

Research Article

Post-laparoscopic GnRH-agonist Therapy does not Improve Spontaneous Conception Rates of Women with Endometriosis

Terapi GnRH-agonis Post-laparoskopi tidak Meningkatkan Angka Kehamilan Spontan pada Perempuan dengan Endometriosis

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Abstract

Objective: To investigate the reproductive benefits of combining laparoscopic surgery with GnRH-agonist hormonal therapy in treating women with endometriosis.

Methods: This is a non-randomized prospective analytic study of patients with endometriosis conducted in a private hospital in Bandung during the period of January 2014 to December 2015, whom were later followed up after 12-24 months for assessment of post-surgical reproductive performance. A total of 121 patients were enrolled, 60 of which received post-surgical GnRH-agonist hormonal therapy.

Results: We discovered that 56 women (46.3%) eventually achieved spontaneous conception after surgery but upon further analysis, it was discovered that GnRH-agonist played no significantly meaningful role in improving the spontaneous pregnancy rates of these patients (OR 1.539; 95% CI 0.750-3.159; p-value 0.239). Furthermore, even though there was a wide range as to when they achieved conception, those untreated with hormonal therapy tended to conceive far more quickly than those who were (5.91 ± 6.28; 8.56 ± 4.24; p-value: 0.011).

Conclusion: Post-laparoscopic GnRH-agonist administration to women with endometriosis does not significantly improve their chances of spontaneous conception. In fact, such administration seems to delay it.

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Keywords: endometriosis, GnRH-agonist, laparoscopy

Abstrak

Tujuan: Untuk menyelidiki efek reproduktif dari terapi kombinasi operasi laparoskopi dan terapi hormonal GnRH-agonis dalam manajemen perempuan dengan endometriosis.

Metode: Penelitian ini adalah studi analitik prospektif tidak teracak pada pasien-pasien dari sebuah rumah sakit swasta di Bandung dari tahun 2014-2015 yang menderita endometriosis dan kemudian diikuti hingga 12-24 bulan untuk mengevaluasi performa reproduktif post-operatif mereka. Terdapat 121 pasien pada penelitian ini, 60 di antaranya mendapatkan terapi hormonal GnRH-agonis post-operatif.

Hasil: Penelitian ini menemukan bahwa 56 pasien (46,3%) berhasil hamil setelah dilakukan laparoskopi tetapi disimpulkan bahwa GnRH-agonis tidak memainkan peranan signifikan dalam meningkatkan angka kehamilan dari pasien-pasien ini (OR 1,539; 95% CI 0,750-3,159; p 0,239). Selain itu, meskipun terdapat variasi cukup luas terkait kapan pasien-pasien ini berhasil hamil, mereka yang tidak mendapatkan GnRH-agonis cenderung berhasil hamil lebih cepat dibandingkan mereka yang dapat (5,91 ± 6,28; 8,56 ± 4,24; p 0,011).

Kesimpulan: Pemberian GnRH-agonis post-laparoskopi pada pasien-pasien dengan endometriosis tidak meningkatkan kemungkinan mereka hamil dan sebaliknya, cenderung menunda kehamilan.

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Kata kunci: endometriosis, GnRH-agonis, laparoskopi

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INTRODUCTION

Endometriosis is a gynecologic disease that stems from the presence of uterine endometrial tissue (both glands and stroma) outside the uterine cavity.¹ These ectopic tissues are often planted on the pelvic viscera, e.g. ovaries, and the peritoneum. It is a disease of primarily women of reproductive age. While studies vary on its prevalence in the general population, it is estimated that endome-

triosis adversely affects 1 in every 10 women.² Endometriosis acquaints itself with numerous risk factors, e.g. infertility, early age at menarche, shorter menstrual cycle length, history of endometriosis in 1st degree relative and diet high in fat and alcohol.¹ Nevertheless, there are numerous protective factors against endometriosis, e.g. use of oral contraceptive drugs, increased BMI, exercise and diet high in vegetables and fruits.^{1,2}

Despite being a common gynecologic disease, the exact cause of endometriosis remains elusive and the available theories seem to offer only part of the explanation. The most widely supported theory is the transplantation theory proposed by Sampson which assumed that retrograde menstruation into the peritoneal cavity allowed the implantation of sloughed endometrial tissue on the pelvic viscera and/or peritoneum.^{1,2} This, together with heightened inflammatory state, reduced apoptosis and evasion from NK cells predation, have allowed the endometrial tissue to not just implant but also persist and flourish in their foreign territories.^{2,3} There are other theories, including the coelomic metaplasia and the induction theories, which attempt to explain the histogenesis of endometriosis and it seems more likely that an eclectic mix of the various theories available today underlies the true pathomechanism of endometriosis.¹

To date, endometriosis has many classification systems, but the original one, proposed for the ASRM remains the benchmark today. This classification divides endometriosis into 4 groups, ranging from stage I (minimal endometriosis) to stage IV (severe endometriosis). There are other systems, such as the Endometriosis Fertility Index (EFI) primarily used to predict pregnancy rates of patients based on their endometriosis severity, and the Enzian classification for classifying deep infiltrative endometriosis.⁴

Endometriosis adversely affects the quality of life of many females as it primarily produces pain. Various types of pain have been reported, including dysmenorrhea, dyspareunia, dyschesia and non-menstrual pelvic pain.⁵ Even more unfortunate has been the revelation that the painful symptoms are only part of the misfortune befalling these patients as endometriosis is also linked to infertility.^{6,7}

There are several causes of infertility, conveniently divided into 3 groups: ovulatory dysfunction (20-40%), tubal and peritoneal pathology (30-40%) and male factors (30-40%).⁸ Endometriosis causes ovulatory dysfunction, induces a heightened inflammatory state in the peritoneum and fertilization-hampering changes in peritoneal fluid while also disrupting the hormonal interaction in the uterus.⁷

Fortunately, the ESHRE has published a guideline for the management of endometriosis, in the hope of providing relief and also restoring the

reproductive function of the patients.^{9,10} The ESHRE recommends laparoscopic surgery as a means to remove the endometriosis lesions and also reduce endometriosis-associated pain.⁹ Another justification for surgery comes from the observation that endometriosis appears to progress in 30-60% of patients within a year of diagnosis and it is not possible to predict which patients' endometriosis will worsen. Fortunately, surgery is deemed to live up to its hype as spontaneous conception is to be expected within the 1st year post-surgery.¹¹

There is also a widespread practice today of adding adjuvant medical therapy in the form of GnRH-agonist injections after laparoscopic surgery for these patients. This hormonal therapy should reduce and/or postpone endometriosis recurrence by inactivating, but not eliminating, the remaining microscopic endometriosis lesions.^{12,13} Current evidence states that this regimen is more effective than surgery alone in reducing the symptoms and recurrence of endometriosis but its effects on increasing pregnancy rate are still up to debate.^{14,15}

Therefore, this study aims to evaluate the reproductive performance of patients with endometriosis who underwent operative laparoscopy 12-24 months post-surgery and also the association, if any, between post-surgical GnRH agonist administration and pregnancy rates. To our knowledge, this is the first study in Indonesia that attempts this approach on endometriosis patients.

METHOD

This is a non-randomized prospective analytic study involving a cohort of patients in a private hospital in Bandung who was operated by a single physician between January 2014 and December 2015 for various complaints, e.g. dysmenorrhea and inability to conceive and subsequently discovered to harbor endometriosis as one of the post-surgical diagnoses. Surgical treatment was performed in a standardized manner following hospital protocols. Laparoscopy was performed under general anesthesia using a 4-port approach. When an ovarian endometrioma(s) was discovered, ovarian cystectomy began with adhesiolysis. Once the ovary was mobilized, the ovarian cortex was grasped with forceps and incision of the cortex was made. If the cyst was opened and

there was a spillage, peritoneal irrigation as performed. Upon cyst decompression, its wall was exposed, inspected and finally stripped from the normal ovarian tissue. Should there be any bleeding from the cortex after stripping, such bleeding zones were coagulated using the bipolar forces. The endometrioma was then removed through a 10-mm trocar. When a peritoneal endometriosis was encountered, endometriosis removal was done through ablation. Adhesiolysis was first performed to obtain proper visualization of the lesions. The lesions were then destroyed using either bipolar coagulation or laser vaporization. Vaporization was continued until no pigment remained to be seen.¹⁶ Documentation of endometriosis location and rASRM stage was undertaken. All the surgeries were undertaken by a single physician (T.D) to minimize operator bias. Routine follow-up consisted of an obligatory post-operative visit at 1-2 weeks where a physical examination was done and patients were questioned regarding their bowel and bladder functions. Planning on whether to treat the patient with an adjuvant hormonal therapy (i.e., GnRH-agonist injections) was made during this consultation and should a patient be recommended to undergo such therapy, a repeat consultation was arranged at 2-4 weeks during which she would receive her first GnRH-agonist injection. Patients would normally receive either 3 or 4 monthly injections, and the decision to assign which regimen to which patients was subject to the physician's (T.D) clinical assessment.

Women identified as having endometriosis of any rASRM stage were then contacted by telephone from November to December 2016 (on at least 2 separate days for those who didn't respond to our first call) and were requested, by phone, for their consent to participate in the study and divulge their post-surgical reproductive performance. The following items were collected during the interviews: any pregnancy and/or abortion post-

surgery; any additional GnRH-agonist injection(s) post-surgery for those whose records were incomplete and/or who had to receive their monthly injections elsewhere due to various reasons; and details of the pregnancy and its outcome for those who did conceive which included the last menstrual date, mechanism of pregnancy (spontaneous conception, intrauterine insemination (IUI), IVF/ICSI)), gender of the child, weight and length of the child at delivery, date of delivery, means of delivery and site of delivery.

Initially, 166 eligible patients were identified from our 2014-2015 databases to participate in this study. However, 45 patients had to be opted out due to one or more of the following reasons: the patient did not respond to telephone calls on 2 separate days; the patient's contact numbers were inactive, out of reach or incorrect; the patient already had children prior to surgery and did not desire to conceive again; the patient was already > 42 years old at the time of surgery; the patient was widowed prior to surgery and did not remarry; the patient was unmarried until the time of follow-up and the patient's successful conception was by assisted reproduction technology (ART). In the end, 121 patients were included in the final cohort for analysis.

Data were then recorded in a purpose-built database on Microsoft Excel with subsequent statistical analysis undertaken with Statistical Package for Social Sciences (SPSS), version 21. An 80% power was assigned at the beginning of the study, which determined the sample size for each group. Shapiro-Wilk's test was then used to determine the data's normality. Chi-squared and Mann-Whitney U tests were later used to analyze the data. Finally, probability values of less than 5% were considered statistically significant.

RESULTS

Table 1. Demographics of Study Population

Variables	GnRH-agonist (+)	GnRH-agonist (-)	p-value (Sig.)
Age during surgery (mean SD)	29.88 ± 3.87	31.62 ± 3.93	0.014
Pre-surgical reproductive history			
Parturition			
0	52	56	
≥ 1	8	5	

Variables	GnRH-agonist (+)	GnRH-agonist (-)	p-value (Sig.)
Abortion			
0	52	56	
≥ 1	8	5	
GnRH-ag inj.			
≤ 3	27	N/A	
≥ 4	34	N/A	
Post-surgical reproductive history			
ongoing pregnancy	12	5	
parturition	15	16	
abortion	4	4	
Timing of pregnancy post-surgery* (mean ± SD)	8.56 ± 4.24	5.91 ± 6.28	0.011
range of timing	(3-21)	(0-26)	
Pregnancy outcome (parturition)	15	16	
Gender			
Male	7	13	
Female	8	3	
Average weight (g)	3008.67 ± 326.49	2980 ± 397.06	0.770
Average length (cm)	49.13 ± 1.25	48.38 ± 1.79	0.232
Status at delivery			
preterm	4	5	
term	9	10	
postterm	2	1	
Weight status at delivery			
SGA	1	2	
AGA	14	14	
LGA	0	0	

*some patients' details who had abortion were missing, so calculation of the average timing could not include all 56 patients

Table 2. Spontaneous Conception Rates among Study Population

	Pregnant (+)	Pregnant (-)	Total
GnRH-agonist (+)	31	29	60
GnRH-agonist (-)	25	36	61
Total	56	65	121

Odd-ratio: 1.539 (95% CI 0.750 - 3.159), p-value: 0.239

From January 2014 to December 2015, 166 patients underwent fertility-preserving operative laparoscopy by a single surgeon for varying states of endometriosis (stages I-IV) at a private hospital in Bandung, Indonesia. Follow-up was performed over the course of 2 months, from November

to December 2016. Data were retrieved from 121/166 patients (72.9%), whom were then divided into two groups: those who received GnRH-agonist injections after surgery and those who didn't. On average, those who received GnRH-agonist injections were younger at the time of

surgery than those who didn't (p-value 0.014). Then, for both groups, most women had never conceived prior to surgery (108/121 patients, 89.3%). Among those who received GnRH-agonist injections, the number of women who received 3 monthly injections or less (27 patients) was slightly lower than those who received 4 monthly injections or more.

After surgery, the reproductive performances of the two groups were compared. Firstly, of those whom are currently pregnant, two-thirds come from those who received GnRH-agonist injections post-surgery (12 to 5, respectively). Secondly, about the same number of patients from both groups have delivered a child after undergoing laparoscopic surgery (15 and 16, respectively). Finally, the same number of patients from both groups have experienced an abortion after the surgery (4 and 4, respectively).

Thus, in total 56 patients managed to spontaneously conceive after surgery. However, when the association between the administration of GnRH-agonist (regardless of the number of injections received by the patients) and spontaneous pregnancy rates was investigated, the Chi-squared test revealed no significant role to be played by GnRH-agonist injections in increasing spontaneous pregnancy rate (OR 1.539; 95% CI 0.750-3.159; p-value 0.239).

Of those who did conceive though, there was a wide range as to when they managed to conceive. Some conceived immediately after surgery (a patient managed to conceive within a single month after surgery) while others had to wait significantly longer to achieve pregnancy (the longest was 26 months). On average, though, those who did not receive GnRH-agonist injections tended to conceive significantly more quickly than those who did (5.91 ± 6.28 ; 8.56 ± 4.24 ; p-value: 0.011).

Of those who delivered, both groups yielded notable results. Firstly, those who received GnRH-agonist injections had more female children while those who did not, delivered predominantly male children. Secondly, there were no significant differences on the average weights and lengths of the children at delivery across the two groups (p-value 0.770 and 0.2332, respectively). Finally, most of the deliveries were at term (19/31; 61.3%) and had normal weights at delivery (28/31; 90.3%)

DISCUSSION

Endometriosis is a benign gynecologic disease defined by the ectopic presence of endometrial tissue outside the uterus.⁸ It affects the pelvic viscera and/or peritoneum and characteristically, it is often present in the most declivitous parts of the pelvis, such as the Douglas pouch. Its characteristic symptom is pain, manifesting as dysmenorrhea, dyspareunia, dyschesia and non-menstrual pelvic pain.⁵ The symptoms may be so severe that it degrades the patient's quality of life (QoL) as well as debilitating the patient from performing her daily activities. It is this painful characteristic of endometriosis that has prompted ESHRE to recommend laparoscopic surgery as a means to both diagnose and treat endometriosis.⁹ ESHRE recommends operative laparoscopy to both relieve the patient of endometriosis-associated pain as well as preserve the patient's fertility. An Australian study by Abbott et al lent support to this ESHRE recommendation as patients who underwent surgery for endometriosis reported significant improvement for the above-mentioned 4 pain symptoms, the patient's QoL and sexual pleasure. Relieved of endometriosis, the patients later should try to conceive naturally for at least 12 months prior to resorting to assisted reproductive technology (ART). This is a recommendation of at least 2 studies from France and Australia.^{5,11}

In the present study, 56 out of 121 patients (46.3%) managed to conceive naturally. This is a comparable rate of conception when compared to a study in Australia in which they analyzed the spontaneous conception rate among nurses who underwent laparoscopic surgery for endometriosis and got a spontaneous conception rate of 46.5% (66/142 patients).¹⁰ In addition, our results are slightly more superior to another similar study in Korea, in which they analyzed the natural conception rate among women who had their endometriosis surgically removed.¹⁷ The Korean study exhibited a 41.4% conception rate but a major difference was their follow-up period, which was limited to only 12 months post-laparoscopy. Had they extended the follow-up period to match ours (12-24 months post-laparoscopy), it would be realistic to assume their natural conception rate would have been higher.

In our present study, our patients were divided into two equally sized groups: those who received

GnRh-agonist monthly injections post-surgery and those who didn't. The GnRH-agonist used in this study was leuprolide, falling under two brand names: Tapros and Divalin. Of those who received the injections, slightly more patients (34 patients) received at least 4 injections than those who received only 3 injections or less (27 patients). When this exposure was accounted for and compared towards the natural conception rates of each group's members, it was revealed that the administration of a GnRH-agonist did not significantly improve natural conception rates. This is in agreement with many other studies that have also been conducted throughout the years.^{14,18-21} A study in Germany by Alkatout et al even went a step further, by analyzing conception rates from women with endometriosis treated with hormonal therapy alone, surgical therapy alone, and combined surgical-hormonal therapy. The results they had led to the same conclusion, that there were not any significant differences in the natural conception rates across the 3 different groups.¹⁴ In fact, this result is to be expected, as the primary rationale to prescribe GnRH-agonist injections after laparoscopic surgery is to prevent endometriosis recurrence by inactivating any remaining microscopic endometriosis lesions and not to directly improve fertility.^{22,23} The mechanism by which GnRh-agonist administration prevent endometriosis recurrence is by abolishing the pulsatile release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), thereby inactivating the ectopic endometrial lesions which would otherwise grow along the pulsatile FSH and LH secretion.²⁴ However, it is important to stress that such hormonal therapy only function to inactivate and not eliminate the ectopic endometrial lesions. GnRH-agonist and all forms of hormonal therapy place the ectopic endometrial tissue in a quiescent state and as long as the drug is administered, the patient may expect to remain free of endometriosis symptoms.¹³

It is interesting to note that upon further analysis, there is a significant difference in the average waiting time to pregnancy after surgery between those who were treated with GnRH-agonist and those who were not. In our results, those who did not receive GnRH-agonist injections had to wait significantly less to conceive (5.91 ± 6.28) than those who did (8.56 ± 4.24), p-value: 0.011. This result does support the views expressed in other studies, which recommended

patients to attempt natural conception for at least 12 months post-surgery before requesting the help of ART.^{10,11}

However, as with all other scientific studies, our study is still replete with limitations from various aspects. The first is selection bias, introduced by the non-randomized nature of this study and also the specific population from which the study participants were recruited, as they all came from a single private hospital. The second limitation was the relatively small cohort of patients this study could work with (only from 2014-2015) and this small pool was further hampered by non-responders, which would have introduced non response bias. Another limitation was with the presence of possible confounders, e.g. male factor infertility and the presence of other gynecologic comorbidities. Finally, missing details from the medical records also disallowed us from stratifying the endometriosis diagnosis into the rASRM classification.

CONCLUSION

To conclude, post-laparoscopic administration of GnRH-agonist to women with endometriosis does not significantly improve their spontaneous conception rates. In fact, those who had post-laparoscopic GnRH-agonist injections tended to wait longer before eventually conceiving.

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