Impact of endometriosis on intracytoplasmic Sperm injection (ICSI) outcome

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Abstract: background: Endometriosis and infertility are correlated in a complex manner, and a number of various pathogenetic cellular and molecular mechanisms interconnect the two issues. Endometriosis is diagnosed in 6-8% of females undergoing assisted reproductive management protocols. Cases suffering endometriosis apparently have similar ART clinical outcomes in comparison to unexplained infertility as regards live birth rates, in spite of a lower oocyte quality retrieved. In case of more severe forms of the disease (e.g. endometrioma, deep infiltrating endometriosis) the benefits of surgery prior to ART are debatable, and must be balanced against risks. **Aim:** The current research study aims to investigate impact of endometriosis on ICSI clinical outcome as regards pregnancy rate. **Methodology:** The current research study was conducted at ART unit Al Azhar university, on 100 cases with endometriosis were recruited in a prospective manner in research group I and 50 cases with unexplained infertility were recruited in a retrospective manner research group II to be used as a control group. Controlled ovarian stimulation for ICSI performance was conducted by using long protocol. The primary research outcome measure was determining the pregnancy rate per case. **Results:** statistically significant difference between research groups according pregnancy rates using chi-square test with p-value <0.001. Women with severe endometriosis have a statistically significant lower pregnancy rate and implantation rate, have lower number of oocytes obtained at retrieval and a lower serum E2 concentration. **Conclusion:** The current research study reveals that the effect of endometriosis is not exclusively on the endometrial respectively but also on the oocyte and embryonic development.
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Keywords: Impact; endometriosis; intracytoplasmic Sperm; injection (ICSI); outcome

1. Introduction

Endometriosis is defined by the presence of ectopic endometrial glands and stroma outside the uterus in association with pelvic pain and infertility**.** Being a chronic inflammatory disease in pathological nature due to the presence of endometrial-like tissue outside the uterine cavity, and leading to a group of clinical symptoms involving dysmenorrhea, dyspareunia and subfertility**.** The exact prevalence of endometriosis is unidentified but estimated to range from 2 to 10% within the general female population but in up to 50% in infertile women**.** Although endometriosis is generally accepted to be related to infertility it's actual impact on fecundity and the exact mechanisms underlying this impact are less clear despite intense and sustained research efforts.**1-5.**

Endometriosis is correlated to subfertility, and up to 50% of females with endometriosis have issues conceiving naturally. The cause and effect of endometriosis pathological impact on subfertility remains debatable. Even though it is proven by evidence based research studies that without interventional management, cases with more severe forms of disease are less capable to achieve conception. There are conflicting results concerning the reproductive outcomes linked with subfertile cases with varying severity degrees of endometriosis undergoing ART management protocols**.6-10**

Most commonly, endometriosis is exists in the dependent regions of the pelvis. The ovary, pelvic perineum, anterior and posterior culde-sac, and uterosacreal ligaments are frequently involved. Additionally, the rectovaginal septum, ureter, and rarely the bladder, pericardium, surgical scars, and pleura could be affected. Interestingly, endometriosis is more frequently encountered in the left than in the right hemipelvis. Similarly ovarian endometriema is found more commonly in the left than in the right ovary**.** It is possible that this is related to decreased fluid movement in the left side of the hemi pelvis due to the presence of sigmoid colon.**11-15.**

ICSI is a laboratory technique in which one or more oocytes are retrieved in which fertilization is achieved by the injection of an individual sperm into each oocyte. Females with and without endometriosis have comparable ICSI clinical outcomes as regards

live birth rates, while cases with severe endometriosis have inferior clinical outcomes. There is insufficient research evidence to recommend surgical intervention routinely before undergoing ICSI management protocols**.16-20**.

2. Methodology

The current research study was conducted at ART unit Al Azhar university, on 100 cases with endometriosis were recruited in a prospective manner in research group I and 50 cases with unexplained infertility were recruited in a retrospective manner research group II to be used as a control group. Laparoscopy was conducted in unexplained and endometriosis associated infertility research group. In unexplained infertility laparoscopy was normal, in endometriosis associated infertility group consisted of untreated cases and cases that received medical or surgical management for endometriosis (ASRM State I, II, III, IV).

Inclusive research criteria

Inclusive research criteria involved the following: cases with primary infertility, first ICSI trial, study subject age range from 20 - 35 years, BMI<30, endometriosis disease of any stage, basal hormonal levels of FSH, LHIn the early follicular phase < 10 IU, regular menstrual cycle, normal serum prolactin levels and TSH within one year till implementation of treatment, at least one semen analysis in each included couple should be within normal. Endometrosis was diagnosed by laparoscopy or laparotomy and classified as minimal to mild endometriosis (American society for reproductive medicine 1/ II n = 38 or moderate to severe endometriosis (American society for reproductive medicine III/IV n=62The control research group consisted of 50 cases patients with unexplained infertility.

Exclusive research criteria

Exclusive research criteria was as follows, age < 20 or > 35 years, BMI> 30, patient with other pelvic pathology as uterine myoma or other ovarian cyst, Polcystic ovarian disease basal FSH and or LH above 10 Iu.

Ovarian stimulation

Ovarian stimulation protocol was conducted as follows: Cases in both research groups have received long protocol with long acting GnRH agonist 0.1 mg triptorelin SC daily started from mid luteal phase of the previous menstrual cycle, 3 ampoules (225 Iu) HMG have been administered from the second day of the cycle. Treatment with HMG and GnRH agonist continued daily afterwards, until and including the day of trigger for final maturation. The doses of induction was adjusted after days of stimulation, relying on the ovarian response, as assessed by E2 levels and ultrasound. As soon as three follicles reached a mean diameter of **1**8 mm, 10,000 Iu of HCG were administered IM. Oocyte retrieval, embryo transfer, luteal support Was conducted consecutively. Oocyte retrieval was conducted 34 - 36 h after the HCG injection by transvaginalsonography - guided double lumen needle aspiration. Sonographic guidance was used for all embryo transfer, which were performed 2 or 3 days post oocyte retrieval luteal support with 400 mg of micronized progesterone was initiated from embryo transfer on day 2. During the research study period the number of embryos transferred was gradually reduced from four to two. Only cycles with fresh embryos were included. Pregnancy was confirmed by serum Beta -hCG>20 Iu/L 14 days after oocyte retrieval. The day oocyte retrieval - oocyte quality and embryo grading were determined and patients were be followed for two weeks until pregnancy test. All sonographic measurements were conducted using a 7.5,6 or 5 MHZ transvaginal probe. FSH, LH, E_2 and prolactin serum levels were assayed using immulite assay kits. Analytical sensitivity was 0-1 mlu/mL for FSH 0.1 mlu/mL for LH, 15 pg/ml for E_2.

Research Outcome measures

The primary outcome measure was the pregnancy rate per case. Ongoing pregnancy and clinical pregnancy were defined as the presence of gestational sac with fetal hear beat detection at 5 - 7 weeks of gestation, Secondly outcome measure will be number of oocyte retrieved, number of metaphase II oocyte and embryo quality.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following statistical tests were performed:

Independent-samples t-test of significance was used when comparing between two means. Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P-value <0.05 was considered significant, P-value <0.001 was considered as highly significant, P-value >0.05 was considered insignificant.

3. Results

Table (1): Comparison between group I and group II as regard quantitative data (age & BMI & FSH & LH & HMG dose & duration of stimulation) shows no statistical significant difference between groups according quantitative data.

Quantitative data	Group I: Endometriosis (N=100)	Group II: Unexplained (N=50)	t-test	p-value
Age (years) Mean±SD Range	 30.21±3.94 20-35	 29.18±2.94 20-33	2.062	0.101
BMI [wt/(ht)^2] Mean±SD Range	 27.98±2.80 18-30	 28.66±2.00 20-30	2.349	0.128
FSH Mean±SD Range	 7.31±2.49 3-15	 6.89±1.80 2.9-10	1.646	0.091
LH Mean±SD Range	 4.07±2.08 1.2-12	 3.57±1.46 1.1-8	2.272	0.134
HMG (dose) Mean±SD Range	 3198.00±1077.69 1050-6600	 3197.50±1432.94 1425-6450	0.000	0.998
Duration of Stimulation Mean±SD Range	 13.77±2.69 2-20	 13.00±2.16 10-18	1.099	0.180

This table displays no statistically significant difference between groups as regards quantitative data.

Table (2): Comparison between positive and negative pregnancy rate according quantitative data in group I.

Group I: Endometriosis	Pregnancy				t-test	
	Positive (N=31)		Negative (N=69)		t	p-value
	Mean	±SD	Mean	±SD		
Age (years)	29.42	4.41	30.01	3.46	-1.179	0.098
BMI [wt/(ht)^2]	27.87	2.70	28.03	2.86	-0.260	0.796
FSH	6.99	2.39	7.46	2.54	-0.875	0.384
LH	4.48	2.61	3.88	1.79	1.329	0.187
HMG (dose)	2900.81	1089.68	3331.52	1052.94	-1.872	0.064
Duration of Stimulation	13.97	1.97	13.68	2.96	0.491	0.624

This table reveals no statistically significant difference between positive pregnancy and negative pregnancy concerning quantitative data.

Table (3): Comparison between positive and negative pregnancy rate according quantitative data in group II.

Group II: Unexplained	Pregnancy				t-test	
	Positive (N=32)		Negative (N=18)		t	p-value
	Mean	±SD	Mean	±SD		
Age (years)	26.97	3.17	27.56	2.53	-0.674	0.504
BMI [wt/(ht)^2]	28.47	2.18	29.00	1.61	-0.902	0.372
FSH	6.19	1.52	6.48	2.25	-0.545	0.588
LH	3.53	1.55	3.64	1.33	-0.247	0.806
HMG (dose)	3167.97	1446.63	3250.00	1448.33	-0.192	0.848
Duration of Stimulation	12.78	2.28	13.39	1.91	-0.955	0.344

This table shows no statistically significant difference between positive pregnancy and negative pregnancy as regards quantitative data.

Table (4): Comparison between group I and group II as regard pregnancy shows statistically significant difference between groups according pregnancy with p-value <0.05 and positive rate in group I is 31% and group II 64% while negative pregnancy rate in group I is 69% and in group II 36%.

Pregnancy	Group I: Endometriosis (N=100)	Group II: Unexplained (N=50)	t-test	p-value
Positive	31 (31%)	32 (64%)	14.901	<0.001**
Negative	69 (69%)	18 (36%)		

This table shows statistically significant difference between groups according pregnancy using chi-square test with p-value <0.05.

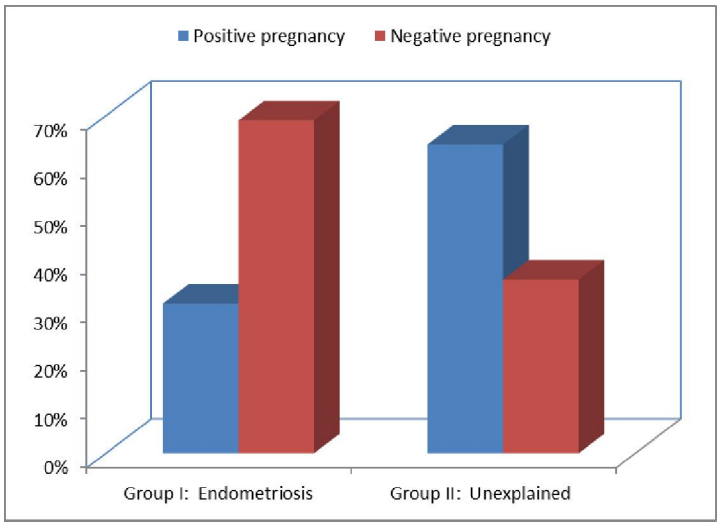

Fig. (1): Bar chart between group I and group II as regard pregnancy.

Table (5): Comparison between group I and group II as regard oocyte retrieved shows statistically significant difference.

Oocyte retrieved	Group I: Endometriosis (N=100)	Group II: Unexplained (N=50)	t-test	p-value
Mean±SD	6.71±4.34	7.38±3.78	2.349	0.017*
Range	1-18	1-20		

This table displays statistically significant difference between groups according to oocyte retrieved, using Independent Sample t-test with p-value <0.05 S

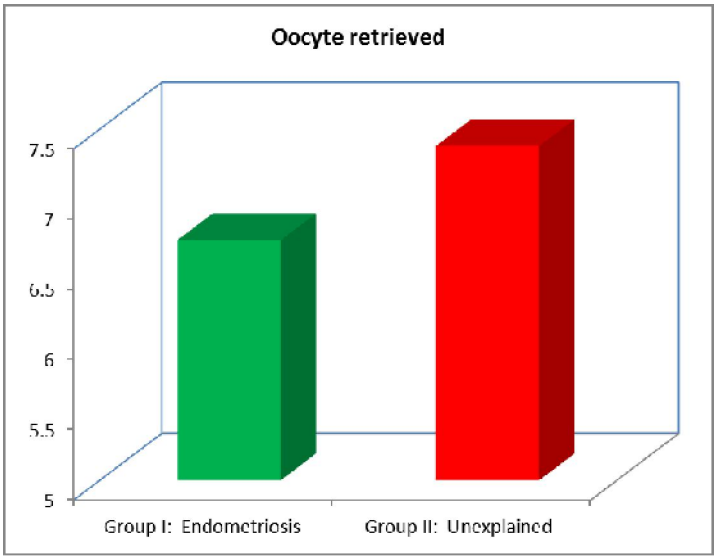

Fig. (2): Bar chart between group I and group II as regard oocyte retrieved.

Table (6): Comparison between group I and group II as regard oocyte fertilization shows statistically significant difference in group II.

Oocyte fertilization	Group I: Endometriosis (N=100)	Group II: Unexplained (N=50)	t-test	p-value
Mean±SD	3.42±2.66	4.24±0.77	9.442	0.003*
Range	1-11	1-9		

The above table displays statistically significant difference between research groups according to oocyte fertilization using Independent Sample t-test with p-value <0.05 S.

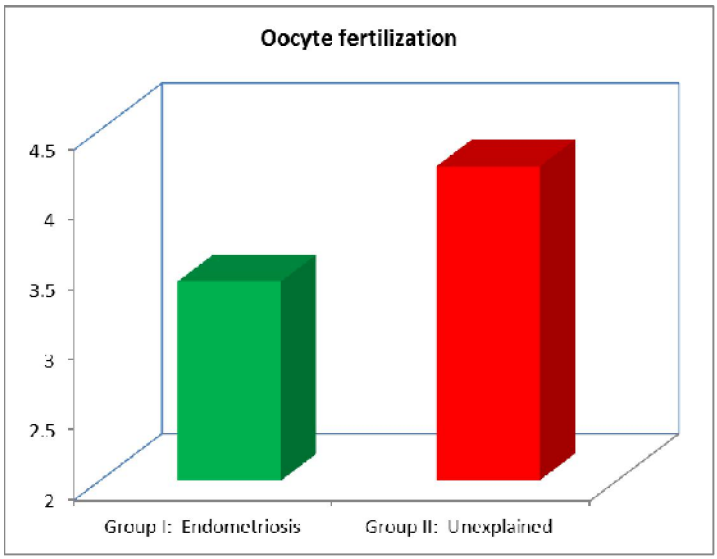

Fig. (3): Bar chart between group I and group II as regard oocyte fertilization.

Table (7): Comparison between group I and group II as regard embryos transferred shows statistically significant difference in group II.

Embryos transferred	Group I: Endometriosis (N=100)	Group II: Unexplained (N=50)	t-test	p-value
Mean±SD	2.17±0.87	2.94±0.82	3.742	0.022*
Range	1-4	1-3		

This table reveals statistically significant difference between research groups according embryos transferred using Independent sample t-test, with p-value <0.05 S.

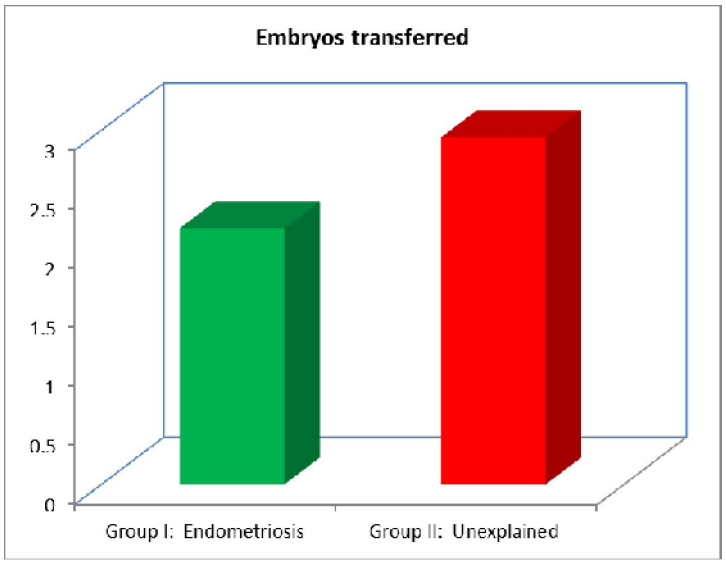

Fig. (4): Bar chart between group I and group II as regard embryos transferred.

Table (8): Comparison between group I and group II as regard fertilization rate shows statistically significant difference in group II.

Fertilization rate%	Group I: Endometriosis (N=100)	Group II: Unexplained (N=50)	t-test	p-value
Mean±SD	57.59±28.09	69.85±29.79	4.291	0.032*
Range	10-123.3	10-130		

This table shows statistically significant difference between groups according fertilization rate, using independent sample t-test, with p-value <0.05 S

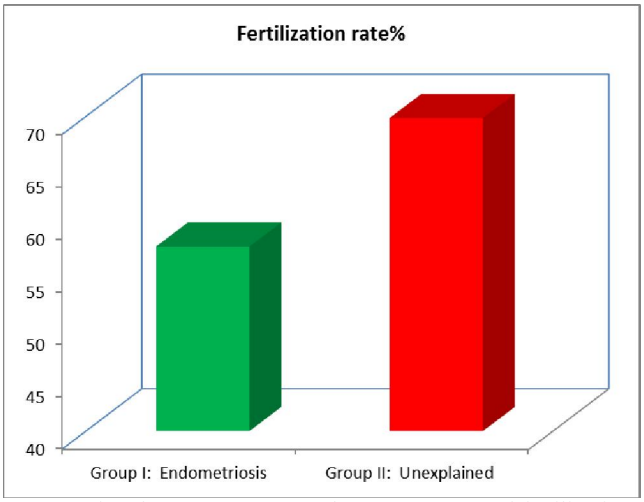

Fig. (5): Bar chart between group I and group II as regard fertilization rate.

Table (9): Intervention distribution of the group I.

Intervention	Group I: Endometriosis	
	No.	%
Untreated	35	35.0%
Treated	65	65.0%
Aspiration cyst	50/65	76.9%
Cystectomy	7/65	10.8%
Laprsco Adhysolysis	8/65	12.3%
Total	100	100.0%

This table shows that the untreated 35% and treated 65% of intervention.

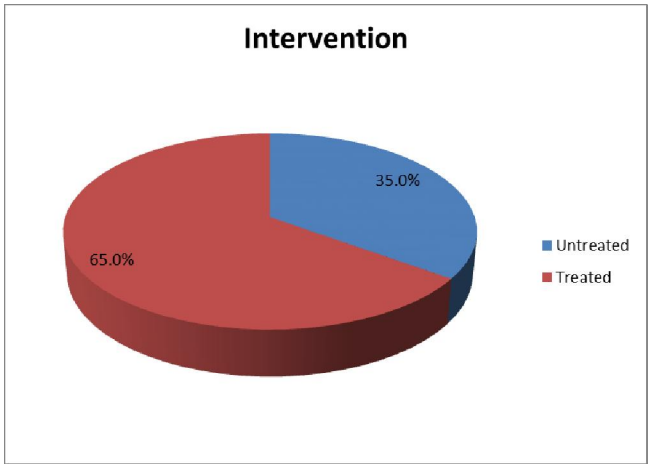

Fig. (6): Pie chart intervention distribution of the group I.

Table (10): Comparison between positive pregnancy and negative pregnancy as regard other parameter in group I, shows statistically significant difference between positive and negative pregnancy.

Group I: Endometriosis	Pregnancy				t-test	
	Positive (N=31)		Negative (N=69)		t	p-value
	Mean	±SD	Mean	±SD		
Oocyte retrieved	8.90	4.57	5.72	3.88	3.582	<0.001**
Oocyte fertilization	4.71	3.06	2.84	2.25	3.427	<0.001**
Embryos transferred	2.68	0.65	1.94	0.86	4.257	<0.001**
Fertilization rate%	68.94	28.79	52.99	27.96	2.320	0.036*

This table shows statistically significant difference between positive pregnancy and negative pregnancy as regard other parameter In group I, using Independent Sample t-test with p-value <0.05 S

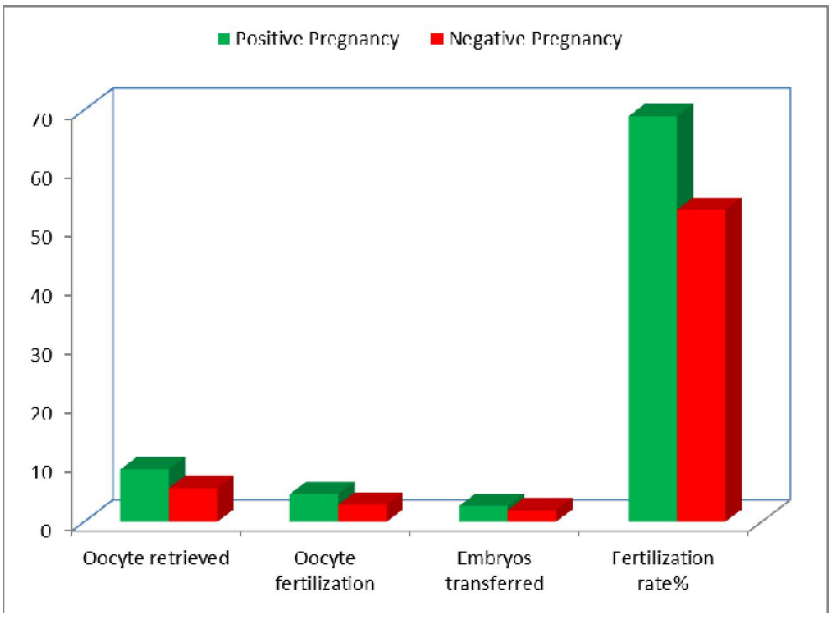

Fig. (7): Bar chart between positive pregnancy and negative pregnancy as regard other parameter in group I.

Table (1): Comparison between positive pregnancy and negative pregnancy as regard other parameter in group II, shows statistically significant difference between positive and negative pregnancy.

Group II: Unexplained	**Pregnancy**				**t-test**	
	Positive (N=32)		**Negative (N=18)**		**t**	**p-value**
	Mean	**±SD**	**Mean**	**±SD**		
Oocyte retrieved	8.06	3.91	6.17	3.29	6.650	0.013*
Oocyte fertilization	4.75	0.75	3.06	0.80	4.888	0.031*
Embryos transferred	3.63	0.80	2.72	0.83	5.458	0.024*
Fertilization rate%	76.44	31.35	53.08	28.83	4.089	0.018*

This table shows statistically significant between positive pregnancy and negative pregnancy as regard other parameters in group II using independent sample t-test, with p-value <0.05 S

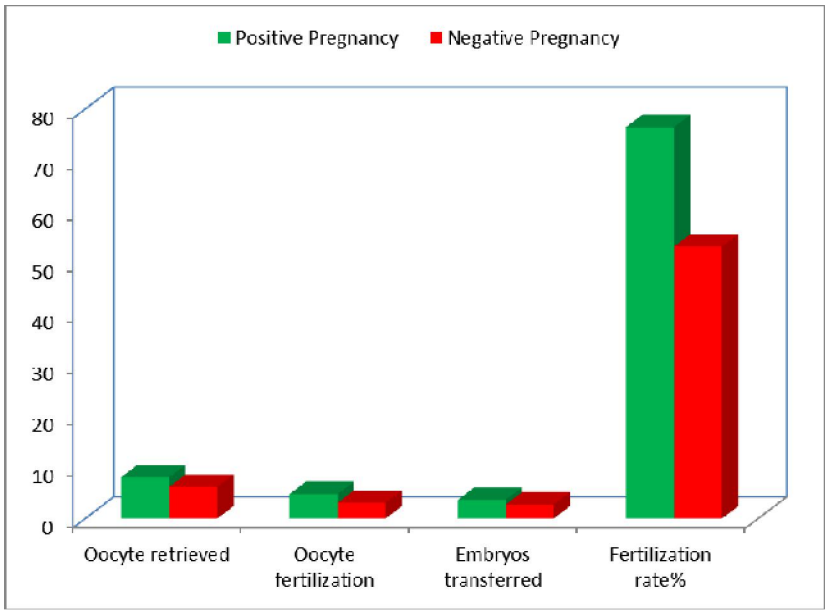

Fig. (8): Bar chart between positive pregnancy and negative pregnancy as regard other parameter in group II.

Table (2): Comparison between treated and untreated in group I as regard pregnancy rate positive rate in treated women is 35.4% and negative 64.6% and untreated women positive rate 22.9% and negative rate 77.1%, while positive pregnancy intervention treated Aspiration cyst 17 (73.9%), Cystectomy 5 (21.7%) and Laprscopic Adhysolysis 1 (4.3%), also Aspiration cyst 33 (78.5%), Cystectomy 2 (4.8%) and Laprscopic Adhysolysis 7 (16.7%) of treated of negative pregnancy.

Pregnancy	**Treated**	**Intervention**	**Untreated**	**x2**	**p-value**
Positive	23 (35.4%)	Aspiration cyst 17 (73.9%)	8 (22.9%)	5.669	0.019*
		Cystectomy 5 (21.7%)			
		Laprsco Adhysolysis 1 (4.3%)			
Negative	42 (64.6%)	Aspiration cyst 33 (78.5%)	27 (77.1%)		
		Cystectomy 2 (4.8%)			
		Laprsco Adhysolysis 7 (16.7%)			
Total	65 (100%)	----	35 (100%)		

This table reveals statistically significant difference between treated and untreated women according pregnancy using chi-square test with p-value <0.05 S

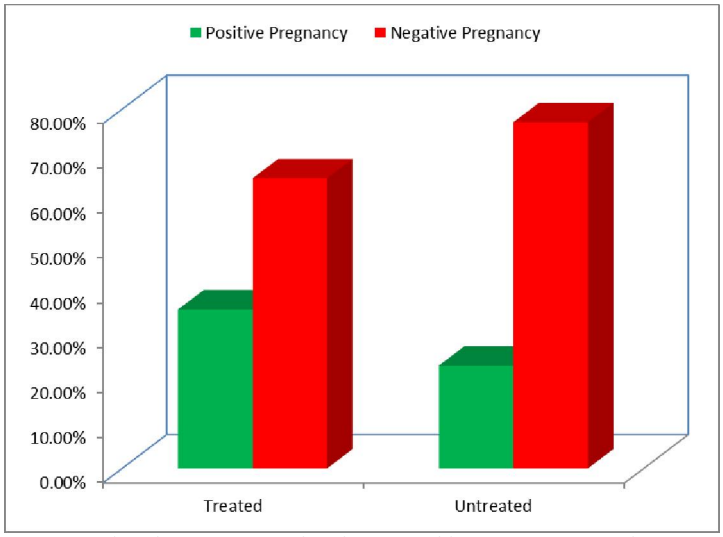

Fig. (9): Bar chart between treated and untreated in group I as regard pregnancy.

Table (3): Comparison between group I (stage I, II) and group II as regard oocyte retrieved, oocyte fertilization, embryos transferred, fertilization rate% and peak of E2.

Outcome	Group I: Endometriosis (N=38)		Group II: Unexplained (N=50)		t-test	p-value
	Mean	±SD	Mean	±SD		
Oocyte retrieved	7.76	4.16	8.38	3.78	4.440	0.013*
Oocyte fertilization	3.92	2.85	4.24	0.77	4.945	<0.001**
Embryos transferred	2.32	0.77	3.94	0.82	2.707	0.027*
Fertilization rate%	55.27	28.28	63.45	29.79	2.966	0.032*
E2	46.85	14.89	58.03	13.88	4.218	0.014*

This table shows statistically significant difference between groups according oocyte retrieved, oocyte fertilization, embryos transferred, fertilization rate% and peak of E2.

Table (4): Comparison between group I (stage III & IV) and group II as regard oocyte retrieved, oocyte fertilization, embryos transferred, fertilization rate% and peak of E2.

Outcome	**Group I: Endometriosis (N=62)**		**Group II: Unexplained (N=50)**		**t-test**	**p-value**
	Mean	**±SD**	**Mean**	**±SD**		
Oocyte retrieved	6.06	4.36	7.38	3.78	3.145	0.023*
Oocyte fertilization	2.11	2.50	3.74	0.77	5.320	0.006*
Embryos transferred	2.08	0.91	2.90	0.82	4.144	0.005*
Fertilization rate%	59.01	28.11	65.45	29.79	4.310	0.003*
E2	44.85	14.89	54.70	15.07	3.259	0.007*

This table shows statistically significant difference between groups according to oocyte retrieved, oocyte fertilization, embryos transferred, fertilization rate% and peak of E2.

Table (5): Comparison endometriosis patients with stage I & II disease with patients with stage III & IV disease as regard outcome.

Outcome	Stage I & II (N=38)		Stage III & IV (N=62)		t-test	p-value
	Mean	±SD	Mean	±SD		
Oocyte retrieved	7.76	4.16	6.06	4.36	3.272	0.008*
Oocyte fertilization	3.92	2.85	2.29	2.50	2.526	0.019*
Embryos transferred	2.79	0.77	2.08	0.91	2.251	0.026*
Fertilization rate%	55.27	28.11	59.01	28.28	2.794	0.044*
E2	43.03	13.88	36.70	15.07	2.077	0.036*

Women with severe endometriosis have a statistically significant lower pregnancy rate and implantation rate, have lower number of oocytes obtained at retrieval and a lower serum E2 concentration, there was significant difference in fertilization rate, one possible reason for this may be that lesions associated with severe endometriosis often do not have endometrial glands instead are ("burnet out" lesion resulting in pelvic adhesions. Thus it may be the secretory component of an active lesion that are affecting oocyte quality and thus fertilization.

4. Discussion

Endometriosis is a chronic inflammatory disease defined as the exsitence of endometrial - like tissue outside the uterine cavity, and common symptoms involve dysmenorrhea, dyspareunia and infertility. It affects around 20 - 40% of females who complaining of infertility; even though it could also be exist in 5 - 10% of fertile females.**21-25.**

The current research study investigated the impact of endometriosis on ICSI clinical outcome as regards pregnancy rate in comparison to unexplained infertility. The study was conducted, on 100study subjects with endometriosis represented by research group I and 50 study subjects with unexplained infertility represented by group II control group.

As regards statistical comparison between research group I and research group II concerning quantitative research indices (age & BMI & FSH & LH & HMG dose & duration of stimulation) p values (0.101,0.128,0.091,0.134,0.998,0.180, consecutively) showed no statistical significant difference between research groups

Concerning statistical Comparison between positive and negative pregnancy rates according quantitative research data in group I. (age & BMI & FSH & LH & HMG dose & duration of stimulation) p values (0.098,0.796,0.384,0.187,0.064,0.624) no statistically significant difference between positive pregnancy and negative pregnancy was displayed according quantitative data.

As regards statistical omparison between positive and negative pregnancy rates concerning research quantitative data in group II. (age & BMI & FSH & LH & HMG dose & duration of stimulation) p values (0.504,0.372,0.588,0.806,0.848,0.344) no statistically significant difference between positive pregnancy and negative pregnancy was displayed according quantitative data.

Statistical Comparison between research group I and research group II concerning pregnancy displays statistically significant difference with p-value <0.001 and positive rate in research group I is 31% and in research group II 64% while negative pregnancy rate in research group I is 69% and in research group II 36%.

Many studies consider laparoscopy is gold standard for treatment of ovarian endometrioses as operative laparoscopy is associated with a shorter hospital stay, faster patients recovery, decreased coasts and a lower incidence of de novo adhesion formation**.** Evidence indicate that the primary benefit of laparoscopic ovarian cystectomy of endometrioma is relief of pelvic pain - a cohrane review in 2008, including two randomized controlled trials, concluded that laparoscopic excision of an endometrioma is associated with a decrease in symptoms of dysmenorrhea. dyspareunia, and non-menstrual pelvic pain**.26-30.**

Several studies have demonstrated that there is a loss of follicular density in ovaries with endometrioma compared with unaffected ovaries**.** The presumptive benefit of laparoscopic ovarian cystectomy to reduce or reverse the inherently damaging effect of endometriomas on the ovarian cortex is more controversial. There may be presurgical endometriosis - mediated damage to ovarian reserve beyond the stretching of ovarian cortex than can lead to loss of primordial follicles**.3, 5,10,20,25.**

A previous research group studied pregnancy rates in women with endometrioses and found that management of infertile women with endometriomas ultrasound guided aspiration was associated with a pregnancy rate of 12% versus a conception rate of 54.2% in women who had laparoscopic removal of the cyst**.15,17,21,29.**

Another study show that laparoscopic ovarian cystectomy of endometriomas may allow for better access of follicles at the time of oocyte and increasing oocyte retrieval fertilization and pregnancy rate and this technically utility is in addition to the benefit of

preventing some pelvic infection after oocyte retrieval**,** and reduction of antibiotics should be given prior to transvaginal oocyte retrieval in patient with endometriomas according to the 2014 European Human reproduction embroyology (ESHRE) guidelines**.** In our study there were 7 patients underwent ovarian cystectomy and more than 5 oocytes retrieved in 5 patients and positive pregnancy occurred in 5 patients from 7 patients. **13,18,19,24.**

Some investigators have questioned use of the laparoscopic technique for ovarian cyst excision, particularly in the case of ovarian endometriomas because stripping of the cyst possible loss of excessive ovarian tissue, with possible loss of follicles. Some indirect evidence from the literature show that ovaries from which ovarian cysts have been excised perform worse than aspirated ovaries when patients undergo ovarian stimulation for assisted reproduction techniques**. 22,23,27,28.**

Laparoscopic excision of endometrioticovaian cysts is associated with significant reduction in functional reverse of operated ovary**.** Ultrasound guided aspiration of endometriomas have application in patient who are not good surgical candidates or who have experienced IVF failure it is consider relatively safe and non invasive**.** The largest experience reported in the literature on aspiration of endometriomas ***was on*** 41 cases with endometriomas who had failed to conceive during previous IVF programs.' These patients underwent transvaginal US guided aspiration of endometrioma before oocyte retrieval, the other reported a higher number of oocyte retrieved and higher pregnancy rate per cycle after aspiration, they concluded that the improved results probably were due to reduction of extensive ectopic endometrial tissue with improved ovarian response and enhanced follicular accessibility. **1,29,30.**

In our current research study 50 cases underwent transvaginal sonographic guided aspiration of endometriomas before oocyte retrieval resulting in more than 5 oocytes were retrieved in 28 patients and positive pregnancy in 17 patients form 50 patients.

Other advantage of sonographic guided aspiration of endometrioma it is easy performed and patients can return to normal activities shortly following the procedure**.** Multiple studies indicated that surgical excision of these cysts does not improve pregnancy rate before IVF.**26-30.**

In a prospective study comparing operated and aspirated ovaries in women who previously underwent laparoscopic cystectomy of endometriomas, a prior research group did find a lower number of developing oocytes and retrieved oocytes from the operated ovary. However there was no difference in fertilization rates or high quality embryos in these women. These results are in accordance with those of a previous research conducted that displayed reduced antral follicular count in women with prior cystectomy compared to women whose aspirated but no difference in IVF pregnancy rates per cycle. This indicate that surgical excision of endometriomas does not confer any additional benefits prior to ICSI. **16,18,20,25.**

As peritoneal endometriosis after a second laparoscopy can be diagnosed in women with previous negative laparoscopic findings, it might not be surprising that hormonal investigation in unexplained and peritional endometriosis associated infertility often yield similar results. Hormonal factors should be influenced and apparently improved with COS for unexplained and endometriosis. **8,13,17,29.**

Endometrosis and in vitro - fertilization pregnancy rates.

Recent outcome studies concerning the correlation between endometriosis and ARTs various investigator have revealed statistically significantly lower success rates in cases with endometriosis**.10,12.**

The current research study displayed higher first treatment cycle pregnancy rate after transfer of embryos in unexplained infertility group. This could indicate more viable embryos and perhaps a more agreeable environment to support a conception after ICSI in unexplained infertility cases in comparison to endometriosis associated infertility research group. Since positive pregnancy rate 64% in unexplained in comparison to endometriosis associated infertility pregnancy rate 31%.

Endometriosis and ovarian stimulation

There are substantial data from studies that investigated the effects of endometriosis on controlled ovarian stimulation. It is clear that endometriosis decrease ovarian responsiveness to gonadotropins**.** A more debatable issue remains as weather peritoneal endometriosis affects controlled ovarian hyper stimulation - in natural cycles women with minor degrees of a significantly longer follicular phase**.** This in agreement with our study that showed a significantly long follicular phase up to 20 days of stimulation in some patients. **7,11,15,28.**

Endometriosis and oocyte quality

Harlow et al, measured aromatase activity and progesterone production from freshly isolated granalosa cells in women undergoing IVF for endometriosis, unexplained infertility. Those investigators found significantly reduced steroidogenic activity in granulosa cells of patient with endometriosis, and speculated that this could affect oocyte function and fertilizing capacity. In addition, levels of interleukin - 6 and vascular endothelial growth factor are altered in women with endometriosis - with or without ovarian stimulation**.** Also this in agreement with our current research study that showed a significantly better, grades of oocytes fertilization in

unexplained in fertility compared to endometriosis associated infertility group.**14,19,22,29.**

Higher levels of inflammatory cytokines such as tumor necrosis factor and have also been demonstrated from granulosa cells obtained at oocyte retrieval in women with endometriosis**.** Thus it has been postulated that aberrant granulosa cell cytokine production in women with endometriosis may disturb the fertilizing capacity of the oocyte.**10,14,20.**

Endometriosis and fertilization

Not all cellular defects in oocyte quality could manifest numerically or morphologically. Instead it could be apparent in functional performance at the time of fertilization or implantation in natural cycle, endometriosis has been associated with statistically significantly reduced fertilization rates**.** Interestingly, ***a prior research study*** conducted in a reterospective manner investigating the impact of the stage of endometriosis on ART clinical outcomes. Those investigators found that patient with stage III - IV endometriosis has significantly reduced fertilization rates as compared with patients with mild endometriosis. Therefore this implies the fact that advanced stages of endometriosis statistically correlate inversely with fertilization capacity. Clearly this places a premium on stimulating an ample number of good quality oocyte, especially in patient with advanced endometriosis. **26,29,30.**

Endometriosis and implantation rates

Various research studies have displayed an impairment of implantation in cases with endometriosis**.** This could be due to intrinsic deficiencies within the endometrial lining or extrinsic factor that exists within the peritioneal fluid. The subendometrial myometrium is enlarged in women with endometriosis. And numerous alteration within the peritoneal fluid of cases with endometriosis have been identified. On the other hand an alternative explanation is simply that implantation rates are reduced because oocyte, and embryonic quality is impaired.**7,12,30.**

The beneficial role of GnRH analogs should not be underestimated**,** prior research studies have suggested superior clinical outcomes with prolonged down - regulation with GnRH analogs before starting ovarian stimulation in cases with endometriosis - whether this impact is due to an improved development environment or better quality oocyte is unclear but pregnancy rates improve with increase time receiving GnRH analogs in ART. **10-20.**

Conclusion

Many studies demonstrate impaired oocyte quality, decreased fertilization, and compromised implantation rates. Such finding give insight into the mechanisms by which endometriosis may impact on fertility, and provide clues as how to focus assisted reproductive technologies in order to overcome these differences. Specially, extended down regulation protocols, ampoules use of gonadotropins for ovarian stimulation, and conservative management of endometriomas have been suggested as means to optimize in vitro fertilization outcomes for women with endometriosis. Stage III, IV endometriosis means a worse prognosis for ICSI treatment compared to milder stages or unexplained infertility Overall better outcome for unexplained infertility group - compared to minimal and milder endometriosis stage I, II and moderate and sever endometriosis stages III, IV might be a guide to select diagnostic groups and be useful in patient counseling. Patient with endometriosis - associated infertility undergoing ICSI respond with significantly decreased levels of all markers of reproductive process, resulting in a pregnancy rate that is almost one half that of women with other indication for ICSI.

Recommendations:

It is important to note that although we have Demonstrated that the success with ICSI is lower for women with endometriosis compared with women without it, the overall chance of achieving a pregnancy with ICSI in this study was still very good. In addition, ICSI success rates have risen success dramatically in recent years, with proportional increases in success for women with endometriosis. Therefore, despite a lower success rate compared with that of women undergoing ICSI for other indication. ICSI is still the most successful form of assisted reproduction that can be offered to an infertile couple with endometriosis IT has already been demonstrated that the presence of endometriosis decreases pregnancy rates for couple who attempt conception without assisted reproductive care technologies on the basis these findings, we recommend that patients with endometriosis should be referred for early aggressive infertility treatment including ICST to increase chances of conception.

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