: a systematic review and meta-analysis

**FIGURE 1**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Endometriomas</th>
<th>No endometriomas</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Chen 2014</td>
<td>1.53</td>
<td>1.37</td>
<td>40</td>
<td>2.58</td>
</tr>
<tr>
<td>Chiang 2015</td>
<td>2.6</td>
<td>2</td>
<td>23</td>
<td>4.2</td>
</tr>
<tr>
<td>Erkan 2010</td>
<td>1.62</td>
<td>1.09</td>
<td>47</td>
<td>2.06</td>
</tr>
<tr>
<td>Ergun 2015</td>
<td>1.92</td>
<td>2.31</td>
<td>26</td>
<td>3.1</td>
</tr>
<tr>
<td>Jeon 2015</td>
<td>4.12</td>
<td>2.42</td>
<td>65</td>
<td>6.02</td>
</tr>
<tr>
<td>Kim J.Y. 2013</td>
<td>2.88</td>
<td>2.98</td>
<td>102</td>
<td>3.61</td>
</tr>
<tr>
<td>Kim Y.J. 2017</td>
<td>4.3</td>
<td>3.07</td>
<td>59</td>
<td>5.6</td>
</tr>
<tr>
<td>Kwon 2014</td>
<td>5.03</td>
<td>3.07</td>
<td>68</td>
<td>4.84</td>
</tr>
<tr>
<td>Lind 2015</td>
<td>2.25</td>
<td>2.14</td>
<td>18</td>
<td>3.31</td>
</tr>
<tr>
<td>Puciharoti 2013</td>
<td>0.97</td>
<td>0.59</td>
<td>65</td>
<td>1.72</td>
</tr>
<tr>
<td>Salihoglu 2016</td>
<td>3.1</td>
<td>1.9</td>
<td>34</td>
<td>5.7</td>
</tr>
<tr>
<td>Somigliana 2014</td>
<td>2.27</td>
<td>2.01</td>
<td>122</td>
<td>2.67</td>
</tr>
<tr>
<td>Streuli 2012</td>
<td>4</td>
<td>3</td>
<td>77</td>
<td>4.1</td>
</tr>
<tr>
<td>Tanprasethkul 2014</td>
<td>2.84</td>
<td>2.47</td>
<td>39</td>
<td>2.33</td>
</tr>
<tr>
<td>Uncu 2013</td>
<td>2.81</td>
<td>2.15</td>
<td>30</td>
<td>4.2</td>
</tr>
<tr>
<td>Widowik 2016</td>
<td>3.64</td>
<td>1.94</td>
<td>144</td>
<td>3.71</td>
</tr>
<tr>
<td>Yoo 2011</td>
<td>1.5</td>
<td>0.9</td>
<td>9</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Total (95% CI): 968

Heterogeneity: Tau² = 0.25, Chi² = 54.50, df = 16 (P < 0.00001) I² = 71%

Test for overall effect: Z = 5.20 (P < 0.0001)

*Weighted mean difference in AMH in patients with ovarian endometriomas compared to patients without ovarian endometriomas.*

Does an endometrioma per se affect ovarian reserve?

Antimüllerian hormone is reduced in the presence of ovarian endometriomas: a systematic review and meta-analysis

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- Included several retrospective reports (30% of studies)
- Did not address the timing of AMH evaluation following surgery
- High Heterogeneity
- Did not address the issue of AMH assay methodology evolvement over the years
Our group has recently concluded a systematic review and meta-analysis to examine the impact of unilateral versus bilateral ovarian E. on serum AMH level, before and after ovarian endometriotic cystectomy.

Only prospective studies that compared cases with unilateral and bilateral E. in the same setting were included.

The issue of AMH assay methodology evolution over the years was taken into account.
Results

• Collectively, the twelve eligible studies included 783 women, 489 and 294 women in the unilateral and bilateral groups, respectively.

• The weighted mean age (± weighted SD) of all women in both groups of the meta-analysis was 29.9 ± 5.5 years.
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication for surgery</th>
<th>Endometrioma size (mm)</th>
<th>Number of endometrioma monocystic/multi-cystic (%)</th>
<th>LPS/LPT</th>
<th>rASRM score</th>
<th>Technique of cyst removal</th>
<th>Haemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ercan et al. (2010)</td>
<td>Pelvic pain, Infertility, Exclusion of malignancy</td>
<td>Unilateral 59.0 ± 8.2</td>
<td>Bilateral 86.0 ± 11.1</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Stripping</td>
</tr>
<tr>
<td>Hirokawa et al. (2011)</td>
<td>ND</td>
<td>Total number 6/32 5/15</td>
<td>Unilateral 5/17 18/2</td>
<td>Bilateral 17/3 3/3</td>
<td>36.7 ± 23.5 63.7 ± 26.3</td>
<td>Stripping</td>
<td></td>
</tr>
<tr>
<td>Celik et al. (2012)</td>
<td>Pelvic pain</td>
<td>Unilateral At least 30 ≥50 (61.5%), &lt;50 (38.5%)</td>
<td>Bilateral 1/17 18/2 15/3</td>
<td>LPS/LPS</td>
<td>ND</td>
<td>ND</td>
<td>Stripping</td>
</tr>
<tr>
<td>Uncu et al. (2013)</td>
<td>Pelvic pain</td>
<td>Unilateral Median 42.5 (38.6–51.7)</td>
<td>Bilateral 12/18 ND</td>
<td>LPS/LPS</td>
<td>ND</td>
<td>ND</td>
<td>Stripping</td>
</tr>
<tr>
<td>Abozzi et al. (2014)</td>
<td>Pelvic pain</td>
<td>Unilateral 30 (91%) ≤30 (9%)</td>
<td>Bilateral 156/37 107/14 49/23</td>
<td>LPS/LPS</td>
<td>Stage III – IV 36% Stage IV – 62%</td>
<td>Cystectomy</td>
<td></td>
</tr>
<tr>
<td>Saito et al. (2014)</td>
<td>Pelvic pain</td>
<td>Unilateral Mean 54.6 (3–100)</td>
<td>Bilateral 51.5 ± 13.6 46.5 ± 21.3</td>
<td>LPS/LPS</td>
<td>ND</td>
<td>ND</td>
<td>Stripping</td>
</tr>
<tr>
<td>Tanprasertkul et al. (2014)</td>
<td>ND</td>
<td>Unilateral 61.9 ± 22.1 (maximal)</td>
<td>Bilateral 55.7 ± 29.0 (maximal)</td>
<td>LPS/LPS</td>
<td>ND</td>
<td>ND</td>
<td>Stripping</td>
</tr>
<tr>
<td>Shao et al. (2016)</td>
<td>Pelvic pain</td>
<td>Unilateral 61.9 ± 22.1 (maximal)</td>
<td>Bilateral 55.7 ± 29.0 (maximal)</td>
<td>LPS/LPS</td>
<td>ND</td>
<td>ND</td>
<td>Stripping</td>
</tr>
<tr>
<td>Kashi et al. (2017)</td>
<td>Pelvic pain</td>
<td>Unilateral 52.0 ± 6.0</td>
<td>Bilateral 52.0 ± 6.0</td>
<td>LPS/LPS</td>
<td>ND</td>
<td>ND</td>
<td>Stripping</td>
</tr>
<tr>
<td>Sweed et al. (2018)</td>
<td>Pelvic pain</td>
<td>Unilateral 52.0 ± 6.0</td>
<td>Bilateral 52.0 ± 6.0</td>
<td>LPS/LPS</td>
<td>ND</td>
<td>ND</td>
<td>Stripping</td>
</tr>
<tr>
<td>Kovačević et al. (2018)</td>
<td>Pelvic pain</td>
<td>Unilateral At least 40</td>
<td>Bilateral 52.0 ± 6.0</td>
<td>LPS/LPS</td>
<td>ND</td>
<td>ND</td>
<td>Stripping</td>
</tr>
</tbody>
</table>

ND: not disclosed. LPS: laparoscopy; LPT: laparotomy; rASRM: revised American Society of Reproductive Medicine.

*Stripping: the technique of endometrioma removal in which twoatraumatic grasping forceps are used to pull the cyst wall and the normal ovarian parenchyma in opposite directions, thus developing the cleavage plane. *Cystectomy: the technique is not defined in the article.
<table>
<thead>
<tr>
<th>Author</th>
<th>AMH assay</th>
<th>Timing of AMH testing and values unilateral group</th>
<th>Timing of AMH testing and values bilateral group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>1 wk-1 mo.</td>
</tr>
<tr>
<td>Ercan et al. (2010)</td>
<td>DSL</td>
<td>2.24 ± 1.95</td>
<td>1.62 ± 1.02</td>
</tr>
<tr>
<td>Hirokawa et al. (2011)</td>
<td>IOT</td>
<td>4.10 ± 2.30</td>
<td>2.90 ± 1.60</td>
</tr>
<tr>
<td>Celik et al. (2012)</td>
<td>DSL</td>
<td>1.58 ± 1.34</td>
<td>1.48 ± 1.25</td>
</tr>
<tr>
<td>Uncu et al. (2013)</td>
<td>DSL</td>
<td>2.04 ± 1.38</td>
<td>2.03 ± 1.18</td>
</tr>
<tr>
<td>Alborzi et al. (2014)</td>
<td>DSL</td>
<td>4.19 ± 3.71</td>
<td>1.99 ± 2.08</td>
</tr>
<tr>
<td>Saito et al. (2014)</td>
<td>IOT</td>
<td>3.90 ± 2.50</td>
<td>1.70 ± 1.70</td>
</tr>
<tr>
<td>Tanprasertkul et al. (2014)</td>
<td>DSL</td>
<td>2.94 ± 2.47</td>
<td>1.75 ± 1.57</td>
</tr>
<tr>
<td>Shao et al. (2016)</td>
<td>DSL</td>
<td>5.02 ± 3.05</td>
<td>4.43 ± 2.13</td>
</tr>
<tr>
<td>Kashi et al. (2017)</td>
<td>DSL</td>
<td>3.01 ± 2.58</td>
<td>2.10 ± 1.28</td>
</tr>
<tr>
<td>Sweed et al. (2018)</td>
<td>Glory Science</td>
<td>4.23 ± 0.97</td>
<td>1.97 ± 0.93</td>
</tr>
<tr>
<td>Kovačević et al. (2018)</td>
<td>DSL</td>
<td>3.31 ± 1.74</td>
<td>1.43 ± 1.01</td>
</tr>
</tbody>
</table>

DSL, Diagnostic Systems Laboratories; IOT, Immunotech.
The weighted mean difference (WMD) before surgery between the two groups did not significantly differ with an estimate of 0.31 ng/mL (95% CI: -0.15 to 0.77, P = 0.19). Heterogeneity between the studies was high (I^2 = 57%, P = 0.01).

![Forest plot for pre-operative AMH levels in women with unilateral versus bilateral endometrioma.](image)

**Figure 2** Forest plot for pre-operative AMH levels in women with unilateral versus bilateral endometrioma.
The WMD at the early post-operative period was significantly lower in the bilateral group with an estimate of 0.78 ng/mL (95% CI: 0.41 to 1.15, \( P = 0.001 \)). Heterogeneity between the studies was high \( (I^2 = 56\%, \ P = 0.04) \).
The WMD at the **intermediate post-operative period** was significantly lower in the bilateral group with an **estimate of 0.59 ng/mL** (95% CI: 0.14 to 1.04, \( P = 0.01 \)). Heterogeneity between the studies was high (\( I^2 = 65\% , P = 0.009 \)).
The WMD at the **late post-operative period** was significantly lower in the bilateral group with an estimate of **1.08 ng/mL** (95% CI: 0.63 to 1.52, \(P = 0.001\)). Heterogeneity between the studies was low (\(I^2 = 37\%\), \(P = 0.21\)).
Table VIII  Separate unilateral and bilateral meta-analysis results of eligible studies showing WMD of AMH level at different periods following surgery as compared to baseline levels and their rate of decrease.

<table>
<thead>
<tr>
<th>AMH timing</th>
<th>Unilateral cystectomy</th>
<th>Bilateral cystectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WMD</td>
<td>N</td>
</tr>
<tr>
<td>1w – 1m</td>
<td>1.42</td>
<td>296</td>
</tr>
<tr>
<td>6w – 6m</td>
<td>0.93</td>
<td>333</td>
</tr>
<tr>
<td>9m – 12m</td>
<td>1.65</td>
<td>194</td>
</tr>
</tbody>
</table>
Endometriotic cyst – open questions

• Does an E. per se affect ovarian reserve?
• What is the impact of E. surgery on ovarian reserve?
• Is ovarian E. surgery damage reversible?
  • Does an E. cystectomy improve IVF results?
  • Does an intact E. adversely affect pregnancy achievement?
  • Does conservative management increase the risk of E. complications?
  • Surgery or IVF should come first?
What is the Current Evidence?

• Although some studies suggest that E. per se is associated with a reduction in the ovarian reserve, the baseline AMH results of our meta-analysis challenge this notion.

• Endometriotic ovarian cystectomy, in women of reproductive age, results in significant reduction of circulating AMH in both the short and long term.
What is the Current Evidence?

• The effect is more profound following bilateral as compared to unilateral E. excision, in the early, intermediate and late terms following surgery.

• Maximal postoperative AMH drop (39.5% and 57.0%), far exceeds any natural decline in AMH. For women in their third decade of life, the natural decline in AMH is approximately 5% per year (Nelson et al., 2014).
What is the Current Evidence?

- The intermediate post-operative period may support other surgery-related reversible mechanisms (ovarian vasculature and inflammation-mediated injuries), however, late post-operative AMH level at 9-12 months suggests that this effect does not persist.
Endometriotic cyst – open questions

• Does an E. per se affect ovarian reserve?
• What is the impact of E. surgery on ovarian reserve?
• Is ovarian E. surgery damage reversible?

• Does an E. cystectomy improve IVF results?
• Does an intact E. adversely affect pregnancy achievement?
• Does conservative management increase the risk of E. complications?
• Surgery or IVF should come first?
Does an E. cystectomy improve IVF results?
Does an E. cystectomy improve IVF results?

- **E.** cystectomy does not improve IVF-ET outcome; clinical pregnancy rate and live birth were shown to be comparable to women with normal ovaries (Hamdan et al., HRU 2015; Nickko-Amiry et al., AGO 2017) or to women with E. that did not undergo surgery (Hamdan et al., 2015 HRU; Tao et al., Plos one 2018).
Does an E. cystectomy Improve IVF results?

- IVF outcome and live birth rate were shown to be significantly more impaired in women with low ovarian reserve caused by a previous E. cystectomy as compared to women with idiopathic low ovarian reserve.
Does an intact E. adversely affect pregnancy achievement?

• E., irrespective of its volume, has been shown not to influence the rate of spontaneous ovulation in the affected ovary.

• It does not preclude a good spontaneous pregnancy rate if the couple has no other risk factors for infertility.
Does conservative management increase the risk of 
E. complications during IVF?

1. Ovarian responsiveness
2. Oocyte competence
3. Technical difficulties during OPU
4. Infection of endometrioma
5. Follicular fluid contamination
6. Progression of endometriosis
7. Pregnancy complications
8. Endometrioma and cancer: Missing occult malignancy at the time of IVF

Cancer development following IVF
Does conservative management increase the risk of E. complications during IVF?

- The risks of conservative management of existing E. has been shown to be modest.

- The hazard of surgery-related ovarian reserve damage surpasses the risks of conservative management.
Endometriosis and Ovarian Cancer

• Life time ovarian cancer risk in the general population is estimated to be 1.31% as compared to 1.80% in women with endometriosis (National Cancer Institute; Kim et al., 2014; Wang et al., 2016).

• Relative risk of 1.42

• Endometriosis-associated cancers tend to be detected at an earlier stage and have a better prognosis than other types of ovarian cancer.

• The possibility of developing ovarian cancer is troublesome but seems to be a rare event and may be prevented by postponing surgery until the fulfillment of reproductive wishes (Somigliana et al., 2015 HRU; Kvakskoff et al., Lancet 2017).
What is the evidence?
Final Conclusions and Wider Implications

- The adverse effect of Endometrioma per se on ovarian reserve is challenged.

- Endometriotic cystectomy is implicated in considerable decrease in ovarian reserve (more profound in bilateral cases) and may have no obvious reproductive advantage.
In infertile women with Endometrioma, therapeutic management ought to be based on individual characteristics such as age, basal ovarian reserve, associated clinical manifestations and informed consent.

Conservative treatment should be counselled as the first line of treatment, until patients’ reproductive aspirations are realized.

Women should be encouraged to prefer early parenthood in these cases. Surgery might be postponed until family planning is complete.
Collaborators:

- Nora Shapso
- Richard Fleming
- Izhar Ben-shlomo
- Ido Izhaki