

INTERAUTERINE INSEMINATION VERSUS CONSERVATIVE MANAGEMENT AFTER LAPAROSCOPIC SURGERY IN INFERTILE WOMEN WITH MINIMAL OR MILD ENDOMETRIOSIS

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ABSTRACT

Background: - Endometriosis is really a serious, estrogen based, inflammatory disease characterized by the growth of endometrial stroma and glandular epithelium in areas outside the uterus and is particularly associated with pelvic pain and infertility. Laparoscopy is the primary method of diagnosis of endometriosis as it can identify superficial peritoneal implants. COS-IUI enhanced fertility in women with minimal or mild endometriosis. **Objective:** - was to evaluate the effectiveness of controlled ovarian stimulation in addition to intrauterine insemination (COS/IUI) versus conservative management after laparoscopic surgery (resection or ablation) in infertile women with ASRM stage I/II endometriosis. **Methods:** - this prospective study included 40 infertile patients with minimal or mild endometriosis. The affected individuals underwent laparoscopic surgical procedures that involves destruction or removal of all visible endometriotic implants and also lysis of adhesions. After laparoscopic surgical management patients were randomly divided into 2 groups:- **Group A:** - included 20 infertile women who were managed surgically and left to conceive spontaneously for one year (follow up period). **Group B:** - included 20 infertile women who were managed surgically and followed by controlled ovarian stimulation and IUI (COS/IUI) up to 4 cycles within one year period. **Results:- In group A,** the pregnancy rat /couple was 15%.and pregnancy rat /cycle was 1.42%.on the other hand in **group B,** Pregnancy rate /couples was (35%), and a pregnancy rate /cycle was (11.47%). in group B the pregnant rates were significantly higher than that in group A. There were highly statistically significant difference regarding pregnancy rates per couple and pregnancy rates per cycle between both groups ($p=0.049$). **Conclusions:** - The present study revealed that the women who underwent COS and IUI up to 4 cycles had a higher pregnancy rates than those who were expectantly managed after surgical removal of minimal or mild endometriosis.

Key words: minimal to mild endometriosis/infertility/laparoscopy / ovulation induction / intrauterine insemination.

INTRODUCTION

Endometriosis is really a serious chronic, estrogen based, inflammatory condition characterized by development of endometrial stroma along with glandular epithelium in areas outside the uterus and is commonly associated with pelvic pain and infertility ⁽¹⁾. It affects approximately 176 million women of reproductive age throughout the world ⁽²⁾.

endometriosis is mostly located on the pelvic peritoneum as well as ovaries but may also be found on rectovaginal septum, ureter, and seldom in the bladder, pericardium, and pleura ⁽³⁾.

The incidence of endometriosis is estimated to be ~3% in women of the reproductive age and it is observed in 20 to 70% of patients presenting with infertility ⁽⁴⁾.

Being a hormonally dependent condition, it is a proliferative, estrogen-based disorder (with developing proof of progesterone resistance) ⁽⁵⁾. It is chiefly found in reproductive-aged women. The anatomic location and inflammatory response to these lesions are

believed to account for the symptoms and signs associated with endometriosis ⁽⁶⁾.

Women with endometriosis typically presented with dysmenorrhea, chronic pelvic pain, dyspareunia, infertility, an adnexal mass or completely asymptomatic disease ⁽⁷⁾.

In endometriosis, the relationship between infertility and the stage I/II disease is not as evident because pelvic adhesions are not severe ample to generate damaging anatomical effects. However, there are possible mechanisms which may result in infertility in patients with mild disease, including ovulatory disorder, impaired folliculogenesis, defective implantation, eutopic endometrium abnormalities, abnormal immunological peritoneal milieu, and luteal phase problems ⁽⁸⁾.

Laparoscopy is the primary method of diagnosis of endometriosis as it can identify superficial peritoneal implants while imaging modalities have low sensitivities for diagnosis. When endo-metriosis causes mechanical distortion of the pelvis, surgery is usually indicated to restore the normal pelvic anatomy. Laparoscopy is the preferred surgical approach

due to 40% lower risks than that of laparotomy. The aim of surgical treatment is to remove endometriotic lesions whenever possible, restoration of normal anatomy together with adhesiolysis and in addition to optimize ovarian and tubal preservation and integrity⁽⁹⁾.

A recently available Cochrane evaluation demonstrated that the use of laparoscopic surgical treatment in minimal and mild endometriosis improve the on-going pregnancy rate and live birth rate. However the optimal surgical management of peritoneal endometriosis, whether by excision or ablation of the implants, is still controversial⁽¹⁰⁾.

Several other research have demonstrated that fertility is usually enhanced in women with minimal or mild endometriosis by controlled ovarian stimulation (COS) together with intrauterine insemination (IUI). whereas without treatment, women with minimal/mild endometriosis-related infertility have chance of spontaneous pregnancy rates of 2% to 4.5% per month⁽⁷⁾.

AIM OF THIS WORK

was to evaluate the effectiveness of controlled ovarian stimulation in addition to intrauterine insemination (COS/IUI) versus conservative management after laparoscopic surgery (resection or ablation) in infertile women with minimal to mild endometriosis.

PATIENTS AND METHODS

This prospective study was carried out in Cytogenic & Endoscopy Unit, at Zagazig University Hospitals, Obstetric and Gynaecology Department during the period from January 2012 till February 2015.

Subjects: 40 infertile women with ASRM stage I/II endometriosis had been included in the study. These patients underwent laparoscopic surgical Management that involves destruction (electrocautery) as well as removal of all visible endometriotic implants and also lysis of adhesions. Laparoscopy was performed by our staff members laparoscopists.

Inclusion criteria:-The Inclusion criteria required to be met prior to the the study are the following:-

- Age range between 18 and 37years.
- Women with laparoscopic findings those were consistent with stage I (minimal) or stage II (mild) endometriosis

according to the revised classification of the American Fertility Society⁽¹¹⁾.

- Duration associated with infertility (at least 12 consecutive months of unprotected intercourse in unsuccessful attempts to become pregnant).
- Day 3 follicle-stimulating hormone levels <10mIU/mL. Normal ovulatory cycles No evidence of intrauterine disease.
- Cases with reasonable chance for natural conception or conception with IUI will be included in the follow up period for 12 months (reasonable chance for conception was determined by the presence of at least one patent tube).
- Semen parameters should be met with the World Health Organization (2010) criteria⁽¹²⁾.

Exclusion criteria:-

- History of previous-surgical treatment to endometriosis.
- History of medical treatment for endometriosis.
- History involving ovulatory drug therapy or intrauterine insemination with partner's sperm in the last month.
- History of medical or perhaps surgical treatment for infertility in the previous 3 months.
- Prior oophorectomy or salpingectomy.
- Patients with severe male factor of infertility necessitating ICSI.
- Patients who have no reasonable chance for natural conception or conception with IUI due to bilateral tubal block will not be included in the follow up period.

Diagnostic laparoscopies:- were carried out in follicular phase of the menstrual cycle, with the patient under general anesthesia. The particular examination involving endometriosis expected the actual existence involving one or more typical bluish or even dark color lesions. The stage of endometriosis had been determined according to the revised classification of the American Fertility Society⁽¹¹⁾. Endometriotic implants on the peritoneum or perhaps ovaries are generally scored, whereas the scoring of adhesions takes into account the density and degree of enclosure.

Total R-AFS scores (implants and adhesions) from 1 to 5, 6 to 15 correspond to minimal and mild stage respectively.

After laparoscopic surgical management patients were randomly divided into 2 groups (Allocation of Patients in the study groups was done by physical random allocation) :-

Group A: included 20 infertile women who were managed surgically and left to conceive spontaneously for one year (follow up period).

Group B: included 20 infertile women who were managed surgically and followed by controlled ovarian stimulation and IUI (COHS/IUI) up to 4 cycles within one year period unless pregnancy achieve. Patients were invited to undergo 4 cycles of IUI (one insemination per cycle).

Technique of Super Ovulation:-

In Group B :- All women under-went ovarian stimulation using combined clomiphene citrate and human meno-pausal gonadotrophin (CC/HMG), as recommended by the consensus of (Bo Hyon et al).⁽¹³⁾

Clomiphene citrate 100 mg had been given once daily, starting on day 3 of the cycle for 5 consecutive days and followed by HMG 150 IU had been given on day 6 and 8 of the menstrual cycle (2-day regimen, on alternate days), an initial dose was individually adjusted according to the patient's diagnosis, the woman's hormonal profile, age and duration of infertility, age, weight, and previous responses to ovarian stimulation and according to her response after 6 days of stimulation.

Monitoring of Ovulation:-Patients were monitored by serial transvaginal ultrasound folliculometry every 2 or 3 days depending on the ovarian response. The patient was evaluated regarding the growth, number and size of the follicles (Serial folliculometry) as well as endometrial thickness and pattern. Ovulation triggering by IM injection of 10,000 IU of hCG was administered as recommended by (Dinelli et al.)⁽¹⁴⁾. When the leading follicle reached ≥ 18 mm in greatest diameter and at least two follicles reach ≥ 16 mm and endometrial thickness > 7 mm.

We withheld the administration of HCG, and IUI was cancelled in the stimulation protocols when no mature follicles were

obtained or when there were more than three follicles of diameter at least 16 mm, or five of diameter at least 12 mm were present to avoid development of OHSS.

Insemination: - All women under-went single insemination by their husband semen (IUI-H) 36h after the HCG injection.

Number of Cycle: - In group B IUI with COS was offered up to 4 cycles.

Technique of IUI: - IUI had been performed 36 h following administration of HCG. The cervix had been easily wiped using a few ml of medium (HEPES buffer medium) and along with a flexible intrauterine catheter had been gently introduced into the uterus using almost all aseptic precautions until eventually it touch the fundus, after that it had been retracted ~1 cm; lastly, 0.5 ml of the suspension had been injected with a slow movement of the piston. The patient remained supine for at least ~20 min and then resumed normal activity.

Luteal Phase Support:-Trans-vaginal micronized progesterone was prescribed 400 mg/day, (Prontogest, IBSA, Egypt) for 15 days after the IUI, beginning around the day time associated with insemination or the next day and also continuing to the subsequent menstrual period and/or diagnosis of pregnancy (intrauterine gestation sac together with evidence of an embryonic cardiovascular beat).

Diagnosis of pregnancy: - Serum β -hCG assay had been done if the patient had a missed period 14 days after intra-uterine insemination. If the result was positive, the assay had been repeated 7 days later to check for an increase of hCG.

A clinical pregnancy was diagnosed at 6 weeks missed period by means of transvaginal ultrasound scan through the presence of an intrauterine gestational sac with fetal pole and cardiovascular activity.

Follow-up of both groups:-The women were followed for one year in out patient clinic of Obstetric and Gynecology Department.

The primary outcome:- was the occurrence of an intrauterine pregnancy, in the first year after laparoscopy. Vaginal ultrasound was performed 2 weeks after the positive serum β HCG test to confirm the presence of an intrauterine gestational sac.

Secondary outcomes:- included the time to get pregnant, clinical pregnancies, ectopic pregnancies, miscarriages rate of multiple pregnancies, and rate of ongoing pregnancy (i.e. after first trimester). Other complication of IUI as the risk of multiple pregnancies and the most significant is the risk of developing ovarian hyperstimulation syndrome (OHSS) occurring from the drugs used for ovulation induction.

For group B:- If ovarian response involved more than three follicles > 1.8 cm in greatest dimension, conversion to IVF-ET was advised and offered and these patients were excluded from the study. However in the current study no cases converted to IVF. On the other hand patients who did not become pregnant after COS+IUI were advised to perform a more sophisticated methods of assisted reproductive technology (e.g:- IVF).

For group A:- Patients who did not become pregnant in unstimulated cycles were advised to perform combined COS+IUI for at least 3 cycles before resorting to other more sophisticated methods.

STATISTICAL ANALYSIS

Data were statistically analyzed using SPSS software (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 16 for Microsoft Windows. Numerical data were expressed as mean and standard deviation or median and range as appropriate. While

qualitative data were expressed as frequency and percentage. P value < 0.05 was considered statistically significant.

Sample Size was calculated using (Ep - 6) according to the following:-

-The pregnancy rate in Group A: was (15.1%) that estimated from the results published before this study began (**Milingos et al., 2002**)⁽¹⁵⁾.

-The pregnancy rate in Group B: was 33.1% reported from study done by (**Wang et al., 2006**)⁽¹⁶⁾. Based on 80% power of the study at 95% CI and a 5% level of significance, assuming a 15% difference in the pregnancy rates. So Consequently, the estimated Sample Size for the trial was, 40 women with minimal or mild endometriosis (20 per group).

RESULTS

During the study period 40 infertile women with ASRM stages I and II endometriosis diagnosed and managed laparoscopically.

All patients were infertile, 28 patients (70%) suffered primary infertility while 12 patients (30%) suffered secondary infertility. 9 patients (75%) of cases with secondary infertility had a history of abortion. The age range of the studied sample was between 18.5 to 37 years of age. The duration of infertility ranged from 3 to 9.5 years (mean was 6.25+1.95 year).

Table (1): Base-line characteristics of women undergoing laparoscopic surgery for endometriosis according to studied groups:-

Characteristics	Group A (N=20)	Group B (N=20)	Test	P value
Age of female [years]	30.25±5.2	27.1±4.5	-0.670 [‡]	0.507
Types of infertility				
Primary infertility No (%)	15(75%)	13(65%)	0.156 [§]	0.692
Secondary infertility No (%)	5(25%)	7(35%)		
Duration of infertility [years]	8.25±4.9	4.8±1.2	0.081 [‡]	0.935
BMI (kg/m ²)	21.5±2.62	22.3±2.43	1.001 [‡]	0.323
Cycle length in previous 6 months (days)	29.5±1.9	28.2±2.1	-1.421 [‡]	0.163
Pain (dysmenorrhoea)				
No	13(65%)	12(60%)	0.089 [§]	0.126
Yes	7(35%)	8(40%)	0.156 [§]	0.87

- There was no significant difference between both groups regarding all parameters of demographics characteristics.

Table (2): Methods of laparoscopic surgical procedures done for the patients with endometriosis and there effect on pregnancy rate.

Surgical Procedures	Group A (N=20)		Group B (N=20)		Test §	P value
	NO (%)	Pregnanc y rate	NO (%)	Pregnanc y rate		
Resection	8(40)	1/8(12.5)	6(30)	3/6 (50)	0.112 §	0.112
Ablation	12(60)	2/12(16.6)	14(70)	4/14(28.5)	0.874 §	0.874

- There was no significant difference regarding surgical treatment modality (Resection or Ablation) and the pregnancy rate in both groups (P> 0.05).

Table (3): Pregnancy rate (PR) per couples and pregnancy rate (PR) per cycle in both groups.

Characteristic	Group A	Group B	Total	χ^2	P value
No. patients	20	20	40	--	--
No. of Cycles	211	61	269	--	--
No. of clinical pregnancies	3	7	10		
PR/couples [%]	3/20 (15%)	7/20 (35%)	10/40 (25%)	15.431	0.001(S)
PR/cycle [%]	3/211 (1.42 %)	7/61 (11.47 %)	10/272 3.67%	11.588	<0.001 (HS)

- ◆ During this prospective study the overall clinical pregnancy rate for all patients was 25%.
- ◆ Out of 40patients, 10 (25%) patients became pregnant, 3 (15%) in group A conceived spontaneously, and 7 (35%) in group B conceived through COH/IUI.

There were highly statistically significant difference regarding pregnancy rates per couple and pregnancy rates per cycle between both groups.

Table (4): Clinical pregnancy rate and outcome among studied groups:-

Pregnancy	Group A n=20		Group B n=20		χ^2	p
	No.	%	No.	%		
No. of pregnancies	3	15	7	35	15.431	0.001(S)
Single pregnancy (n)	3	15	6	30	10.573	0.048(S)
Gestational sac (n)	3	15	8	40	12.006	0.0569(S)
Multiple pregnancy(twins)	0/3	0.00	1/7	14.2	13.211	0.0189 (S)
spontaneous abortions	0/3	0.00	1/7	14.2	12.431	0.048 (S)
Ongoing pregnancy	3	100	6	85.7	0.573	0.049(S)
Ectopic pregnancy rate	0	0.00	0	0.00	0.0250 [§]	0.874
OHSS	0	0.00	0	0.00	0.0250 [§]	0.874

Of the 20 patients in group A, 3 became pregnant (15%) and 7 patients (35%) in group B became pregnant. Twin pregnancies were reported only in one patient in groups B. One patient who conceived after IUI had spontaneous first trimester abortion. There were statistically significant differences regarding clinical pregnancy rat and outcome between both groups. None of the 40 patients in the present study developed ovarian hyperstimulation syndrome (OHSS) or ectopic pregnancy.

Table (5): Distribution of couples having pregnancy according to number of IUI cycles in group B:-

Cycle NO.	Group B (n=20)		χ^2	p
	Total NO of IUI cycle	Per-cycle Pregnancy Rate. N (%)		
(1 st)	20	5/20 (25.00)	13.431	0.046 (S)
(2 nd)	15	2/15 (13.33)		
(3 rd)	13	0/13 (0.00)		
(4 th)	13	0/13 (0.00)		
Total	61	7/61 (11.47)		

The pregnancy rate was highest after the 1st cycle. The result of 3rd and 4th IUI cycle was disappointing. This result was statistically significant (P< 0.05).

Table (6): Effect of the number of treatment cycles on pregnancy rate in group B.

Gro	Number Pregnant	Positive pregnancy		Treatment cycles
		Number	%	
	7			

In group B, All patients who became pregnant did so in the first 2 cycles of treatment while the rest completed 4 cycles without becoming pregnant. 5 out of 7 patients (71.4%) became pregnant in the first cycle while 2 patients (28.6%) became pregnant in the second cycle. This result was statistically significant (P< 0.05).

Table (7): Outcome according to rASRM classification.

rASRM Classification	Group A n=20		Group B n=20		Total N=40		Test	p
	No. (%)	Conceived Cases No. (%)	No. (%)	Conceived Cases No. (%)	No. (%)	Conceived Cases No. (%)		
Stage I	6(30)	2(33.33)	12(60)	5(41.6)	18(45)	7(38.8)	12.4310	0.048 (S)
Stage II	14(70)	1(7.1)	8(40)	2(25)	22(55)	3(13.6)		

The patients were divided into 2 groups (Stage I and Stage II endometriosis) regarding rASRM classification. In patients with **Stage I** (18 patients), 7 patients became pregnant (38.8%) and 11 did not become pregnant (71.88%). In patients with **Stage II** (22 patients), 3 patients became pregnant (13.6%) and 19 did not become pregnant (71.88%).

DISCUSSION

In stage I/II endometriosis, the relationship between infertility and the disease is not as evident because pelvic adhesions are not severe enough to create damaging anatomical effects. There are, however, possible mechanisms that could cause infertility in patients with mild disease, including impaired ovarian reserve and reduced ovarian response, as indicated by lower anti-müllerian hormone, higher FSH and aberrant expression of some proteins, impaired

folliculogenesis, defective implantation, eutopic endometrium abnormalities, abnormal immunological peritoneal environment, and luteal phase problems **Fadhlaoui et al.**,⁽¹⁷⁾. Besides, affected endometrial receptivity in endometriosis patients may also contribute to endometriosis-associated infertility. Some studies demonstrated that the expression pattern of various endometrial receptivity related factors were altered in endometriosis patients,

such as Integrin, HOXA-10, IL-11 and P53 **Lu et al.**,⁽¹⁸⁾.

Complete resolution of endometriosis is not yet possible and current therapy has three main objectives: (1) to reduce pain; (2) to increase the possibility of pregnancy; and (3) to delay recurrence for as long as possible. Despite significant developments in medical and surgical approaches for treating endometriosis, the optimal treatment of subfertile women with ASRM stages I and II endometriosis is controversial. Guidelines on endometriosis by **ESHRE**.,⁽¹⁹⁾; **ASRM**.,⁽⁷⁾; **RCOG**.,⁽²⁰⁾. Recommend surgery for minimal and mild disease.

Laparoscopy can be used not only for diagnosis, but also for treatment. The major objectives of conservative surgery are to ablate or excise all visible endometriotic lesions, preserve the uterus and ovarian tissue, and restore normal pelvic anatomy. In conservative operations Various surgical options are available *via* electrocoagulation, laser ablation, or excision of the lesions, and adhesions are lysed all of which have similar efficacy in the therapy of endometriosis **Dunselman et al.**,⁽²¹⁾

Earlier studies on intrauterine insemination (IUI) outcomes demonstrated significantly lower clinical pregnancy rates in women with surgically untreated minimal to mild endometriosis **Omland et al.**,⁽²²⁾. However, a recent study showed that when minimal to mild endometriosis was surgically treated before ovarian stimulation and IUI, there were significantly differences in clinical pregnancy rate and LBR, compared with surgically untreated women with minimal to mild endometriosis **Abdelkader et al.**,⁽²³⁾.

In this study all patients were infertile, 28 patients (70%) suffered primary infertility while 12 patients (30%) suffered secondary infertility. 9 patients (75%) of cases with secondary infertility had a history of abortion. The age range of the studied sample was between 18.5 to 37 years of age (mean was 35.8±5.1 year). The duration of infertility ranged from 3 to 9.5 years (mean was 6.25±1.95 year). The two groups were compared regarding age, BMI, Types and duration of infertility and Cycle length in previous 6 months and that there was no significant difference between both groups

regarding all parameters of demographic characteristics of women undergoing laparoscopic surgery for endometriosis.

In the current study, we have assessed the laparoscopic surgical procedures (Resection vs Ablation) done for the patients with endometriosis and there effect on pregnancy rate. In group A, out of 8 patients who undergo resection of endometriotic implants one patients became pregnant (12.5%) and 7 did not became pregnant (87.5 %). And out of 12 patients who undergo ablation of endometriotic implants 2 patients became pregnant (16.6%) and 10 did not became pregnant (83.3 %).

While in group B, out of 6 patients who undergo resection of endometriotic implants 3 patients became pregnant (50%) and 3 did not became pregnant (50%). And out of 14 patients who undergo ablation of endometriotic implants 4 patients became pregnant (28.5%) and 10 did not became pregnant (71.4 %). There was no significant difference regarding surgical treatment modality (Resection or Ablation) and the pregnancy rate in both groups ($P > 0.05$). Our findings are comparable to recently performed study by **Tulandi et al.**,⁽²⁴⁾, who compared the reproductive performance of infertile women after laparoscopic treatment of minimal or mild endometriosis by electrocoagulation and by surgical excision. The results show that there is no difference in the reproductive performance after surgical excision (57.1%), or after electrocoagulation (53%).

Similar results were also found by **Wright, et al.**,⁽²⁵⁾. Their study was conducted as a small RCT showed that excision and ablation equally improved infertility associated with mild endometriosis. A more recent RCT including women with all stages of endometriosis showed that ablation was as effective as excision **Healey, et al.**,⁽²⁶⁾. However, this study did not specify how ablation or excision was carried out. Furthermore, the excision group had higher American Fertility Society (AFS) staging system scores.

Similarly, based on the studies performed to date, by **Johnson et al.**,⁽⁹⁾ and **Todd et al.**,⁽²⁷⁾. They demonstrated that. Firstly, the use of laparoscopic surgery (excision or ablation) has been shown to improve fertility in women with

minimal or mild endometriosis, but evidence is lacking in women with more advanced endometriosis. Secondly, laparoscopic excision of endometriosis, when technically feasible, should be the standard of care, whereas visual diagnosis of endometriosis is correct in only 57% to 72% of cases, excisional surgery yields specimens for histological confirmation and identifies endometriosis in 25% of "atypical" pelvic lesions as well. The availability of such specimens would prevent unnecessary treatment and ensure more reproducible research findings. Excision should also reduce the incidence of persistent disease secondary to inadequate "tip of the iceberg" destruction, removing both invasive and microscopic endometriosis to provide the best possible symptom relief. Thirdly, ablation is quicker, easier, less vascular and technically less difficult than excision, but is not necessarily safer than excision. Finally, the results of excision are comparable to or better than those of ablation. Endometriosis usually recurs, but excision both prolongs the time to reoperation and reduces the severity at second surgery. Excision provides the greatest benefit for patients with extensive disease without increasing complication rates or morbidity.

Regarding to the pregnancy rate (PR) per couples and pregnancy rate (PR) per cycle in both groups. In group A, the pregnancy rate /couple was 15%.and pregnancy rate /cycle was 1.42%.on the other hand in group B, Pregnancy rate /couples was (35%), and a pregnancy rate /cycle was (11.47%). There were highly statistically significant difference regarding pregnancy rates per couple and pregnancy rates per cycle between both groups ($p=0.049$).

The findings of this study were in accordance with Another study conducted by **Ashraf et al.**,⁽²⁸⁾ , **Hassa et al.** ⁽²⁹⁾. They demonstrated that the pregnancy rate / cycle was highest (19.9%) among couples with Surgically managed Minimal to mild endometriosis associated infertility after COH- and the best PRs were seen after CC plus gonadotropins stimulation.

Our findings are comparable to those of **Paul et al.**,⁽³⁰⁾ who performed a retrospective study including 313 infertile Women with stage I and II endometriosis that diagnosed and

managed laparoscopically (n =313) underwent consecutive COH-IUI (202 patients, 648 cycles)and (111 patients, 139 cycles underwent conservative management). 69 patients conceive after COH-IUI, and 20 conceived with conservative management (PR were 42.1%, 15% , respectively).

Our data show a higher pregnancy rate (35%) followed superovulation and IUI cycles and (15%) in no treatment cycles than study conducted by **Ian et al.**,⁽³¹⁾. Who evaluate the efficacy of superovulation and IUI versus no treatment for infertility associated with minimal or mild endometriosis. in a randomized controlled trial after conservative laparoscopic surgery, they concluded that the clinical pregnancy rate were 14 of 127 (11%) followed superovulation and IUI cycles and 4 of 184 (2%) in no treatment cycles. The odds ratio was 5.6 (95% confidence interval 1.8 to 17.4) in favor of superovulation and IUI. And concluded that Treatment with superovulation and IUI was associated with superior outcome regarding live-birth rates.

However, other study have yielded controversial results. **Fedele et al.**,⁽³²⁾ Reported that the results of superovulation and IUI compared with conservative management for minimal or mild endometriosis after laparoscopic surgery have not been uniform. Fedele and co-workers found no difference in PRs in a randomized comparison of three cycles of superovulation and IUI versus no treatment for 12 months. And the estimated PR was (15 versus 12% respectively).

In opposition with our results **Cramer et al.**,⁽³³⁾ Concluded that the pregnancy rates rate among women with minimal or mild endometriosis who underwent laparoscopic surgery (6.1%) was much lower than the rate expected in fertile women (20%). This indicates that the destruction of visible endometriotic implants and adhesiolysis do not affect all factors by which minimal and mild endometriosis contributes to infertility or that factors other than endometriosis interfere with fertility.

Regarding the Clinical pregnancy rate and outcome among studied groups: - **In group A**, out of 20 patients who were managed surgically and left to conceive spontaneously, 3 patients

became pregnant. All pregnancies in group A, occurred spontaneously and neither miscarriages nor ectopic pregnancies were observed. **While in group B**, 20 couples underwent 61 consecutively completed ovulation induction cycles using sequential CC/HMG with IUI, resulted in 7 clinical pregnancies and a pregnancy rate /couple was (35%), and a pregnancy rate /cycle was (11.47%). Out of the 7 clinical pregnancies, twin pregnancy was reported only in one patient. One patient who got pregnant after IUI had spontaneous first trimester abortion. There was no higher order multiple gestations. In group B The pregnancy rate was significantly higher compared with group A ($p < 0.05$).

The overall clinical pregnancy rate for all patients in the study period was 25% (10/40). None of the 40 patients in the present study developed ovarian hyper stimulation syndrome (OHSS) or ectopic pregnancy. There were statistically significant differences regarding clinical pregnancy rate and outcome between both groups. The findings of the present study were comparable to those of **Johnson et al.**,⁽⁹⁾, **Dunselman et al.**,⁽²¹⁾.

the findings of the present were comparable to those of **Wang et al**⁽¹⁶⁾, who performed a retrospective study including 75 Patients with minimal to mild endometriosis with ≥ 2 years of infertility, after laparoscopic surgical management of endometriosis COH/IUI was performed at either 24 hr or 36 hr after hCG injection in 40 Patients. And 35 Patients underwent expectant management, Pregnancy rates were reported to be 33.1% in group 1 and 12.1% in group 2, respectively.

Our findings demonstrate that Surgical eradication of minimal and mild endometriosis has been shown to increase the clinical pregnancy rate both spontaneously and after intrauterine insemination.

Also in a retrospective cohort study, **Opqien et al.**,⁽³⁴⁾ who evaluate the effects of laparoscopic surgery (using ablation of endometriotic lesions) on subsequent COH-IUI treatment ($n = 399$). Compared with women who only received ablation of endometriotic lesions ($n = 262$), women who underwent complete removal of endometriotic lesions followed by COH-IUI had a significantly

improved in pregnancy rate (40.1% vs 29.4%, $p = 0.004$) and live birth rate (27.7% vs 20.6%, $p = 0.04$). And they concluded that surgical removal of minimal and mild endometriotic lesions reduced the time to first pregnancy and resulted in higher pregnancy rate, both spontaneously and after intrauterine insemination.

Regarding the distribution of couples having pregnancy according to number of IUI cycles in group B. The pregnancy rate was highest after the 1st cycle (25%), 2nd cycle (13%). However the result of 3rd and 4th IUI cycle was disappointing. The pregnancy rate was 25%, 13%, 0.00%, and 0.00% for 1st, 2nd, 3rd, 4th cycles respectively. This result was statistically significant ($P < 0.05$). The results of the current study were in agreement with conclusions from a previous study done by **ASRM**,⁽³⁵⁾ ;**Dam et al.**,⁽³⁶⁾.

Regarding the effect of number of Treatment cycles on pregnancy rates. In the present study all patients who conceived after COH-IUI did so in the first 2 cycles of treatment, 5 out of 7 patients (71.4%), became pregnant in the first treatment cycle, while the remaining 2 patients (28.6%) became pregnant in the second treatment cycle. Accordingly, all of the pregnancies in current study occurred within the first two treatment cycles and no pregnancy was achieved in the third and fourth cycles. This result was statistically significant ($P < 0.05$).

The results of the current study concurs with the results of **Opqien et al.**,⁽³⁴⁾ They showed that most pregnancies (84.4%) were obtained within the first two treatment cycles. All of the pregnancies occurred within the first four treatment cycles and no pregnancy was achieved in the fifth, sixth and seventh cycles.

Similarly in study by **Ashraf et al.**,⁽²⁸⁾ reported that pregnancy was significantly more likely to occur in the first 2 cycles of treatment than beyond 4 cycles. And decreasing of pregnancy rates with an increased number of treatment cycles has also been shown.

In the current study, we also found that the rank of attempt had an impact on IUI outcome. Indeed, our study showed a significant decrease of PR after the 2nd attempt. This is in agreement with conclusions from previous studies **Steures**

et al.,⁽³⁷⁾; Nuojuua-Huttunen et al.,⁽³⁸⁾. And in opposition with Dinelli et al.,⁽¹⁴⁾; Boomsma et al.,⁽³⁹⁾. they showed no statistically significant variation of PR according to rank of attempt.

In general, repetitive COS / IUI cycles show a plateau effect after 3-4 cycles, therefore patients must be counseled to switch to IVF after 3-4 cycles Kennedy et al.,⁽⁴⁰⁾; National Institute of Clinical Excellence,⁽⁴¹⁾.

The outcome according to rASRM classification. In this study the patients were divided into 2 groups (Stage I and Stage II endometriosis) regarding rASRM classification. In patients with Stage I (18 patients), 7 patients became pregnant (38.8%) and 11 did not (71.88 %). While in patients with Stage II (22 patients), 3 patients became pregnant (13.6%) and 19 did not (71.88 %). There was a statistically significant increase in pregnancy rate in patients with Stage I compared to Stage II (38.8% and 13.6% respectively, $P < 0.05$). The results of the current study were in agreement with Lee et al.,⁽⁴²⁾. Who reported that the PR for stage I and stage II was (54.4%, 35.7%, respectively). And there was a statistically significant increase in pregnancy rate in patients with Stage I compared to Stage II.

On the contrary to the results of the present study Werbrouck et al.,⁽⁴³⁾. Reported that there was no difference in clinical pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal- and mild endometriosis after COH-IUI. They concluded that the PR was similar in women with minimal endometriosis (12%), and in mild endometriosis (9.8%).

CONCLUSIONS

In conclusion, endometriosis is associated with infertility, even in its mildest forms. This study demonstrated that surgical eradication of minimal and mild endometriosis at the time of diagnostic surgery has been shown to increase the clinical pregnancy rate both spontaneously and after controlled ovarian stimulation and intrauterine insemination (COS/IUI).

Furthermore, the present study revealed that the women who underwent super ovulation and IUI for 4 cycles had a higher Pregnancy rates than those who were expectantly managed after surgical removal of minimal or mild endometriosis.

RECOMMENDATIONS

In infertile women with ASRM stage I/II endometriosis, when laparoscopy is performed clinicians should perform operative laparoscopy (excision or ablation of endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, since there is a positive effect on pregnancy rate.

After surgical removal of minimal and mild endometriosis treatments with COS and IUI was associated with a higher clinical PR than in women who were managed expectantly.

COS-IUI, is an efficient and safe technique with a relatively low cost, for treatment of infertile women with endometriosis stage I/II. However, since most of pregnancies occur in the first cycles of IUI and the probability of pregnancy markedly decreases after the 2nd cycles of IUI thus we can recommend the use of COS and IUI for 3 consecutive cycles only, as the first choice of treatment before reverting to more sophisticated and more expensive assisted reproductive technique (ART).

Ovarian stimulation using clomiphene citrate in addition to human menopausal gonadotrophin (CC/HMG), was recommended as it confers specific advantages related to reduce cost-effectiveness and minimizing the risk of OHSS and multiple gestations. For those choosing natural conception if it does not occur within one year after surgery, the clinician may consider combined COS+IUI for at least 3 cycles before resorting to other more sophisticated methods.

Duration of infertility, Female age, family history, pelvic pain and stage of endometriosis should be taken into account when formulating a management plan.

In women with stage I/II endometriosis-associated infertility, expectant management or superovulation/IUI after laparoscopy can be considered for younger patients. Women 35 years of age or older should be treated with SO/IUI or IVF-ET.

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude and appreciation to Prof. Dr. Mahmoud Ahmed Ghareeb, Professor of Obstetrics & Gynecology, Faculty of Medicine Zagazig University for giving me the

opportunity to work under her meticulous supervision and for his excellent guidance and powerful support.

Also, I would like to express my true thanks to Prof. Dr. Magdi Ragab ELsaied, Professor of Obstetrics & Gynecology, Faculty of Medicine Zagazig University for his great guidance and advices throughout this work.

My deepest thanks and appreciation go to Prof. Dr. Soha Galal Siam, Professor of Obstetrics & Gynecology, Faculty of Medicine Zagazig University, who honored me by her great supervision, valuable guidance and precious time.

Disclosure of interests:-

None of the authors have a conflict of interest.

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