Induction of Ovulation by Clomiphene Citrate Following Laparoscopic Surgery for Endometriosis Stage I and Stage II with and without Suppression by Dienogest (A Randomized Controlled Trial)

Thesis

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Abstract

The main adverse effect of dienogest was irregular vaginal bleeding experienced by about half of the patients in the first group. Other adverse effects but less prominemt were headache and breast tenderness.

All these patients discontinued the dienogest or OI before performing a pregnancy test. In group A 153 (36%) out of 424 had a positive pregnancy test. In group B, 98 patients (23.3%) had a positive pregnancy test. This shows that dienogest suppression of endometriosis prior to induction increases live birth rate.

Key words: Ovulation induction - Intra uterine insemination - Intra cytoplasmic sperm injection - Invitro fertilizetion

INTRODUCTION

Endometriosis is a chronic disease primarly affecting women of childbearing age, in which endometriotic lesions form outside the uterus, typically leading to painful symptoms, fatigue and infertility. Endometriosis affects approximately 10% of women of reproductive age, with a peak incidence in the age range of 25-30 years ***(Rogers et al., 2009; Nasir and Bope, 2004; Eskenazi and Warner, 1997)***. Up to 50% of women with endometriosis experience infertility ***(Holoch and Lessey, 2010)***. Estimates of prevalence based upon visualization of the pelvic organs include the following: 1 percent of women undergoing major surgery for any gynecologic indication, 1 to 7 percent of women undergoing tubal sterilization, 12 to 32 percent of women of reproductive age undergoing laparoscopy to determine the cause of pelvic pain, 9 to 50 percent of women undergoing laparoscopy for infertility versus 6.7 percent of women undergoing laparoscopy with no past infertility, 50 percent of teenagers undergoing laparoscopy for evaluation of chronic pelvic pain or dysmenorrhea ***(Missmer et al., 2004)***.

Data analysis of 909 women demonstrated that the average annual total cost per woman was €9579. Costs of productivity loss of €6298 per woman were double the health care costs of €3113 per woman. Health care costs were mainly due to surgery (29%), monitoring tests (19%) and hospitalization (18%) and physician visits (16%) ***(Simoens et al., 2012)***.

It is hypothesized that minimal or mild endometriosis is associated with overproduction of prostaglandins, metalloproteinases, cytokines, and chemokines, and that the resulting inflammatory process impairs ovarian, peritoneal, tubal, and endometrial function, leading to defective folliculogenesis, fertilization, and or implantation ***(Gupta et al., 2008)***.

The major pelvic adhesions present in advanced endometriosis may contribute to reduced fertility by impairing oocyte release, blocking sperm entry into the peritoneal cavity, or inhibiting tubal pickup. The functional mechanisms discussed above for mild/moderate disease probably also contribute to impaired fertility in women with advanced stage disease ***(Pal et al., 1998)***.

Reduced pregnancy rates for women with advanced endometriosis (compared to women with early stage endometriosis or tubal factor infertility) may also be due to premature depletion of the ovarian follicle pool, abnormal folliculogenesis, or reduced fertilization potential of oocytes ***(Pal et al., 1998)***.

There is no permanent cure for endometriosis. As stated by the American Society for Reproductive Medicine, "Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures" ***(Huntington and Gilmour, 2005)***.

A reasonable approach to treatment is to Initially identify and treat all reversible causes of infertility in the couple. For women under 35 years of age, a reasonable approach is laparoscopy with resection of endometriosis, if present, followed by an extended period (up to six months) of attempted conception before resorting to ovulation induction (trial of clomiphene then gonadotropin injections) plus 1UI. Alternatively, clinicians may proceed directly to clomiphene and 1U1. In older women, however, clinicians may skip laparoscopy and move directly to gonadotropin induction plus IUI or, if laparoscopy is performed and endometriosis can be resected, decrease the length of the post-surgical period before attempting ovulation induction (trial of clomiphene then gonadotropin injections) plus IUI. The more rapid pace to intervention in older women is to ensure that if IVF is necessary, the treatment will be started before the ovarian follicle pool wanes and the success of IVF decreases. In women with high stage disease, moving directly to IVF is an option ***(Hughes et al., 2007)***.

Specific medical therapies that are approved for the treatment of endometriosis include gonadotropin-releasing hormone (GnRH) agonists, danazol, and certain progestins. These agents and the combined oral contraceptives (COCs) share a common hormonal mechanism of action in endometriosisJIowever A Cochrane review of 23 trials including over 3000 women addresses the latter question. It

demonstrated no difference in pregnancy rates with preceding ovulation suppression with oral contraceptives, progestins, or danazol in subfertile women with endometriosis (OR 1.02, CI 0.70 to 1.52, p=0.82). Therefore, while oral contraceptive pills, progestins, and GNRH agonists can be very effective in treating symptoms of endometriosis before and after pregnancy, pretreatment with these agents does not appear to improve fecundity and therefore implementation of medical management will only delay attempts at conception ***(Hughes et al., 2007)***.

Dienogest is an oral progestin that has been investigated systematically for the treatment of endometriosis in dose-ranging, placebo-controlled, active comparator-controlled, and long-term trials performed in Europe and Japan ***(Telimaa, 1987; Lippert and Mueck, 1995)***.

Based on the available data, dienogest provides complete ovulation inhibition at a daily dose of 2 mg ***(Oettel et al., 1999; Klipping et al., 2010; Moore et al., 1999).*** Women with endometriosis may desire pregnancy once sufficient pain relief is achieved. Recent pharmacodynamic data in volunteers indicate that ovarian activity resumes rapidly (range 1-43 days) after cessation of dienogest ***(Klipping et al, 2010).*** These observations support studies that describe a prompt return to fertility (e.g., mean about 30 days) and include cases of

successful pregnancy in women with endometriosis following the cessation of dienogest treatment 2 mg daily for durations up to one year ***(Momoeda and Taketani, 2007; Petraglia et al., 2011; Momoeda et al., 2009).***

AIM OF THE WORK

This study aims at investigating the fertility outcome of endometriosis suppression with dienogest 2mg / day for 3 month followed by induction of ovulation for 3 month in endometriosis patients stage I and II.

Research hypothesis:

There is an advantage for the fertility outcome of endometriosis suppression with dienogest 2mg / day for 3 month followed by induction of ovulation for 3 month in endometriosis patients stage I and II.

Research Question:

Does Dienogest 2mg daily increases pregnancy rates in patients with endometriosis with suppression with dienogest 2mg / day for 3 month followed by induction of ovulation for 3 month in endometriosis patients stage I and II.

Chapter 1
EPIDEMIOLOGY OF ENDOMETRIOSIS

Endometriosis is a common gynecologic condition that affects 5% to 15% of reproductive-age women and up to 3%-5% of postmenopausal women ***(Viganò et al., 2004)***.

The number of women with endometriosis is estimated at 7 million in the United States and over 70 million worldwide ***(Vinatier et al., 2001),*** and in industrialized nations, it is one of the foremost gynecologic causes of hospital admission ***(Vercellini et al., 2007).***

Endometriosis is defined as the implantation of endometrial stroma and/or glandular epithelium at extrauterine sites ***(Gao et al., 2006),*** and may involve several structures, including the ovaries, peritoneum, uterosacral ligaments, retrocervical area, rectovaginal septum, rectum, sigmoid colon, terminal ileum, vermiform appendix, bladder, and ureters ***(Vinatier et al., 2001; Vercellini et al., 2007; Arruda et al., 2003; Abrao et al., 2006; Podgaec et al., 2008).***

Although some patients are asymptomatic, most have clinical manifestations of varying intensity. The main symptoms of endometriosis are dysmenorrhea, chronic pelvic pain, infertility, deep dyspareunia, cyclic intestinal and urinary symptoms (such as pain or bleeding on defecation/urination during the menstrual period). Delays in diagnosis may be

explained by the nonspecific nature of symptoms and, in some cases, by impaired access to specialized diagnostic modalities ***(Vinatier et al., 2001; Arruda et al., 2003; Stefansson et al., 2002; Hemmings et al., 2004; Kashima et al., 2004; Heilier et al., 2007; Petta et al., 2007)***.

Furthermore, practices that may decrease exposure to estrogen, such as physical exercise and smoking, appear to confer protection ***(Vercellini et al., 2007; Lebovic et al., 2001),*** some aspects of endometriosis are still the subject of research. Investigations have placed particular emphasis on the etiology and pathogenesis of the condition, as an understanding of the causal mechanisms behind formation of endometriotic lesions would help direct efforts towards improved diagnosis and management ***(Abrão and Podgaec, 2004; Podgaec and Abrão, 2004).***

A case series assessed epidemiological and clinical data from 892 consecutive patients that underwent laparoscopy with histological confirmation of endometriosis at the Endometriosis clinic of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo Department of Gynecology. Results Mean patient age was 33.2 ± 6.3 years (mean ± SD). Most patients were white (78.7%) and married or in stable domestic partnerships (69.5%).

The prevalence of higher levels of educational attainment was remarkably high; as shown in Table 1, 76.9% of patients in

the sample had completed secondary education or obtained a higher degree. Approximately 5.3% of patients reported a family history of endometriosis in first-degree relatives. Analysis of obstetric history showed that 56.5% of patients were nulliparous and that, of the 387 remaining patients (43.4%), 191 had been pregnant only once (49.3%). Tables 2 and 3 show the presenting complaints reported by the 892 patients in the study sample. Table 2 shows the most common chief complaint of patients with endometriosis, whereas Table 3 lists all objective symptoms reported. Table 2 shows dysmenorrhea as the most common presenting symptom, with a prevalence of 62.2%. However, when all symptoms were considered rather than the chief complaint alone, chronic pelvic pain and dyspareunia were most prevalent, reported by 56.8% and 54.7% of patients respectively. Infertility was also a prevalent symptom, reported by 355 patients (39.8%); however, 237 patients (26.6%) claimed they had never tried to become pregnant. Table 4 shows the surgical staging of patients in the sample. The prevalence of advanced (stage III and IV) disease was 66.4%, showing the severity of endometriosis.

Table (1): Demographic data on patients with athoanatomical diagnosis of pelvic endometriosis (n = 892)

	n	%
Race or skin color		
White	702	78,7%
Black	143	16,0%
Yellow (Asian)	41	4,6%
N/A	6	0,7%
Marital status		
Married / Dom. partner	620	69,5%
Divorced	40	4,5%
Single	224	25,1%
Widowed	5	0,6%
N/A	3	0,3%
Educational attainment		
Primary	189	21,2%
Secondary	223	25,0%
Higher	463	51,9%
None	7	0,8%
N/A	10	1,1%
Total	**892**	**100,0%**

Table (2): Chief complaints of patients with endometriosis

Chief Complaint	n	%
Cyclical urinary complaints	1	0,1%
Cyclical intestinal complaints	33	3,7%
None (asymptomatic)	23	2,6%
Dysmenorrhea	555	62,2%
Deep dyspareunia	19	2,1%
Chronic pelvic pain	119	13,3%
Infertility	125	14,0%
Total	892	100,0%

Table (3): Symptoms reported by patients in the sample

Symptoms reported	n	%
Incapacitating dysmenorrhea	253	28,4%
Chronic pelvic pain	507	56,8%
Infertility	355	39,8%
Cyclical intestinal complaints	431	48,3%
Cyclical urinary complaints	104	11,7%
Deep dyspareunia	488	54,7%

Table (4): Surgical staging

	n	%
Stage		
I	133	14,9%
II	166	18,6%
III	208	23,3%
IV	385	43,1%
Total	**892**	**100,0%**

Endometriosis is rare before menarche, and its frequency tends to decrease after menopause ***(Heilier et al., 2007; Parazzini et al., 2004).*** Mean patient age is 33.2 years, which is consistent with prior reports ***(Arruda et al., 2003),*** of women presenting with infertility and those presenting with pain and related complaints. In a ***2003*** study, ***Arruda et al.*** found a mean age at diagnosis of 30 years for women presenting with infertility and 33 years for those presenting with pain.

A review of the literature shows endometriosis prevalence rates of up to 97% in Caucasian women; some studies have also reported predominance in Japanese women ***(Viganò et al., 2004; Hemmings et al., 2004; Kashima et al., 2004).***

A major difference in prevalence was also found between black and Asian women. In ***2002, Kuohung et al.*** found a similar patient age range in endometriosis patients from the United States and United Kingdom, but reported a significant predominance of white (88%) versus non-white patients (13%) ***(Kuohung et al., 2002).***

Women with endometriosis tend to have higher educational attainment and socioeconomic level ***(Stefansson et al., 2002; Hemmings et al., 2004).*** Accordingly, 51.9% of women in the study sample had a college- or university-level education. This may simply be due to bias, as women of higher socioeconomic standing have greater access to medical care and are more concerned with personal health in the event of pelvic pain or infertility ***(Stefansson et al., 2002; Parazzini et al., 2004; Makhlouf et al., 1986; Van Langendonckt et al., 2002).***

Regarding obstetric history, nulliparity has consistently been reported as having a strong association with endometriosis ***(Kuohung et al., 2002).*** In fact, it is impossible to determine whether nulliparity is a risk factor for the condition or if women with endometriosis find it harder to conceive1. Miscarriage does not appear to correlate with endometriosis or risk of endometriosis ***(Stefansson et al., 2002; Parazzini et al., 2004).***

Endometriosis is associated with twentyfold odds of infertility ***(Vinatier et al., 2001),*** interestingly, analysis of