

Original Article

Determining the Fertility Benefit of Controlled Ovarian Hyperstimulation With Intrauterine Insemination After Operative Laparoscopy in Patients With Endometriosis

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ABSTRACT **Study Objective:** To determine the fertility benefit of controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI) in surgically treated endometriosis.
Design: Retrospective cohort study (Canadian Task Force classification II-2).
Setting: Cleveland Clinic Foundation, tertiary care center.
Patients: Ninety-six women of reproductive age who underwent operative laparoscopy to treat endometriosis-related infertility (endometriosis stage I/II n = 67; stage III/IV n = 29) from 2001 to 2011 at the Cleveland Clinic Foundation.
Interventions: COH via letrozole, clomiphene, or gonadotropins, with or without IUI.
Measurements and Main Results: Kaplan-Meier estimations of cumulative pregnancy rates were compared by stage between COH/IUI and spontaneous cycles. Patients with stage I/II endometriosis attempted spontaneous pregnancy for 669 months and 216 COH + IUI cycles, and patients with stage III/IV endometriosis attempted spontaneous pregnancy for 379 months and 74 COH + IUI cycles. Crude pregnancy rates were 45.7% in stage I/II and 40.5% in stage III/IV. Twelve-month cumulative pregnancy rates in stage I/II were 45% for spontaneous attempts and 42% for COH + IUI, and in stage III/IV were 20% for spontaneous attempts and 10% for COH + IUI (not significant). Cumulative pregnancy rates for COH/IUI in stage I/II were significantly higher than in stage III/IV. Monthly fecundity rates were 3.81% for stage I/II spontaneous, 4.59% for COH/IUI, 3.05% for stage III/IV spontaneous, and 1.68% for COH/IUI (not significant).
Conclusions: COH + IUI did not improve pregnancy rates in any stage of endometriosis. In stage III/IV we recommend post-operative in vitro fertilization. Journal of Minimally Invasive Gynecology (2014) 21, 101–108 © 2014 AAGL. All rights reserved.

Keywords: ASRM staging system; Controlled ovarian hyperstimulation; Endometriosis; Intrauterine insemination; Laparoscopy

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Infertility affects as many as half of women with endometriosis [1]. Investigations of operative laparoscopy to address endometriosis-related infertility generally have been favorable. In a randomized controlled trial, Marcoux et al [2] found significantly different monthly fecundity rates of 4.7 and 2.4 pregnancies per 100 person-months in operative laparoscopy and diagnostic laparoscopy groups, respectively. However, in a similar study, Parazzini [3] found no significant difference between the 12-month cumulative pregnancy rates for operative and diagnostic laparoscopy in stage I/II

endometriosis. While no randomized controlled trials have been performed for stage III/IV endometriosis, a systematic review cited a postoperative monthly fecundity rate of about 2% to 3% [4], and a prospective study showed a 12-month cumulative pregnancy rate of 40% [5]. Because the postoperative monthly fecundity rate in endometriosis stage III/IV remains suboptimal for achieving pregnancy [4], additional fertility interventions must be considered. For example, controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI) in surgically treated endometriosis has had variable success in matching fertility rates of the reference population, women with unexplained infertility. In 2006, Werbrouck et al [6] reported cumulative pregnancy rates of 21% in surgically treated stage I endometriosis, 18.9% in stage II endometriosis, and 20.5% in women with unexplained infertility. Conversely, Omland et al [7] found significantly different crude pregnancy rates of 16.3% in stage I/II endometriosis and 33.6% in unexplained infertility. Not all patients with endometriosis in the study by Omland and colleagues underwent operative laparoscopy before COH + IUI, however; thus the true success of COH + IUI after surgery remains unclear. In addition, the aforementioned studies were dedicated to milder stages of endometriosis, perhaps given the body of evidence that supports in vitro fertilization (IVF) over COH + IUI in women with stage III/IV endometriosis [8,9]. Cost-benefit analysis demonstrated that 4 cycles of ovulation induction via IUI resulted in similar pregnancy rates as with IVF, and with less financial burden [9]. Given the favorable cost-profile of COH + IUI over IVF, some clinicians argue for use of COH + IUI before IVF [10]. However, the field lacks consensus as to how to proceed with persistent postoperative infertility, and assessing the actual fertility or utility of COH + IUI in advanced endometriosis may help guide treatment protocols in affected patients. The objective of the present study was to assess the usefulness of COH + IUI after operative laparoscopy in all stages of endometriosis. It was hypothesized that COH + IUI would be superior to spontaneous attempts at achieving pregnancy in women with surgically treated stage I/II endometriosis but that COH + IUI would not improve pregnancy rates beyond those of spontaneous attempts in surgically treated stage III/IV endometriosis.

Material and Methods

This retrospective study included a cohort of patients who underwent ablative or excisional operative laparoscopy to treat endometriosis-related infertility at the Cleveland Clinic Foundation between 2001 and 2011. Endometriosis was staged according to the updated 1996 ASRM (American Society for Reproductive Medicine) classification criteria [11]. If no stage was specified in the operative report, an experienced reproductive surgeon staged the disease according to the ASRM criteria on the basis of documented operative findings. We surveyed for pregnancy outcomes using medical reviews of the updated electronic medical record (Epic

Systems Corp., Verona, WI) and/or telephone follow-up. A standardized telephone script was created to model our online data collection form. Our institutional review board approved the final protocol and script (application No. 11-486).

Inclusion and Exclusion Criteria

The study included women with a clinical diagnosis of infertility (defined as actively attempting pregnancy for ≥ 12 continuous months before surgery) who underwent operative laparoscopy to treat endometriosis between 2001 and 2011 at the Cleveland Clinic Foundation, were between the ages of 18 and 35 years at the time of surgery, had an operative report from the Cleveland Clinic Foundation within the electronic medical record, and had undergone assessment of at least one patent fallopian tube via hysterosalpingography or laparoscopic chromotubation. In certain patients with endometriosis, surgery may have initially been indicated to treat pain; however, if they also experienced infertility before the surgery they were included. We would have preferred to exclude patients with additional causes of infertility; however, a large percentage of patients who met the inclusion criteria had multiple contributors to infertility, and these patients were included if the associated condition was mild. Specifically, those with mild male factor (<20 million but >10 million motile sperm per ejaculate before washing), uterine myomas with a normal uterine cavity, ovulatory dysfunction, and polycystic ovarian syndrome were included. In all groups, patients were excluded who proceeded directly to IVF after surgery or underwent IVF during a COH + IUI treatment cycle after sonographic detection of ≥ 4 follicles >1.8 cm. Patients with documented abnormal partner semen analyses (<10 million motile sperm per ejaculate) were excluded.

Patient Identification and Recruitment

Patients with endometriosis were identified by extracting all patients from our electronic medical record system who had undergone surgery to treat endometriosis. To identify the COH + IUI cohort, this endometriosis list was cross-matched with a separate list containing the medical record numbers of all patients who had undergone COH + IUI from 2001 to 2011. The remaining patients with endometriosis who met our criteria were part of the spontaneous cohort.

Electronic medical records were searched for baseline data including date of birth, body mass index at surgery, duration of infertility before surgery, date of laparoscopy, stage of endometriosis, extent and treatment of ovarian disease, confirmation of endometriosis via pathology, additional diagnoses related to infertility, partner's semen count, and postoperative hormone levels (including estrogen, progesterone, follicle-stimulating hormone, luteinizing hormone, and anti-müllerian hormone) if available. Pregnancy outcome data were then extracted from the electronic medical

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