

## Research Report

**The Effect of Analog GnRH before Laparoscopic Cystectomy to Ovarian Reserve which was Measured with anti Müllerian Hormone at Bilateral Endometriosis Cyst***Dampak Pemberian GnRH Analog sebelum Laparoskopi Kistektomi pada Kista Endometriosis Bilateral terhadap Cadangan Ovarium yang Diukur dengan Hormon Anti-Müller (Anti Müllerian Hormone)*

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Jakarta***Abstract**

**Objective:** To know the effect of preoperative GnRH-a treatment to preserve the ovary after laparoscopic excision of endometriomas by measuring antimüllerian hormonal before and after operation and analyze the correlation with age and size of the endometrioma.

**Methods:** Double blind randomized control trial, which is done to patients with bilateral endometriomas in Raden Saleh Clinic. Subject divided into groups GnRH-a and placebo. Patient was undergoing laparoscopic excision after four weeks of medication (GnRH-a or placebo). AMH Serum levels was measured before preoperative medication and four weeks after operation.

**Result:** There were eight bilateral endometriomas (25% patients requirement), 4 patient GnRH-a and four patients placebo, all with primary infertility. The average changes of AMH serum level before and after laparoscopy ovarian cystectomy in GnRH-a groups was 0.011 ng/ml and placebo groups was 1.502. The average changes of AMH serum level, in age stratification on both groups show the same result, GnRH-a 0.035 and placebo 1.681. In diameter cyst stratification, GnRH-a 0.011 and placebo 1.090.

**Conclusions:** With the restrictiveness of the patient, this study find GnRH-a therapy initiated before laparoscopic cystectomy has better outcomes in ovarian reserve compared with placebo, and also the same result in age and size of cyst stratification analyze.

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**Keywords:** laparoscopic cystectomy, GnRH-a, ovarian reserve

**Abstrak**

**Tujuan:** Mengetahui peran GnRH-a sebelum operasi untuk mempertahankan cadangan ovarium, pada tindakan pembedahan kista endometriosis dengan mengukur perubahan kadar AMH serum (sebagai parameter cadangan ovarium) sebelum dan sesudah kistektomi, dan mengetahui korelasi antara usia dan ukuran kista dengan rerata perubahan kadar AMH serum.

**Metode:** Penelitian ini bersifat double blind randomized control trial terhadap pasien kista endometriosis bilateral yang dilakukan laparoskopi kistektomi di pusat endoskopi Klinik Raden Saleh. Pasien dipisahkan secara acak dalam kelompok GnRH-a dan placebo. Setiap pasien diambil darah untuk pemeriksaan AMH serum sebelum mendapat suntikan (GnRH-a atau placebo). Secara acak, pasien disuntikkan obat, sesuai randomisasinya. Empat minggu setelahnya dilakukan laparoskopi kistektomi, dan empat minggu setelah kistektomi dilakukan pengukuran kadar AMH serum setelah operasi.

**Hasil:** Terdapat 8 pasien endometrioma bilateral yang seluruhnya dengan infertilitas primer. Didapatkan hasil rerata perubahan kadar AMH serum pada kelompok GnRH-a 0,011 ng/ml dan kelompok placebo 1,502. Berdasar stratifikasi usia < 37 tahun, rerata perubahan kadar AMH serum pada kelompok GnRH-a 0,035 dan kelompok placebo 1,681. Berdasar stratifikasi ukuran kista > 3cm, rerata perubahan kadar AMH serum pada kelompok GnRH-a 0,011 dan kelompok placebo 1,090.

**Kesimpulan:** Dengan keterbatasan sampel yang ada, didapatkan hasil kelompok pasien yang mendapat GnRH-a sebelum kistektomi, mempunyai cadangan ovarium lebih baik (perubahan kadar AMH serum lebih kecil) dari kelompok pasien yang mendapat placebo. Analisa korelasi berdasar stratifikasi usia dan ukuran kista juga mendapatkan perubahan kadar AMH serum lebih kecil pada kelompok GnRH-a dibandingkan placebo.

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**Kata kunci:** laparokopi kistektomi, GnRH-a, cadangan

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**INTRODUCTION**

The study by Busacca observed spontaneous ovulation occurs less frequent after laparoscopic cystectomy.<sup>1</sup> Giving GnRH-a preoperative medical treatment, find better overall outcome.<sup>2,3</sup> Incidence endometriosis in reproductive age, is about 25%. It is hard to measure the accurate incidence, cause the symptom can be masking by other pelvic disorders.<sup>4</sup>

Laparoscopy is considered to be the gold standard for treatment of benign ovarian cysts. However the

side effect laparoscopic procedure, especially stripping technique has been questioned, because it is associated with removal of ovarian tissue together with the wall of ovarian cysts. Especially endometriomas, it cause loss of many follicles.<sup>5</sup>

Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas, are reported in 3 cases from 126 patients (2.4%).<sup>5</sup>

Decreasing ovarian reservoir (measured by AMH) can be related to the surgical procedure, by accidentally removal of normal ovarian cortex, or damaging

electrosurgical coagulation for hemostasis. A consequence of damage to ovarian vasculature damage is the loss of healthy ovarian follicles.<sup>6</sup>

Hughesdon demonstrated that 93% of endometriosis cysts were formed by invagination of the cortex after the accumulation of menstrual debris from endometriotic implants. In the late stages of cyst formation, the cortex was progressively replaced by pigmented fibroreactive tissue and forming a dark fibrotic cyst. In the surface of the cyst focal endometrial epithelial lining, was located adjacent to the ovarian cortex.<sup>7</sup>

The more easy to remove the ovarian capsules, showed less follicles in focal endometrial epithelial lining, histologically.<sup>8</sup>

GnRH analogues (GnRH-a) appear to be effective for reducing the growth of endometrial cells, not only due to their classical pituitary endocrine effects, but also via a direct effect on the endometrial cells themselves and inhibit their growth and proliferation by regulation of apoptotic and angiogenic mechanisms.<sup>9</sup>

Angiogenesis is an important process in the development of endometrial tissue, and it is regulated by vascular endothelial growth factors (VEGFs) and angiopoetins. GnRH-a reduces the production of VEGF-A and IL-1beta in eutopic endometrial cell. It is suggesting it can inhibit the development of endometriosis.<sup>9</sup>

GnRH-a induce change in Plasminogen Activation, Matrix Metallo Protease system. It may alter fibrinolysis and extracellular matrix remodeling and induced decrease in adhesion formation.<sup>10</sup>

The value of preoperative medical treatment in the management of endometriosis has been controversial. There are no data to justify that prior hormonal treatment can improve the success of surgery (the issues are resolution and persistence cases).<sup>11</sup> Preoperative medical treatment with GnRH-a, can decrease the volume of the cyst, which is requiring a surgical treatment, elimination of functional ovarian cysts and the result was greater convenience of surgical procedure.<sup>2,3</sup> It was found the relative ease of removal of the capsules showed histologically focal endometrial epithelial lining and no follicles.<sup>8</sup>

It is questioned if GnRH-a, prior to laparoscopic excision bilateral endometrioma, could reserve ovarian cortex and save follicles loss? This is very important with the consideration that of most all laparoscopic endometrioma patient comes with infertility problems.

This study wanted to know the effect of preoperative medical treatment with GnRH-a to preserve the ovary after laparoscopic excision of endometriomas by measuring antimüllerian hormone before and after operation and analyzing its correlation with patient age and size of the endometrioma.

## METHOD

Double blind randomized control trial, which is done to well informed patients with bilateral endometriomas undergoing laparoscopic excision of bilateral endometriomas in Raden Saleh Clinic. Exclusion criterias are menopause, oophorectomy, suspected malignancy by histopathology, hormonal treatment before, loss to follow up and not informed patient. After col-

lecting medical anamnesis and physical examination, and measure size of by Ultrasound E8 Volusson. Patients were divided into groups of GnRH-a and placebo. Four weeks before operation, we gave GnRH-a (3.75 leuprolide acetate) or placebo (vitamin B) intramuscular to every endometrioma patient undergoing laparoscopic excision. In every patient AMH serum level was measured before preoperative medication and 4 weeks after operation. AMH serum was collected and saved in Prodia Laboratory, and lab processing was performed in Makmal Immunoendocrinology Laboratory with AMH Gen II quantitative assay calibration and control (Beckman Coulter). The result of AMH concentration is in ng/ml. All of data is analyzed by SPSS 14 programs.

## RESULTS AND DISCUSSION

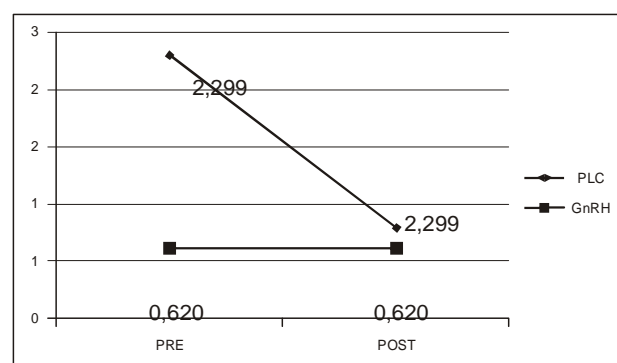
Subject 8 with bilateral endometrioma and infertility. (Table 1.)

**Table 1.** Subject characteristic.

Groups	Subject	Age (year)	Size of cyst (cm)	AMH pre op	AMH post op
GnRH	1	32	4	1.239	1.275
	2	39	7.5	0.248	0.16
	3	30	7	0.746	0.78
	4	43	4	0.248	0.223
Placebo	1	35	5	0.869	1.239
	2	34	4.5	0.955	0.16
	3	30	2.5	4.266	1.529
	4	27	4	3.106	0.261

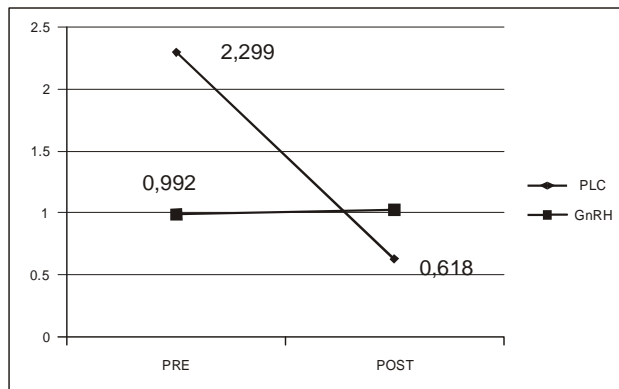
Age of patient range from 27 to 43 years, size of cyst from 2.5 to 7.5 cm. AMH pre operation from 0.258 to 4.266 ng/ml and post op 0.160 to 1.529 ng/ml.

Mean of delta AMH after and before laparoscopic cystectomy in GnRH-a groups was 0.011 ng/ml, which were smaller than placebo groups 1.502 ng/ml. The same result both groups with age and size of the cyst stratification.



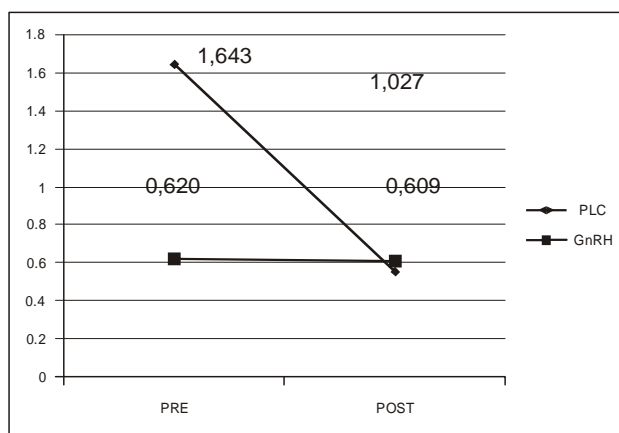
**Figure 1.** Mean of delta AMH after and before laparoscopic cystectomy.

This study found that the mean of delta AMH after and before laparoscopic cystectomy in GnRH groups was smaller than in placebo groups.



**Figure 2.** Mean of delta AMH after and before laparoscopic cystectomy (age stratification < 37 years).

For age stratification, this study found also that in GnRH groups mean of delta AMH was smaller than in placebo groups.



**Figure 3.** Mean of delta AMH after and before laparoscopic cystectomy (cyst size stratification  $\varnothing < 3$  cm).

For cyst size stratification, this study found that in GnRH groups mean of delta AMH was smaller than in placebo groups.

The limitation of this study were, small sample size, characterize of the patient not good stratified yet (because of small sample size). There were two patient in placebo groups with significant high level in AMH 4.266 and 3.106 ng/ml, but not the same level in GnRH-a groups.

Lee and Anders found the higher basal AMH serum level, the more decreasing of AMH level. (both study in ovarian stimulation and effect of chemotherapy in ovary). The explanation of this phenomena is a cohort theory of cyclic recruitment of follicle, the better ovarian reserve, much more follicle retrieved.<sup>12,13</sup>

In this study, it was very difficult to differentiated, the small mean of delta AMH in GnRH-a group, either caused of GnRH-a or caused of poor initial AMH serum level.

For the next study, better to separate from beginning those two groups GnRH-a and placebo, based on initial AMH serum level. Cut of point level 1.4 ng/ml based on good predicted ovarian response. (good ovarian reserve).

The ideal timing to measure AMH serum level is preoperative, one week, one month and three months postoperative. The change of AMH level is statistically significant from preoperative to one month period postoperative, but not between one and three months, after the data suggest that the maximum time of ovarian tissue recovery is three months.<sup>6</sup>

In this study, the postoperative AMH serum measurement at one month, was possibly not accurate, because the recovery of ovarian tissue was still not achieved.

The cause of a decrease of AMH serum level has been considered to be an accidentally removal of normal ovarian cortex, damaged by electrosurgical coagulation for hemostasis, or a consequence of inflammation-mediated injury resulting in the loss of healthy ovarian follicles.<sup>6</sup>

Sixty five percent AMH serum level after surgery was recovered at an early 3 months. Several mechanisms about recovery of AMH level have been postulated. First, reperfusion of ovarian tissue. Second the function of granulosa cells can be hyperactivated compensatory to ovarian damage in remaining follicles. Third, follicles maybe rescued from atretic follicles. The increased of AMH serum level reflects either reperfusion of ovarian tissue and activation of follicles or regeneration of ovarian follicle pool.<sup>6</sup>

Objectives evaluation should be done by performing hystopatological evaluation of endometriotic cyst wall originated from laparoscopic excision, to see either GnRH-a or placebo, resulting small amount of follicles loss.

## CONCLUSION

Mean of delta AMH after and before laparoscopic cystectomy in GnRH-a groups was smaller than placebo groups. The higher basal AMH serum level is the higher the decreasing AMH level.

## SUGGESTION

Further studies are required with adequated amount of patient. Better to separate from the beginning those two groups GnRH-a and placebo, based on initial serum of AMH level, to differentiated, the small mean of delta AMH in GnRH-a group, either caused by GnRH-a or caused by poor initial AMH serum level. Post operative AMH serum measurement was done after three months, better compered with hystopatological evaluation of follicle loss.

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