Case Report

Clinical Pregnancy Rate in in-Vitro Fertilization (IVF) among Endometrioma Patients Underwent Cystectomy Laparoscopy

Kejadian Kehamilan Klinis setelah Fertilisasi In Vitro pada Pasien Endometrioma Postsistektomi Laparoskopi

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Abstract

Objective: to discuss the clinical pregnancy rate and factors influencing fecundity among endometriosis women having cystectomy laparoscopically who underwent IVF.

Methods: The search was conducted on Pubmed®, EBSCOhost®, and Proquest®, Cochrane Library®, ClinicalKey® using MeSH.

Case: A 38-years woman, P0A0 come to the gynecology clinic with a chief complaint of primary infertility for eight years. The patient had undergone a bilateral endometrial cyst resected with laparoscopy and failed for two cycles of IVF. What is the clinical pregnancy rate of women that undergo IVF with a history of ovarian endometrioma cystectomy?

Results: There were six articles appropriate to the inclusion criteria and further appraised using the Centre for Evidence-Based Medicine, University of Oxford appraisal tools. The studies consisted of five prognostic studies and one meta-analysis. The studies were appraised for their validity, Importance, and Applicability.

Conclusion: The pregnancy rate in patients undergoing IVF after ovarian cystectomy ranges from 14%-45.2%. A prudent consideration and carefulness during cystectomy surgery are essential for patients that wish to be fertile.

Keywords: clinical pregnancy rate, endometrioma, in vitro fertilization, laparoscopy, ovarian cystectomy.

Abstrak

Tujuan: *Untuk menelaah tentang kemungkinan terjadinya kehamilan secara klinis pada perempuan yang menjalani IVF dengan riwayat laparoskopi sistektomi dan faktor-faktor yang mempengaruhi kesuburannya.*

Metode: *Pencarian jurnal dilakukan dengan menggunakan search engine Pubmed®, EBSCOhost®, dan Proquest®, Cochrane Library®, ClinicalKey® menggunakan MeSH.*

Kasus: *Perempuan P0A0 berusia 38 tahun datang ke poliklinik dengan keluhan utama infertilitas selama delapan tahun. Pasien memiliki riwayat kista endometrioma bilateral yang sudah di kistektomi dengan laparoskopi dan dua kali gagal menjalani siklus IVF. Berapa kemungkinan terjadinya kehamilan secara klinis pada perempuan yang menjalani IVF dengan riwayat kistektomi endometrioma?*

Hasil: *Dari hasil pencarian didapatkan enam artikel jurnal yang sesuai dengan kriteria inklusi dan dianalisis lebih lanjut menggunakan telaah kritis Evideence-Based Medicine, University of Oxford. .Terdapat lima jurnal studi prognostic dan satu meta-analisis. Studi-studi tersebut akan ditelaah kritis lebih lanjut berdasarkan validitas, kepentingan, dan aplikabilitasnya*

Kesimpulan: *Kemungkinan terjadinya kehamilan secara klinis pada pasien yang menjalani IVF setelah kistektomi endometrioma ovarium adalah 14%-45,2%. Pertimbangan yang bijaksana dan hati-hati diperlukan untuk melakukan operasi kistektomi pada pasien yang mengalami endometrioma dan ingin tetap subur.*

Kata kunci: *endometrioma, fertilisasi in vitro, kehamilan klinis, kistektomi ovarium, laparoskopi.*

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INTRODUCTION

Endometriosis is characterized by endometrial-like tissue in both glands and stroma outside the uterus, which induces a chronic inflammatory reaction, scar tissue, and adhesion.[1] Although endometriosis could be asymptomatic, many complain about abdominal pain, painful periods, dyspareunia, dyschezia, and infertility.[2,3] From that complaint, infertility in endometriosis may pose a chronic and complicated socioeconomic and health problem for women. Among 30-50% of endometriosis women who had infertility, and vice versa, 25-40% of infertile women, had endometriosis.[4,5] Thus, we should be careful about ovarian function in deciding on a therapeutic approach in endometriosis women complicated with infertility. Women with endometriosis often require assisted reproduction technology (ART), and the severity of endometriosis has been linked to the outcome. Although the exact mechanism in endometriosis that affects fecundity is still unclear, several reasons tried to explain this phenomenon, such as altered folliculogenesis resulting in reduced quality oocytes, mechanical interference with oocyte pickup and transportation, exposure to a hostile environment of macrophages, cytokines, and vasoactive substances in peritoneal fluid, and peritubular and ovarian adhesions.[6]

Endometriosis usually presents in different entities that may appear together or alone, such as a peritoneal lesion, deep endometriosis, and ovarian endometriotic cysts or endometriomas.[7] From all those entities, endometriomas is the most common form of endometriosis, with the prevalence of 17%-44% of women who has endometriosis.[8] Because endometriomas are cysts, visualization of the cyst's color and location is essential. Some imaging modalities, such as transvaginal ultrasound, are commonly used. The endometrioma lesion may appear as a low-level homogenous echo with ground glass appearance with no vascularity in ultrasound and Doppler flows. The gold standard of examination uses laparoscopy with biopsy to perfectly visualize the cysts and their severity. Endometriomas typically appear blue or black or, in rare cases, may appear into red, white, or non-pigmented lesions.[3,7]

In infertile patients with endometriosis, laparoscopic treatment is superior to diagnostic laparoscopy regarding clinical pregnancy and live birth. It improves in vitro fertilization (IVF) outcomes in minimal-mild endometriosis and deep infiltrative disease.[2,9] Several approaches to endometriomas include aspiration, cystectomy, fenestration, and ablation of the cyst; nevertheless, there is no consensus on which approach is the best to preserve ovarian reserve and subsequent ART outcome. Cystectomy is commonly performed for endometriomas more than 3 cm in diameter before the ART procedure.[10] However, it has detrimental effects of excision on the ovarian function, which is signed by serum anti-Mullerian hormone (AMH) level. Some studies found 40-60% decreased AMH levels from baseline after endometrioma surgery. Furthermore, endometrioma patients had significantly lower levels than their counterparts, amplifying the detrimental effects after endometrioma surgery.[4,5]

The benefits and harms of surgery in endometrioma should be carefully considered, as the goal is future fertility. Although IVF may be offered an increased chance of conception in infertile patients, the rate of pregnancy in endometrioma resected patients should be calculated to educate the patients in making choices. Therefore, this evidence-based case report would like to discuss the clinical pregnancy rate and factors influencing fecundity among endometriosis women having cystectomy laparoscopically who underwent IVF.

CASE

A 38-year-old P0A0 woman came to the gynecology clinic for eight years due to primary infertility. She had ever performed bilateral endometrial cyst via laparoscopy 12 years ago. She only complained of dyspareunia without dysmenorrhea, dyschezia, and dysuria. We did not find any abnormal uterine bleeding and no palpable mass. Patients already underwent two cycles of IVF. In 2015, we obtained seven oocytes in the first ovum pick up (OPU), but after ICSI, the eggs were unfertilized. In the second IVF in 2019, there were five oocytes after OPU, after ICSI 4 unfertilized, and one fertilized; unfortunately, no clinical pregnancy was found. In physical examination, she had a normal BMI. Her gynecological examination was a cystic nodule on the left adnexa, sized 4 cm. Ultrasonography examination shows normal shape and size of the uterine cavity, left endometrial cyst with 24x22x33mm, and adhesion of right ovarium with posterior corpus. Laboratory parameter showed low AMH level (0.17 ng/mL). The couples had undergone infertility investigation resulting from

bilateral varicocele from malefactors, submucosal leiomyoma, and ovarian endometrioma from female factors. Bilateral varicocele has been repaired with sperm analysis showed normal limit. Submucosal leiomyoma has been resected through operative hysteroscopy. Therefore, the diagnosis was primary infertility for 8 years due to female factors (ovarian endometrioma, poor ovarian reserve) and a history of failed IVF two times. She planned for performing IVF.

CLINICAL QUESTIONS

What is the clinical pregnancy rate of women that undergo IVF with a history of ovarian endometrioma cystectomy?

Searching strategy To answer the clinical question, the search was conducted on Pubmed®, EBSCOhost®, and Proquest®, Cochrane Library®, ClinicalKey® (figure 1). The searching strategy was performed on August 15th, 2020, there were five studies in Pubmed®, two studies in Cochrane Library®, 80 studies in Clinical Key®, 10 Studies in EBSCOhost®, and 79 studies in Proquest®; respectively. The articles were screened using the criteria consisting of abstracts answering the clinical question, written in the English language, full-text paper availability, and omitting all duplication papers. After screening, there were six articles inappropriate to the inclusion criteria. It consisted of 2 retrospective cohort studies, three retrospective, and one meta-analysis study. Critical appraisal determining the validity, importance, and applicability (VIA) was conducted by two independent authors. The critical appraisal steps are used in this article as prognostic studies.

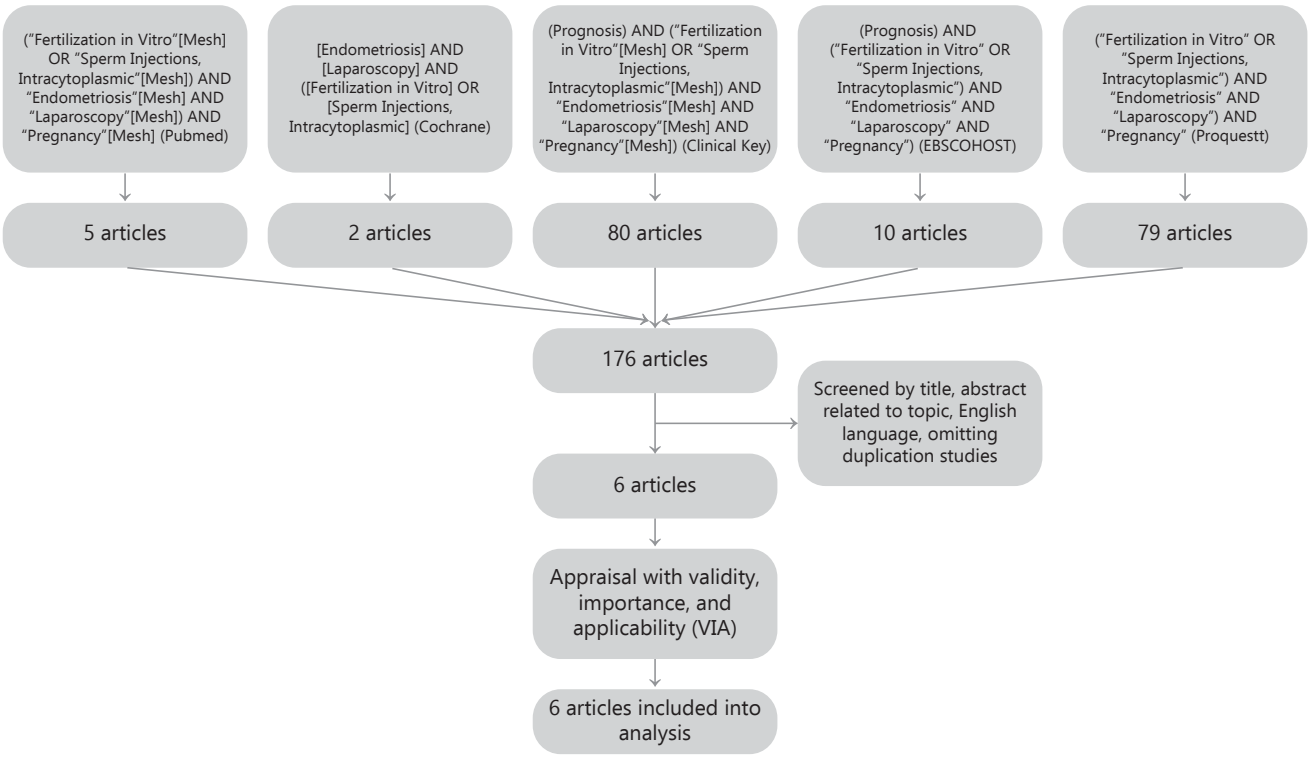


Figure 1. Flowchart of searching strategy

RESULTS

There were six studies appraised using VIA criteria based on critical appraisal of the systematic review and prognostic studies by the Centre for Evidence-Based Medicine, University of Oxford, 2010. From the systematic review form, the study was valid and important. In prognostic appraisal form, all studies were valid and important. All prognostic studies could apply to our patients. Table 1 describes the characteristics of studies, table 2 and 3 show the result of appraisal form on prognostic studies—meanwhile, the result of the pregnancy rate of each study is described in tables 4 and figure 2.

Table 1. Characteristics of each Study Included in this Evidence-Based Case Report

Study	Design	Intervention	Population	Study group	Control group	Cystic size cm	Outcomes
Loo TC, et al.[11]	Retrospective cohort study	Controlled ovarian stimulation (COS) by long agonist protocol	Patient who had at least one endometrioma larger than 3 cm	Laparoscopic ovarian cystectomy for endometrioma	Tubal occlusion	>3	Implantation and pregnancy rate per cycle
Esinler I, et al.[12]	Retrospective case-control study	Controlled ovarian hyperstimulation (COH) and recombinant FSH and intracytoplasmic sperm injection (ICSI)	Women <40 years, Unilateral/bilateral endometrial cyst >3cm histopathology of endometrioma First ICSI cycle	Unilateral or bilateral laparoscopy cystectomy	Tubal factor infertility	>3 in diameter	Cycle cancellation rate, number of oocytes, fertilization rate, embryo quality, clinical pregnancy rate (PR), implantation rate
Nakagawa K, et al.[13]	Retrospective case-control study	Hyperstimulation protocol with GnRH agonist	Women with inadequate tubal patency or severe pelvic adhesion	Ovarian endometrioma who received laparoscopic cystectomy	Expectant management	4.3 ± 2.1	Cumulative pregnancy rate
Harada M, et al.[14]	Retrospective case-control study	COS by daily injection of hMG with GnRH agonist or antagonist	Unilateral endometrioma >3cm. No other intervention before for ovaries. Absence of endometrioma when IVF conducted.	Excision of unilateral endometrioma by laparoscopically	Healthy ovaries	>3 in diameter	Number of oocytes, clinical pregnancy/ embryo transferred, on-going pregnancy/ embryo transferred
Guler I, et al[15]	Retrospective cohort study	COS (either antagonist or long GnRH analog)	-	Minimal peritoneal endometriosis and endometrioma underwent laparoscopic ablation and unilateral/ bilateral cystectomy	Expectant management	>3	Clinical pregnancy and live birth rates
Nickkho-Amiry M, et al.[16]	Systematic review and meta-analysis		Subfertile women with endometrioma undergoing ART	Surgical removal of endometrioma	Expectant management		Clinical pregnancy rate, pregnancy rate, live birth rate, number of oocytes retrieved and number of embryos, and

Table 2. Validity of Systematic Review and Meta-analysis Included in this Evidence Based Case Reports

Study	Validity					Results
	PICO	Relevant studies	Criteria for inclusion appropriate	Included studies valid	Similar from study to study	
Nickkho-Amiry M, et al.[16]	Impact of surgical management of endometrioma on the outcome of ART	Yes	Yes	Yes Original paper and clinical study about ovarian endometrioma	Yes	Below

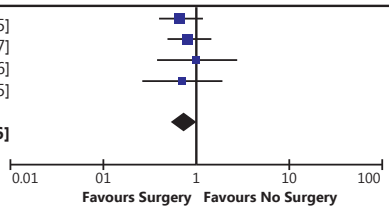
Table 3. Validity and Applicability of Prognostic Study included in this evidence based case reports

Study	Validity				Applicability	
	Representative sample	Follow-up sufficiently long and complete	Outcome applied in "blind" fashion	Adjustment for prognostic factors	Different patient	Clinically important to patient
Loo TC, et al. [11]	Yes	Yes	Yes	Yes	No	Yes
Esinler I, et al. [12]	Yes	Yes	Yes	Yes	No	Yes
Nakagawa K, et al. [13]	Yes	Yes	Yes	Yes	No	Yes
Harada M, et al. [14]	Yes	Yes	Yes	Yes	Yes	Yes
Guler I, et al. [15]	Yes	Yes	Yes	Yes	No	Yes

1. Live birth rate / cycle

Study or Subgroup	Treated Endometrioma Events	Total	Non Treated Endometrioma Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bongioannil 2011	29	112	49	142	39.4%	0.66 [0.38, 1.15]
Dong 2014	58	153	29	68	34.8%	0.82 [0.46, 1.47]
Lee 2014	12	36	12	36	12.3%	1.00 [0.38, 2.66]
Tinkanen 2000	11	55	12	45	13.5%	0.69 [0.27, 1.75]
Total (95% CI)		**356**		**356**	**100.0%**	**0.75 [0.54, 1.06]**
Total events	110		102			

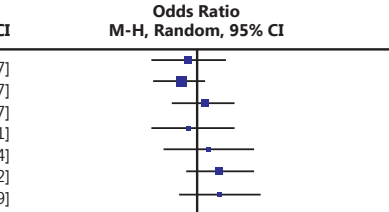
Heterogeneity. Tau²=0.00; Chi²=0.65, df =3 (P=0.88); I²=0%
Test for overall effect: Z=1.61 (P=0.11)



2. Clinical Pregnancy / cycle

Study or Subgroup	Treated Endometrioma Events	Total	Non Treated Endometrioma Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Demirol 2005	17	49	19	50	12.8%	0.87 [0.38, 1.97]
Dong 2014	66	153	35	68	26.3%	0.72 [0.40, 1.27]
Garcia-Velasco 2004	37	147	14	63	17.6%	1.18 [0.58, 2.37]
Lee 2014	13	36	14	36	9.5%	0.89 [0.34, 2.31]
Pabuccu 2004	11	44	8	40	8.1%	1.33 [0.47, 3.74]
Pabuccu 2007	27	81	15	67	15.9%	1.73 [0.83, 3.62]
Wong 2004	17	36	13	38	9.8%	1.72 [0.67, 4.39]
Total (95% CI)		**546**		**362**	**100.0%**	**1.08 [0.80, 1.45]**
Total events	188		118			

Heterogeneity. Tau²=0.00; Chi²=5.17, df =6 (P=0.52); I²=0%
Test for overall effect: Z=0.50 (P=0.62)



3. Pregnancy / cycle

Study or Subgroup	Treated Endometrioma Events	Total	Non Treated Endometrioma Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bongioannil 2011	41	112	59	132	32.7%	0.81 [0.49, 1.35]
Garcia-Velasco 2004	44	147	18	63	24.9%	1.07 [0.56, 2.05]
Suganuma 2002	18	62	11	30	14.2%	0.71 [0.28, 1.78]
Tinkanen 2000	12	55	17	45	15.3%	0.46 [0.19, 1.11]
Wong 2004	18	36	13	38	13.9%	1.92 [0.75, 4.90]
Total (95% CI)		**412**		**318**	**100.0%**	**0.88 [0.60, 1.29]**
Total events	133		118			

Heterogeneity. Tau²=0.05; Chi²=5.43, df =4 (P=0.25); I²=26%
Test for overall effect: Z=0.66 (P=0.51)

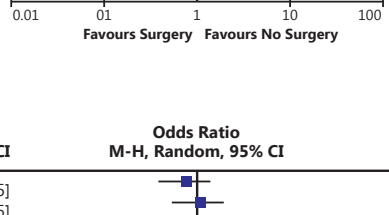


Figure 2. Importance of Nickkho-Amiry M, et al. study

Table 4. Clinical Pregnancy Rate in Prognostic Study Included in this Evidence Based Case Reports

Study	Clinical Pregnancy Rate: Study Group (n,%)	Control Group(n,%)	*P-Value*
NS	Endometrioma group (27/85 – 31,8)	Tubal group (21/71 - 29.6)	NS
NS	Unilateral (34, 45.2) Bilateral (23, 44.4)	Tubal Factor (99, 47.8)	NS
NS	IVF in laparoscopy cystectomy (50)	Expectant Management (41.4)	NS
NS (*P*=0.39)	Endometrioma-excised (4/10 – 40)	Healthy ovaries (6/24 – 25)	NS (*P*=0.39)
NS (*P*=0.056)	Operated endometrioma (8.14)	Expectant Management (11. 25)	NS (*P*=0.056)

*NS: Not significant (p>0.05)

DISCUSSION

Nowadays, 10% of the world's population is affected by infertility. Fifty million couples worldwide were infertile. Almost half of infertility is caused by the female factor, with 33.33% having unexplained causes of infertility. The common etiologies coming from female factor includes ovary (ovulatory disorder, PCOS, endometrioma), tube (tubal abnormalities/ blockage, endometriosis), and other (Endocrine or uterine abnormalities). Similar to the other study, endometriosis affects 15% of infertile women, the second-highest prevalence after ovulatory disorders (25%). This finding proves that after PCOS, Endometriosis is one of the leading causes of fertility.[17,18] Current treatment of endometriosis-associated infertility focuses on improving fecundity by removing or reducing ectopic endometrial implants and restoring normal pelvic anatomy. The goal can be achieved by surgical treatment with or without fertility preservation techniques such

as oocyte cryopreservation. If after the surgery women could not conceive naturally, assisted reproductive technology such as intrauterine insemination or In-Vitro Fertilization.[19,20]

First, clinicians should decide which patient is eligible or benefit from IVF after surgery. First of all, endometrioma size is essential to assess, in which large endometrioma sized more than 4-5 cm limits the access to retrieve oocyte. Furthermore, oocytes that had been exposed to endometrioma fluid could be damaged.[16,21] After size, other indication to resect an endometrioma was the rapid growth of the mass, malignancy feature in imaging, disturbing symptoms such as pain, and reducing risk for rupture during pregnancy.[16,21] At last, it is necessary to put on utmost care that clinicians should carefully resect the endometrioma since careless dissecting may hazard healthy ovarian tissue.

The surgery for endometrioma can be both diagnostic and therapeutic, in which surgery through laparoscopy is preferred due to less pain, shorter hospital stay, and quicker recovery. Several techniques can be performed, such as cystectomy, drainage and coagulation, and laser vaporization. Cystectomy is preferred as the mainstay of treatment because of lower recurrence rate, decreasing pain, and increased spontaneous pregnancy.[22] Nowadays, using hemostatic agents such as thrombin-gelatin matrix or fibrin sealant for hemostasis when doing ovarian cystectomy also minimizes damage given to healthy ovarian tissue rather than bipolar energy.[23] Furthermore, hemostatic agent oxidized regenerated cellulose or surgicel® can be used after drainage or cystectomy to reduce the risk of endometriomas recurrence compared with cystectomy only (Hazard ratio cystectomy only 0.806 vs Drainage and surgicel® 0.355 vs cystectomy and surgicel® 0.271 p = 0.02).[22] This opens a new option to decrease the risk of recurrence endometriosis.

In the light of this study, surgery may not improve clinical pregnancy in IVF. A meta-analysis found that clinical pregnancy/cycle in IVF was not statistically significant between treated endometrioma and non-treated endometrioma (OR 1.08; 95% CI 0.80-1.45).[16] Our appraisal also showed no significant difference in fertility outcome between patients undergoing IVF with a history of endometrioma cystectomy and patients with tubal factors. The difference in clinical pregnancy rate between the post-operative endometrioma and tubal factor group was not significant.[11,12,15] Patients performing cystectomy continued with IVF had a clinical pregnancy rate of 50% in 12 months and higher than the control group about 41.4%. There was also no significant difference in clinical pregnancy per embryo transfer from endometrioma and healthy ovarian (4/10 and 6/24; respectively), although the number of oocytes retrieved in healthy ovarium was higher than in endometrioma ovarium significantly.[14] At last, the number of antral follicles and AMH levels respectively in bilateral groups was significantly lower than unilateral groups. Although bilateral endometrioma has a more deleterious effect than unilateral endometrioma, the clinical pregnancy rate compared to tubal factor was not significantly different.[12]

The effect of endometriosis and its effect on achieving pregnancy during IVF is controversial. In our study, IVF patients with endometrioma had similar pregnancy rates among patients with a tubal factor or even non-operated endometrioma. Another study also reported that the birth rate of women with endometriosis is higher than other factors tubal/unexplained (42.5% vs 38.7% and 39.6%). Although women with endometriosis and one other etiology (tubal/unexplained) had the worst birth rate, 33.4% after IVF.[24] It was expected since the more pathology they had, the worse the outcome. In IVF endometriosis patients, the pregnancy and birth rate are most likely affected by the oocyte quality and impaired implantation. In endometriosis patients, the oocyte yield after stimulation was likely lower than with patients with tubal or unexplained causes. Also, the impaired implantation is caused by altered HOXA 10 gene expression, a transcription factor that stimulates αvβ3 expression to promote uterine receptivity. Furthermore, some transplantation factors are disrupted in endometriosis patients, such as glycodelin A, osteopontin, leukemia inhibitory factor, and lysophosphatidic receptors 2 and 4.[25]

Finally, the strength in our appraisal is that there is a meta-analysis/systematic review journal. The study compared much research about clinical pregnancy rate among patients undergoing IVF after endometrioma laparoscopy and homogenous criteria for cystic size in endometrioma more than 3 cm. The limitation is that the studies appraised had some control groups starting from tubal factor, healthy ovarian, and expectant management, and it can be attributed to a different outcome of clinical pregnancy rate.

CONCLUSION

The pregnancy rate in patients undergoing IVF after ovarian cystectomy ranges from 14%-45.2%. Endometriomas should not be routinely resected in patients undergoing ART. Some indications to perform cystectomy before ART are improving access to ovarium, the rapid growth of endometrioma, suspicion of malignancy, disturbing symptoms such as pain that cannot be relieved by medication, and prevention of rupture during pregnancy. A prudent consideration and carefulness during cystectomy surgery are essential for patients that wish to be fertile.

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