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In Vitro Fertilization (IVF) Success Rates After Surgically Treated Endometriosis and Effect of Time Interval between Surgery and IVF

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Short title: Endometriosis fertility

Precis

IVF pregnancy rate negatively correlates with endometriosis severity on laproscopy prior to IVF performance. Optimal time to perform IVF appears to be between 7-25 months after endometriosis surgery.

Abstract

Study objective: To evaluate the impact of endometriosis staging and endometriomas on IVF outcome and to assess the optimal time interval between laparoscopy and IVF.

Design: Retrospective clinical study.

Design Classification: II1

Setting: University affiliated private infertility clinic

Patients: 216 infertile patients with endometriosis and 209 infertile patients without endometriosis.

Interventions: Laparoscopy, In Vitro Fertilization (IVF).

Measurements and main Results: Patients with endometriosis were classified according to ASRM criteria: 58, 67, 63 and 28 patients had stages 1-4 disease, respectively. Patients with endometriosis had significantly lower E2 on trigger day (9986±6710 vs. 12220±9414 pg/ml, respectively) and number of retrieved oocytes (12.7±8.6 vs. 14.0±10, respectively) compared to controls. We found consistent decline in clinical and ongoing pregnancy rates with increasing stage of endometriosis. The presence of endometrioma in patients with stages 3 and 4 endometriosis did not alter IVF outcome. Patients with time interval of 7-12 and 13-25 months after surgery had favorable outcome.

Conclusions: IVF pregnancy rate was negatively correlated with endometriosis severity.

Presence of endometriomas had no impact on IVF clinical outcome. Optimal time to perform IVF appears to be between 7-25 months after endometriosis surgery

Keywords: Endometriosis, Infertility, Laparoscopy, IVF, Pregnancy rate.

Introduction

Endometriosis is a chronic inflammatory gynecological disorder characterized by the presence of endometrial tissue outside the uterus cavity, most commonly presented among women of reproductive age [1, 2]. While dysmenorrhea and dyspareunia are the most common complaints, endometriosis has higher prevalence in women presenting for infertility evaluation (25-50%) compared to general fertile population (3-10%) [3, 4, 5]. Classification systems of endometriosis, developed by several professional organizations, traditionally have been based on lesion appearance, pelvic adhesions, and anatomic location of disease [6]. Unfortunately, none of them predict clinical outcome except better fertility prediction by the endometriosis fertility index only [7].

Laparoscopy is a common approach for diagnosis and treatment of endometriosis, especially with regard to pelvic pain [8]. Surgical approach becomes specifically relevant among infertile patients, since pharmacological treatment endometriosis is associated with ovulation suppression [9]. On the other hand, its possible damage to ovarian reserve [10] should not be neglected. Laparoscopic treatment of minimal or mild endometriosis has been shown to improve pregnancy and live birth rates compared with diagnostic laparoscopy alone [3, 8, 11, 12] in both spontaneous and advanced reproductive technologies (ART) -related pregnancies [13]. Singh et al (2017) have recently recommended on surgical approach among infertile patients in various clinical scenarios such as severe pain, mild-to-moderate endometriosis and others [14].

Several studies have shown a negative effect of endometriosis on In Vitro Fertilization (IVF) pregnancy outcome [15, 16, 17, 18, 19, 20, 21], while many other studies have reported no effect [22, 23, 24, 25, 26]. In their large meta-analysis, Barbosa et al reported similar clinical outcome among patients with endometriosis treated with IVF compared to controls without correlation between endometriosis severity and clinical outcome. [27]. However, the data regarding the possible impact of laparoscopy and specific surgical interventions (ex. laser vaporization, endometrioma cystectomy etc.) on consequent IVF outcome is still unclear. One study reported an increased spontaneous pregnancy rate within the first 6 months after endometriosis surgery [28]. Others found no interval effect from surgical management and IVF regarding ovum retrieval and pregnancy rate, although in two studies there was a trend towards a reduced pregnancy rate with increasing time between endometriosis surgery and IVF [29, 30, 31].

In this study, we correlated stage of endometriosis prior to surgical treatment and the following IVF outcomes with three aspects: a) the impact of endometriosis staging after surgical treatment; b) the effect of endometriomas and c) the optimal time interval between laparoscopy and IVF.

Materials and Methods

Population

This retrospective study included charts of infertile patients who underwent both laparoscopy and autologous IVF cycle at the CReATe Fertility Center, Toronto, Canada between January 2009 and June 2014.

All included patients had infertility defined as ≥ one year of unprotected intercourse among patients younger than 35 years old or ≥6 months for patients ≥35 years of age. Pharmacological treatment for endometriosis, which commonly involves ovulation prevention such as oral

contraceptives or GnRH agonist has not been used in our attempting to conceive population. Intra uterine inseminations with or without controlled ovarian hyperstimulation were performed in cases of total motile sperm ≥ 5 million spermatozoa with documented patent fallopian tube\s prior to IVF performance. Number of COH\IUI cycles depended mainly on clinical parameters such as patients' age, infertility duration and endometriosis staging during laparoscopy as well as ovarian response to hormonal stimulation throughout these cycles (ex. E2 on trigger day, number of growing follicles).

All had undergone a diagnostic laparoscopy at either Women's College or Sunnybrook hospitals, Toronto, with treatment of any endometriosis found at the time of the surgery. Endometriosis lesions were treated by CO_2 laser vaporization or bipolar electrocoagulation of all visible endometriosis lesions, together with lysis of adhesions when possible. Patients with an endometrioma were managed with either cystotomy, drainage and irrigation; or CO_2 laser vaporization or bipolar electrocoagulation of the cyst wall, according to the surgeon’s preference and size of the cyst.

Endometriosis staging was performed utilizing the operative report, a schematic diagram made by the surgeon on the day of surgery and any photos taken. Two independent researchers (B.A. and D.B.) reviewed these documents and staging was assigned according to the American Fertility Society revised criteria (1997). Eight patients required additional evaluation by third researcher (P.S.) due to disagreement on stage between the researchers. Control group comprised women who had undergone a diagnostic laparoscopy prior to IVF cycle where no endometriosis was detected. These patients underwent laparoscopy as part of the initial work up or after failed IUI procedures before going to IVF. Most patients (92%) negative to endometriosis had normal pelvis. Others were found to have some pathology: 7 hydrosalpinx with salpingectomy, 5 simple

ovarian cyst with cystectomy, 3 paraovarian cysts only with cystectomy and 2 with minor filmy adhesions with adhesiolysis and negative biopsy for endometriosis.

Exclusion criteria were female patient age ≥ 43 years and severe male factor defines as azoospermia or oligospermia <1 million/ml.

Controlled Ovarian Hyperstimulation (COH)

Patients underwent either GnRH agonist or GnRH antagonist protocols for controlled ovarian hyperstimulation, according to physician preference. The starting FSH/HMG dose was individualized based on age, antral follicle count (AFC), anti mullerian hormone (AMH) and previous response during COH+ IUI (if previously performed). The gonadotropin throughout stimulation dose was adjusted according to ovarian response. Final follicle maturation was induced with 5,000 – 10,000 IU hCG given 36 hours prior to oocyte retrieval. Fertilization mode (IVF vs. ICSI) and number of embryos transferred were decided according to the clinical judgement of the attending physician.

Fertilization rate was defined as the ratio of zygotes with two pronuclei (2PN) observed 18-20 hours after insemination divided by the number of oocytes (MII). Implantation rate was defined as the number of gestational sacs seen on ultrasound scan 4–7 weeks after ET divided by the number of embryos transferred. Chemical pregnancies were not included in the implantation rate.

Endpoints and Statistical Analysis

Data collected included age, parity, underlying cause(s) of infertility, duration of infertility, body mass index (BMI), smoking status, AMH, mean interval from surgery to IVF, total dose of gonadotropin, days of gonadotropin stimulation, number of oocytes retrieved, number of mature

oocytes (MII), fertilized oocyte number (2PN), number of embryos transferred, clinical and ongoing pregnancies. Clinical pregnancy rate was defined as visualization of a gestational sac on the first ultrasound after embryo transfer performed during sixth gestational week. Ongoing pregnancy rate was defined as viable pregnancy (determined by fetal cardiac activity) at 12-13 weeks gestational age before referral for obstetric care. Pregnancy rate was calculated per fresh embryo transfer and per cycle initiated (which included both fresh and frozen embryo transfers). Continuous data with normal distribution were expressed as mean ± standard deviation (SD), and data with a non-normal distribution were expressed as a median. Statistical comparisons involving categorical variables were made using Pearson's chi-squared test. To investigate the association between endometriosis stage and clinical outcome, multivariate logistic regression analysis was utilized. The four clinical outcomes examined were fertilization rate, implantation rate, clinical pregnancy rate and ongoing pregnancy rate. All models were adjusted for the following confounders: age, parity, BMI, smoking status, infertility duration and AMH level. Multi-variable logistic regression analysis was also used to examine the association between interval from surgery to IVF and the ongoing pregnancy rate after controlling for age and stage of endometriosis.

University of Toronto Ethics Board approval was obtained for this study.

Results

The study included 216 patients with endometriosis and 209 controls. Endometriosis classification according to the ASRM criteria resulted with 58 patients with stage 1 disease, 67 patients with stage 2, 63 with stage 3 and 28 patients with stage 4. Therefore total of 125 patients

were had mild (stage 1+2) compared to 91 with severe (stages 3+4) endometriosis. Control group included 209 patients who had no endometriosis on laparoscopy. The only statistically demographic significant difference with regards to patients' characteristics between endometriosis and the control group was age (35.2 vs 36.4 years, p=0.003) while no differences were found regarding gravity, infertility duration, BMI, smoking and AMH.

Endometriosis was characterized by impaired ovarian response to hormonal stimulation. Patients with endometriosis had significantly lower E2 on trigger day (9986 ±6710 vs. 12220 ±9414 pg/ml, respectively, p=0.01) and number of retrieved oocytes (12.7±8.6 vs. 14.0±10, respectively, p=0.03) compared to controls. Impaired response was found among advances endometriosis stages, as 11.9±9.3 oocytes were retrieved among patients with severe endometriosis compared to 13.3±8.1 in the mild cases ($p<0.05$, table 1). No significant difference was demonstrated specifically between the 4 endometriosis stages (data not shown).

IVF clinical outcomes were evaluated by fertilization, implantation and pregnancy rates (FR, IR and PR, respectively). FR among all patients with endometriosis was 70% compared to 67.1% among controls ($p>0.05$). Furthermore, FR of 66%-74% was found among stages 1-4. No significant differences were demonstrated between either endometriosis patients and controls or endometriosis subgroups. IR was similar among all cohorts as well: 23.6%-30% in the endometriosis subgroups, 27.7% in total endometriosis group and 29% among control ($p>0.05$). Interestingly, our results demonstrate a consistent decline in clinical and ongoing pregnancy rates with increasing stage of endometriosis. Patients with severe endometriosis (stages 3 and 4) had significantly lower clinical and ongoing PR per fresh ET compared to controls (35% vs. 44.5%, respectively, p=0.03 and 29% vs. 38.8%, respectively, p=0.023). Severe endometriosis (stages 3 and 4) and the total endometriosis cohort had significantly lower clinical and (45% and 50%,

respectively) and ongoing PR per cycle (36% and 41%, respectively) compared to controls (54% and 46%, respectively, all $p<0.05$).

Twenty five (40%) among patients with stage 3 endometriosis had unilateral endometrioma, while 93% (26/28) of patients with stage 4 endometriosis had at least one endometrioma. 44 (86%) underwent ovarian cystectomy, 3 (6%) had only incision and drainage, 2 (4%) had bipolar electrocoagulation, 1 (2%) had Co2 laser vaporization to the endometrioma cyst wall, and frequent irrigations were performed in cases of cyst spillage. Therefore, majority of patients had an ovarian cystectomy which reflects on data homogeneity. The presence of endometrioma in patients with stages 3 and 4 endometriosis did not alter ovarian response to hormonal stimulation or clinical outcome compared to patients without endometrioma (table 2).

All patients with endometriosis were divided to five interval groups between laparoscopy and IVF cycle. Those with time interval of 7-12 and 13-25 months after surgery had favorable outcome with significantly higher PR compared to those with 0-3 months used as control. In comparison to the first interval group (0-3 months), women with endometriosis that had their IVF at an interval of between 7 and 25 months from surgery had a significant higher ongoing pregnancy rate as shown. Interval group of 4-6 months had a higher ongoing pregnancy rate than the 0-3 months and >25 months, but this did not reach significance (table 3). Interestingly, IVF performance interval from laparoscopy among patients with bilateral endometrioma was distributed as: 0 for 0-3 months, 2 for 4-6 months, 1 for 7-12 months, 4 for 13-24 months and 5 patients for the duration >24 months. These low numbers, accompanied with homogenous surgical intervention of 86% treated by cystectomy, prevented reliable statistical stratification by unilateral vs. bilateral endometriomas or by surgical technique.

Discussion

Endometriosis is one of the most common gynecological pathologies with well-known negative impact on female fertility [4]. Several classifications systems have been suggested with limited success to achieve consensus [6]. However, the impact of surgical treatment for reproduction capability in both mild [11] and severe [32] endometriosis remains controversial. The current study focused on the revised ASRM classification systems, which has been published in 1997 and became a popular methodology during the clinical and academic evaluations of endometriosis. To the best of our knowledge, the current research adds initial possible prognostic value for that staging system.

The current study resulted with impaired ovarian response to hormonal stimulation among endometriosis patients compared to control as previously described [27] in spite of significantly higher average age in control group. That decline seems to be related to endometriosis severity. Moreover, we found reduced pregnancy rates among patients with endometriosis compared to controls, further supported by consistent decline over endometriosis exacerbation. Patients with stage 1 endometriosis had 55% and 50% clinical and ongoing PR, respectively, while those with stage 4 had only 43% and 32%, respectively. These results confirm prior published data regarding the correlation between endometriosis severity and infertility [33] and may be explained by increased pelvic inflammatory response and oxidative stress [34, 35]. Additional explanation may arise from exacerbating surgical approach among patients with advanced pathology, which may impair ovarian reserve in cases of ovarian involvement.

Barnhart 2002 concluded that patients with mild and severe endometriosis had 30% and 48% lower pregnancy rate than controls respectively [15]. Our results showed clinical and ongoing

pregnancy rate per cycle to be lower than the control group by 1.8 and 2.2% in patients with mild endometriosis and 17 & 22% in patients with severe endometriosis, respectively. This is consistent with a recent meta-analysis by Harb 2013 who concluded that patients with mild and severe endometriosis had 6% and 21% lower pregnancy rate then the control group respectively [18]. Hamdan et al, 2015, found no significant difference in IVF live birth, rate but lower pregnancy rate in patients with endometriosis, in comparison to patients without it. In their subgroup analysis, there was a lower pregnancy and live birth rate in patients with severe (stages 3&4) endometriosis in comparison to patients without endometriosis [17].

The presence of endometrioma did not have an impact on IVF outcome, when comparing patients with severe (stages 3 and 4) endomentriosis. Management of endometriomas prior to IVF remains controversial. Some previous studies found no difference in clinical pregnancy rates between surgery for endometriomas vs. expectant management prior to ART [36, 37, 38]. In contrast, Opøien et al found a lower pregnancy/live birth rate in patients with at least one endometrioma in comparison to patients without it [13]. Two meta-analysis showed a significant postoperative decrease in circulating AMH after endometrioma excision [39, 40], while a more recent meta-analysis showed no significant postoperative AFC decrease [41].

Interval from endometriosis surgery to IVF had a significant effect on pregnancy rate in our study. After controlling for age and stage of endometriosis, we found that the highest ongoing pregnancy rate was achieved in patients who underwent their IVF cycle 6-25 months after their endometriosis surgery. IVF delay may be considered to around 6 months from endometriosis surgery but no more than 25 months. While the exact mechanism for impaired fertility during the first 6 months remains to be investigated, reduced pregnancy rates after 2 years may be explained by either endometriosis recurrence and/or age factors. Previous studies found no effect of

interval from surgical management of endometriosis and IVF ovum retrieval on pregnancy rate [29, 30] while Nesbitt-Hawes et al have reported 12 and 13 months median time among patients who conceived naturally or by ART, respectively, following laparoscopy for stages III-IV endometriosis [32]. However, unlike current study, they did not divide their cases into smaller intervals for a more detailed analysis.

The current has several limitations. The major limitation of this study is its retrospective nature which involves dominance of clinical management during patients' management and the lack of live birth rate evaluation as our primary outcome. Second, the surgical approach to treating endometriosis was not uniform including the surgical treatment for endometriomas, although most cases were treated by cystectomy. Photos absence or presence may be related as potential bias on measured outcome. On the other hand, we believe that inclusion of patients who underwent laparoscopy without endometriosis improved the reliability of our control group. Third limitation arises from the lack of specific percentages of GnRH agonist vs. antagonist cycles.

In conclusion, IVF pregnancy rate was negatively correlated with severity of endometriosis. The presence of endometriomas had no impact on IVF outcome. Optimal time to perform IVF appears to be between 7 and 25 months after endometriosis surgery. While several publications have emphasized to possible positive impact of laparoscopy on pregnancy rates especially in minimal-mild stages I-II, we feel that laparoscopy's cost effectiveness in advances disease is still far from being confirmed. However, the current study is important and relevant for both surgeons and reproduction specialists due to the high incidence of endometriosis among infertile patients and the importance of the surgical approach for treating endometriosis. We hope that the long-

term study period and large sample size will contribute to the existing literature in that controversial clinical discussion.

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394 **Table 1:** IVF stimulation parameters

	Stages 1+2 (mild)	Stages 3+4 (severe)	P value	All endometriosis	Control	P value
No. of patients	125	91		216	209	
P4 HCG day (pg/ml)	3.83±2.2	5.19±5.6	NS	4.4±4.0	4.1±3.6	NS
E2 day (pg/ml)	9998 ±5956	9968 ±7706	NS	9986 ±6710	12220 ±9414	0.01
Mean days of Gonadotropins	10.6±1.5	10.7±2.0	NS	10.7±1.7	10.5±1.8	NS
Total FSH (i.u.)	3718±1690	4117±1799	NS	3882±1743	3781 ±1626	NS
Retrieved oocytes	13.3±8.1	11.9±9.3	0.046	12.7±8.6	14.0±10	0.03
Mature oocytes	7.7±4.6	6.7±6.3	NS	7.3±5.4	7.8±4.9	NS
2PN	6.3±4.7	5.6±5.2	NS	6±4.9	6.8±6.0	NS

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398 **Table 2:** Outcome of the first fresh cycle in patients with ASRM stage III-IV with and without

399 an endometrioma

	Endometrioma	**No Endometrioma**	**p-value**
No. of Patients	51	40	
Stage 3	25	38	
Stage 4	26	2	
Total dose of FSH	4088 ±1741	4185 ±1800	0.83
Fertilization rate	72% (182/254)	70% (131/186)	0.55
Implantation rate	20% (22/110)	20% (16/82)	0.61
Clinical pregnancy	43% (22/51)	47% (19/40)	0.48
Ongoing pregnancy	37% (19/51)	35% (14/40)	0.8

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403 **Table 3:** Interval groups between endometriosis surgery and IVF-ET.

Interval group (months)	Patients	Ongoing PR*	*p* value	OR* (95% CI)
0 – 3	43 (20%)	32.5% (14/34)	-	-
4 – 6	44 (20.4%)	38.6% (17/44)	0.3	1.59 (CI: 0.64-4.57)
7 – 12	44 (20.4%)	50% (22/44)	0.02	2.58 (CI: 1.22-8.52)
13 – 25	42 (19.2%)	52.4% (22/42)	0.01	2.66 (CI: 1.35-9.87)
>25	43 (20%)	32.5% (14/43)	0.15	1.36 (CI: 0.77-6.40)

404 *PR – Pregnancy rate; OR – Odds ratio; CI – Confidence interval.

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