

Effects of Different Stages of Endometriosis on the Outcome of In Vitro Fertilization

Raedah Al-Fadhli, MD, Simon M. Kelly, MD, Togas Tulandi, MD, MHCM, Seang Lin Tan, MD, MBA

Department of Obstetrics and Gynecology, McGill University, Montreal QC

Abstract

Objective: This study was undertaken to evaluate the effects of different stages of endometriosis on the outcome of treatment in an in vitro fertilization (IVF) program.

Methods: This was a retrospective, matched case-control study in an academic tertiary referral centre. The study group consisted of 87 women with laparoscopically diagnosed endometriosis, and the control group consisted of 87 age-matched women undergoing IVF for different reasons. The primary outcomes were duration of stimulation, total gonadotropin dose requirement, peak serum estradiol level, total number of oocytes retrieved, fertilization rate, embryo quality, implantation rate, and clinical pregnancy rate. The effect of obliteration of the cul-de-sac by endometriosis was also evaluated.

Results: Women with endometriosis required significantly higher gonadotropin doses than women in the control group ($P < 0.01$). The fertilization rate was significantly lower for women with endometriosis ($P < 0.05$), although there was no difference in embryo quality or in the number of embryos transferred. In patients with an obliterated cul-de-sac, fewer oocytes were retrieved than in patients in the control group ($P < 0.01$).

Conclusion: The presence of endometriosis, including stages III and IV, does not affect IVF outcome. However, women with endometriosis require more gonadotropin stimulation than those with no endometriosis. Women with an obliterated cul-de-sac have fewer oocytes retrieved than women without obliteration.

Résumé

Objectif : La présente étude a été menée afin d'évaluer les effets de différents stades d'endométriose sur l'issue du traitement dans le cadre d'un programme de fécondation *in vitro* (FIV).

Méthodes : Il s'agissait d'une étude cas-témoins appariés rétrospective menée au sein d'un centre tertiaire spécialisé universitaire. Le groupe d'étude comprenait 87 femmes présentant une endométriose diagnostiquée par laparoscopie et le groupe témoin, 87 femmes appariées en fonction de l'âge se soumettant à la FIV pour diverses raisons. Les issues primaires étaient les suivantes : durée de la stimulation, dose totale de gonadotrophine requise, pic sérique d'estradiol, nombre total d'ovocytes récupérés, taux de fécondation, qualité de l'embryon, taux d'implantation et

taux de grossesse clinique. L'effet de l'oblitération du cul-de-sac par l'endométriose a également été évalué.

Résultats : Les femmes présentant une endométriose ont nécessité des doses de gonadotrophine considérablement plus élevées que celles qu'ont nécessitées les femmes du groupe témoin ($P < 0,01$). Le taux de fécondation a été considérablement inférieur chez les femmes présentant une endométriose ($P < 0,05$), bien qu'aucune différence n'ait été constatée en ce qui concerne la qualité de l'embryon ou le nombre d'embryons transférés. Chez les patientes présentant un cul-de-sac oblitéré, le nombre d'ovocytes récupérés était moins élevé que chez les patientes du groupe témoin ($P < 0,01$).

Conclusions : La présence d'une endométriose, y compris les stades III et IV, n'affecte pas l'issue de la FIV. Cependant, les femmes qui présentent une endométriose nécessitent une stimulation accrue (au moyen de gonadotrophine) que les femmes qui n'en présentent pas. Un nombre moins élevé d'ovocytes peut être récupéré chez les femmes dont le cul-de-sac est oblitéré que chez les femmes ne présentant pas une telle oblitération.

J Obstet Gynaecol Can 2006;28(10):888-891

INTRODUCTION

Endometriosis is a common gynaecological disorder with an estimated prevalence in infertile women of 25% to 50%.^{1,2} The reasons for an association between endometriosis and infertility are still unclear. Pelvic adhesions and distorted pelvic anatomy arising from endometriosis may cause a mechanical disturbance of the fallopian tube or the ovary.^{3,4} Other possible factors interfering with fertility are endometriosis-associated immunologic defects and alterations in the inflammatory response, including impaired cytokines and macrophages in the peritoneal fluid.⁵⁻⁷

In vitro fertilization (IVF) offers an effective means of bypassing some of these factors. However, some women with endometriosis have less ovarian response to gonadotropin stimulation than women without endometriosis.⁸⁻¹⁰ For example, in one study of IVF treatment, women with previous resection of ovarian endometriosis had higher cancellation rates than those with tubal infertility.¹⁰ Donnez et al., however, found no

Key Words: Endometriosis, infertility, in vitro fertilization, IVF, laparoscopy

Competing Interests: None declared.

Received on May 19, 2006

Accepted on July 11, 2006

Table 1. Characteristics of patients with and without endometriosis

	Group A (patients with endometriosis)	Group B (control)
No. of patients	87	87
Age (years)	34.7 ± 0.4	34.0 ± 0.4
Duration of infertility (years)	4.2 ± 0.3	5.0 ± 0.3
Primary infertility (%)	57 (65.5)	47 (54.0)
Basal serum FSH (IU)	6.2 ± 0.2	6.5 ± 0.3
Basal serum LH (IU)	5.1 ± 0.2	4.9 ± 0.2
Basal serum estradiol (pmol/L)	191.8 ± 20.8	153.9 ± 12.0
Basal antral follicle count	10.3 ± 0.6	11.2 ± 0.9

Data are mean ± standard error

difference in ovarian response between women who had previously undergone laser vaporization of ovarian endometrioma and women with tubal infertility.¹¹ The effect of different stages of endometriosis on IVF outcome remains unclear.^{12–15}

The objective of this study was to evaluate the effect of different stages of endometriosis on IVF outcome, and to evaluate the effect of obliteration of the cul-de-sac.

MATERIALS AND METHODS

During the period from December 1999 to July 2003, 87 women with a diagnosis of endometriosis underwent IVF treatment (group A). Their characteristics and outcomes were compared with those of an age-matched control group of 87 women undergoing IVF treatment for infertility not related to endometriosis (group B). The women in group B were known not to have endometriosis. Parity, duration of infertility, and smoking history were also matched between the two groups. Only the first treatment cycle was included in the analysis.

All of the women had undergone a laparoscopy, and staging of endometriosis was done using the revised American Fertility Society classification.¹⁶ Women in the study had not had any surgery for endometriosis apart from the laparoscopy performed for diagnosis, staging, and treatment. As is our standard practice, we excised all endometriotic lesions including ovarian endometrioma. In the control group, the causes of infertility were tubal factor (22 patients), male factor (28 patients), polycystic ovary syndrome (5 patients), and unexplained (32 patients). As the sperm concentration in all male partners, including those with male factor infertility, was greater than 5 million/mL, we did not perform intracytoplasmic sperm injection.

We used a standard IVF protocol in all patients. Briefly, a combined oral contraceptive pill was administered for

14 days from day 1 of the menstrual cycle, followed by subcutaneous injection of buserelin acetate (a gonadotropin-releasing hormone analogue) 500µg daily. Once pituitary down-regulation was achieved, the dose of buserelin was reduced to 200µg daily and continued at this dose until the day of human chorionic gonadotropin (hCG) injection. On baseline ultrasound, none of the women in the study had an ovarian cyst or residual ovarian endometrioma.

After pituitary down-regulation, gonadotropins were administered daily until at least three follicles of at least 18 mm mean diameter were seen on ultrasound. The daily dose of gonadotropins was determined before the start of the cycle based on the patient's age and antral follicle count. Women under the age of 35 received 150 IU of gonadotropins daily and women over the age of 35 received between 150 and 225 IU daily. After five days of stimulation, the dose was adjusted according to the ovarian response.

Oocyte retrieval was performed 36 hours after hCG injection. Embryo quality was assessed using the cumulative embryo score. A pregnancy test was performed two weeks after embryo transfer. Pregnancy was confirmed when fetal heart activity was detected on transvaginal ultrasound four weeks after embryo transfer.

The primary outcome measures included duration of stimulation, total gonadotropin dose, peak serum estradiol level, total number of oocytes retrieved, fertilization rate, embryo quality, implantation rate, and clinical pregnancy rate. The effect on outcome of different stages of endometriosis and of obliteration of the cul-de-sac was also evaluated.

The normality of data distribution was evaluated using Shapiro-Wilks test. Data were analyzed using Student *t* test, Mann-Whitney test, or chi-square test as appropriate. The differences were considered to be statistically significant at the *P* < 0.05 level.

Table 2. Results of IVF treatment in women with endometriosis

	Group A (all patients with endometriosis)	Stage III & IV	Obliterated cul-de-sac	Group B (control group)
No. of patients	87	47	27	87
No. of ampoules of gonadotropins	44 ± 2.4 [†]	48 ± 3.7 ^{**}	50 ± 5.8 [†]	34 ± 2.3
Duration of stimulation (days)	11 ± 0.2	11.4 ± 0.3	11.1 ± 0.4	10.9 ± 0.2
Peak serum estradiol (pmol/L)	6890 ± 452	6544 ± 622	5340.6 ± 603	6922 ± 414
No. of oocytes obtained	11.5 ± 0.7	10.6 ± 0.9	8.6 ± 1.1 [†]	12.7 ± 0.7
No. of mature oocytes	11 ± 0.7	10.1 ± 0.9	8.1 ± 1.0 [†]	12.3 ± 0.6
Fertilization rate (%)	64.8 ± 2.7 [†]	73.8 ± 3.9	61.0 ± 5.7	72.1 ± 2.4
Cumulative embryo score	35 ± 2.0	32.4 ± 2.7	29.3 ± 2.3	36.9 ± 2.3
Clinical pregnancy rate per transfer (%)	27/83 (32.53)	12/44 (27.27)	5/24 (20.83)	27/85 (31.77)
Implantation rate (%)	19.7	16.5	15	17.8

Data are mean ± standard error

* $P < 0.01$; ** $P < 0.001$; [†] $P < 0.05$ compared with the control group

RESULTS

The characteristics of the women in each group were comparable (Table 1). There was no significant difference in the duration of stimulation, the peak serum estradiol level, the number of oocytes retrieved, or the number of mature oocytes (Table 2). However, patients with endometriosis required higher doses of gonadotropins than the control group (Mann-Whitney test: $P < 0.01$; 95% confidence interval [CI] 3–14 for difference between means), and the fertilization rate was significantly lower in patients with endometriosis (Mann-Whitney test: $P < 0.05$; 95% CI 0–13). The cumulative embryo scores, the implantation rate, and the clinical pregnancy rate per transfer were similar in each group.

We found no difference in the implantation and clinical pregnancy rates between women with stage III and IV endometriosis and women in the control group. The number of oocytes retrieved and the embryo quality were similar (Table 2). In addition, we did a subset analysis of 26 patients who had undergone excision of ovarian endometrioma. The mean antral follicle count in these patients was 8.8, and the pregnancy rate was 30.8%.

These results were not significantly different from those of the control group. The mean total gonadotropin dose used in these patients (44.8 ampoules) was higher than that in the control group (Mann-Whitney test: $P < 0.01$; 95% CI: 4–20).

Although the mean antral follicle count was not significantly different between women with obliterated cul-de-sac and controls, the mean number of oocytes retrieved and the mean number of mature oocytes were 8.6 and 8.1,

respectively, compared with 12.7 and 12.3 in the control group (Mann-Whitney test: $P < 0.01$; 95% CI 2–7). The rates of clinical pregnancy and implantation were similar in each group.

DISCUSSION

For endometriosis-related infertility, medical management has a limited role. Surgical treatment of endometriosis and, especially, IVF will result in a better pregnancy rate.¹⁷ In stages I and II endometriosis, Marcoux et al.¹⁷ reported that surgical ablation of mild endometriosis slightly improved subsequent fertility. A later Italian study did not confirm this finding.¹⁸

Whether the presence of endometriosis or surgical treatment of endometriosis has any effect on the outcome of IVF is also unclear. There is concern that ovarian surgery for endometriosis may affect ovarian reserve.^{9,14,19,20} The evidence concerning this issue is conflicting. In our study, we found that women with endometriosis required a higher dose of gonadotropins per cycle of treatment than those without endometriosis, despite the observation that antral follicle counts in each group before stimulation were comparable. The number of oocytes retrieved and the number of mature oocytes also were similar. These results were found in all patients with endometriosis as well as in those who had undergone excision of ovarian endometrioma.

Garcia-Velasco et al.²¹ carried out a case-control study comparing the results of IVF treatment in women who had had laparoscopic cystectomy for ovarian endometrioma with the results in a control group. Their findings suggest that

excision of ovarian endometrioma does not impair ovarian function, but it also does not increase the IVF pregnancy rate. In contrast, Al-Azemi et al.⁹ reported that women with stage III and IV endometriosis had a poorer IVF outcome than those with tubal factor only. The status of the cul-de-sac in these women was not described.

We found that when the posterior cul-de-sac was obliterated, treated women required higher doses of gonadotropin. However, both the number of oocytes retrieved and the number of mature follicles were less for these women than for women in the control group. Perhaps this resulted from difficulty in oocyte retrieval because of the marked distortion of the cul-de-sac. It is also possible that the ovaries of these patients were less responsive to gonadotropin treatment. In any event, this did not have a negative effect on the clinical pregnancy rate.

In a meta-analysis, Barnhart et al.¹⁵ found that women with severe endometriosis have fewer oocytes retrieved and lower implantation and pregnancy rates than matched controls. Their findings are in contrast to the results of our study, but this may be a result of the relatively small number of cases in our series. Another limitation of our study is the retrospective nature of the data collection. Instead of data from different centres, however, our study used matched cases from one centre.

The overall fertilization rate in women with endometriosis was lower than in the control group. This effect was, however, not apparent in the subgroups of patients. This could be due to type I statistical error. Again, this did not affect the clinical pregnancy rate. The findings that women with advanced stages of endometriosis require higher gonadotropin doses than the control group with a similar pregnancy rate suggest that these women require aggressive ovarian stimulation. In view of the acceptable pregnancy rate in these patients, we propose that women with advanced stages of endometriosis and infertility are better managed with IVF treatment.

CONCLUSION

The presence of endometriosis, including stages III and IV disease, in infertile women does not affect IVF outcome. However, compared with women with no endometriosis, those with endometriosis require more gonadotropin stimulation. Women with an obliterated cul-de-sac have a lower number of oocytes retrieved.

REFERENCES

1. Strathy JH, Molgaard CA, Coulam CB, Melton LJ 3rd. Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women. *Fertil Steril* 1982;38:667–72.
2. Berube S, Marcoux S, Maheux R. Characteristics related to the prevalence of minimal or mild endometriosis in infertile women. Canadian Collaborative Group on Endometriosis. *Epidemiology* 1998;9:504–10.
3. Lyons RA, Djahanbakhch O, Saridogan E, Naftalin AA, Mahmood T, Weekes A, et al. Peritoneal fluid, endometriosis, and ciliary beat frequency in the human fallopian tube. *Lancet* 2002;360:1221–2.
4. Tummon IS, Maclin VM, Radwanska E, Binor Z, Dmowski WP. Occult ovulatory dysfunction in women with minimal endometriosis or unexplained infertility. *Fertil Steril* 1988;50:716–20.
5. Pellicer A, Albert C, Mercader A, Bonilla-Musoles F, Remohi J, Simon C. The follicular and endocrine environment in women with endometriosis: local and systemic cytokine production. *Fertil Steril* 1998;70:425–31.
6. Harada T, Iwabe T, Terakawa N. Role of cytokines in endometriosis. *Fertil Steril* 2001;76:1–10.
7. Jha P, Farooq A, Agarwal N, Buckshee K. In vitro sperm phagocytosis by human peritoneal macrophage in endometriosis-associated infertility. *Am J Reprod Immunol* 1996;36:235–7.
8. Azem F, Lessing JB, Geva E, Shahar A, Lerner-Geva L, Yovel I, et al. Patients with stages III and IV endometriosis have a poorer outcome of in vitro fertilization-embryo transfer than patients with tubal infertility. *Fertil Steril* 1999;72:1107–9.
9. Al-Azemi M, Bernal AL, Steele J, Gramsbergen I, Barlow D, Kennedy S. Ovarian response to repeated controlled stimulation in in-vitro fertilization cycles in patients with ovarian endometriosis. *Hum Reprod* 2000;15:72–5.
10. Aboulghar MA, Mansour RT, Serour GI, Al-Inany HG, Aboulghar MM. The outcome of in vitro fertilization in advanced endometriosis with previous surgery: a case controlled study. *Am J Obstet Gynecol* 2003;188:371–5.
11. Donnez J, Wyns C, Nisolle M. Does ovarian surgery for endometriomas impair the ovarian response to gonadotropins? *Fertil Steril* 2001;76:662–5.
12. Dmowski WP, Rana N, Michalowska J, Friberg J, Papierniak C, El-Roeiy A. The effect of endometriosis, its stage and activity, and of autoantibodies on in vitro fertilization and embryo transfer success rates. *Fertil Steril* 1995;63:555–62.
13. Olivennes F, Feldberg D, Liu H-C, Cohen J, Moy F, Rosenwaks Z. Endometriosis: a stage by stage analysis—the role of in vitro fertilization. *Fertil Steril* 1995;64:392–8.
14. Pagidas K, Falcone T, Hemmings R, Miron P. Comparison of reoperation for moderate (stage III) and severe (stage IV) endometriosis-related infertility with in vitro fertilization-embryo transfer. *Fertil Steril* 1996;65:791–5.
15. Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril* 2002;77:1148–55.
16. The American Fertility Society. Revised American Fertility Society Classification of Endometriosis. *Fertil Steril* 1985;43:351–2.
17. Marcoux S, Maheux R, Bérubé S. Laparoscopic surgery in infertile women with minimal endometriosis. Canadian Collaborative Group on Endometriosis. *N Eng J Med* 1997;337:217–22.
18. Gruppo Italiano per lo Studio dell'Endometriosis. Ablation of lesions or no treatment in minimal–mild endometriosis in infertile women: a randomized trial. *Hum Reprod* 1999;14:1332–4.
19. Loh FH, Tan AT, Kumar J, Ng SC. Ovarian response after laparoscopic ovarian cystectomy for endometriotic cysts in 132 monitored cycles. *Fertil Steril* 1999;72:316–21.
20. Tinkanen H, Kujansuu E. In vitro fertilization in patients with ovarian endometriomas. *Acta Obstet Gynecol Scand* 2000;79:119–22.
21. Garcia-Velasco J, Mahutte N, Corona J, Zuniga V, Giles J, Arici A, et al. Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case-control study. *Fertil Steril* 2004;81:1194–7.