

Implications of the diagnosis of endometriosis on the success of infertility treatment

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Summary

Purpose: Endometriosis is a clinically very heterogeneous disorder and its implications on the resolution of infertility are not clear.

Methods: Clinical data of 783 consecutive infertile couples were retrospectively analyzed in three groups: A – with minimal/mild endometriosis; B – with moderate/severe endometriosis; C – without endometriosis. Subgroups of groups A and C with unexplained infertility were also compared.

Results: Endometriosis was found in 349 patients (44.6%) - 263 in group A and 86 in group B. Group C comprised 434 patients. Overall pregnancy rates were 57.0% for group A, 48.8% for B and 55.8% for C (not statistically different). Of couples in groups A, B, C, respectively, 39.2%, 51.1% and 39.2% needed IVF (B vs C – $p = 0.042$; B vs A – $p = 0.059$). Of couples in group A 45.6% that underwent IVF achieved a pregnancy by this technique; corresponding numbers were 43.2% for group B and 46.5% for C. Overall pregnancy rates in couples with unexplained infertility in groups A ($n = 116$) and C ($n = 110$) were respectively, 58.6% and 56.4%; IVF was needed in 40.5% and 32.7% of those couples, and the cumulative pregnancy rates resulting from IVF were 40.4% and 47.2% (NS).

Conclusion: The diagnosis of endometriosis had no influence on the successful resolution of infertility although moderate/severe endometriosis was related to a greater need for IVF. Couples with unexplained infertility had similar pregnancy rates either in the presence or in the absence of minimal/mild endometriosis.

Key words: Endometriosis; Infertility outcome; Unexplained infertility; IVF.

Introduction

Endometriosis remains a controversial disorder not only in its pathogenesis and natural evolution but also in its relevance as an infertility factor. It is even likely that endometriosis is not a single disorder but represents a variety of diseases. Evidence has been gathered that suggests that subtle endometriotic lesions may represent a physiological condition occurring intermittently in most, if not all, menstruating women [1-3]. An “endometriotic disease theory” was proposed [3, 4] contending that only in a small proportion of (genetically predisposed) women would some kind of cellular modification enable the onset and progression of a disease that behaves like a benign tumor. The observation that ovarian endometriotic cysts are typically monoclonal, whereas superficial peritoneal implants of endometriosis appear to be polyclonal [5] supports that theory.

In most advanced stages of endometriosis, the mechanical effects of adhesions or the presence of ovarian cysts seem obvious causes of infertility. In these cases the approach is widely accepted – surgery with assisted reproduction technologies (ART) either as an alternative for cases of non-successful correction of the pelvic anatomy or as a final option if no pregnancy results after a reasonable post-surgery time-period. The disputed issues are the surgical approach to endometriomas [6-9] and the use of postoperative medical therapy, whose

benefit in improving pregnancy rates has been questioned in recent reports [10, 11].

As regards the minimal or milder forms of endometriosis, there is endless dispute about its true relationship with infertility – is it a causal or a casual one? A multitude of mechanisms has been suggested to explain infertility in those cases – ovulation disturbances, abnormalities of peritoneal fluid (e.g. altered concentrations of several cytokines, growth factors or interleukins), inhibition of ovum uptake, dysfunction of oviducts, decrease in implantation, immune system modifications and recurrent abortions [12]. As a consequence, several therapeutic strategies have been designed and advocated over the last decades. At present, medical treatment is not considered useful in solving infertility in such couples [13] and laparoscopic destruction of pelvic peritoneal lesions in patients with otherwise unexplained infertility is both supported by a huge and well-designed trial [14] and questioned by a smaller but also technically correct study [15]. Other approaches have been expectant management, controlled ovarian hyperstimulation (COH), alone or with intrauterine insemination (IUI), and ART.

After their first description [16], the different types of peritoneal endometriotic lesions have received widespread attention and standardized classification [17]. Papers on basic science reported some differences in the peritoneal environment of red, black and white lesions with most intense proliferative, angiogenic and biochemical activity in the red lesions [18-20].

Against such a background, published papers usually

focus on specific aspects of this complex problem and use very selected groups of patients. One great series of unselected patients reported more than ten years ago [21] showed no impact of endometriosis on the reproductive outcome of infertile patients unless the anatomy of the pelvic organs was heavily distorted.

In the present study a retrospective analysis of the clinical data of our non-selected infertile population was performed to evaluate the implications of the diagnosis of endometriosis on the resolution of their infertility. In particular, the questions to be addressed were: 1) is the chance of becoming pregnant different for an infertile couple in which endometriosis is diagnosed in comparison with another without endometriosis? And what is the prognosis for the several stages of the disorder? 2) Does a couple with unexplained infertility have a different chance of achieving a pregnancy if minimal/mild endometriosis is found? And is the outcome of the infertility different if those couples have red endometriotic peritoneal lesions?

Material and Methods

Seven hundred and eighty-three infertile consecutive couples whose female partner was submitted to either diagnostic or therapeutic laparoscopy in our Unit up to the end of 2000 were included in this retrospective evaluation. Endometriosis was confirmed by direct visualization or biopsy of lesions and the characteristics of endometriotic lesions were prospectively registered in a specific database. The stage of the disorder was determined according to the latest revised classification of the American Society for Reproductive Medicine [17]. The local Ethics Committee approved the study.

Patients were divided into three groups: A – with endometriosis I or II; B – with endometriosis III or IV; C – without endometriosis. Subgroups of groups A and C presenting unexplained infertility were also individualized. Unexplained infertility was diagnosed in the presence of regular cycles with biphasic BBT and/or normal progesterone concentrations in the luteal phase, normal hysterosalpingogram, normal semen characteristics and normal pelvis at laparoscopy. Characteristics of the populations, pregnancy rates, the need to be included in an IVF program and results after IVF were compared. Time between laparoscopy and last consultation (named follow-up), time elapsed between laparoscopy and pregnancy or first pregnancy in case of more than one in the same couple (i.e., time to conception) and proportion of lost pregnancies were also studied.

Management of patients with minimal or mild endometriosis. All diagnosed infertility factors were treated. Minimal/mild endometriosis was not considered an infertility factor in itself and peritoneal endometriotic lesions were not destroyed. Medical therapy was used in only a few cases (10.6%) mainly due to pelvic pain, and one patient was treated surgically (adhesiolysis). If pregnancy did not occur after a reasonable period of treatment of identified disturbances or after a period of expectant management, couples started COH alone or followed by IUI when sperm characteristics were adequate. ART was suggested either in the presence of severe infertility factors or to couples with more than 3 years of infertility not successfully solved with conventional treatments.

Management of patients with moderate or severe endometriosis. Seventy-eight (90.7%) patients in group B were submitted

to surgical treatment of endometriosis (cystectomy of endometriomas and/or lyses of pelvic adhesions) and 78.2% received postoperative medical treatment (mainly a GnRH analogue) for three to four months. Seven percent were given purely medical treatment because of pain or while waiting for ART. Additional major infertility factors were treated when suitable.

Management of patients without endometriosis. These couples were treated individually, by correcting the identified infertility factors using medical and/or surgical means. Again, ART was suggested either in the presence of severe infertility factors or to couples with more than three years of infertility not successfully solved previously.

IVF protocol. The long protocol with GnRH agonist started in the early follicular phase is used as a standard methodology in our center. Ovarian stimulation with gonadotrophins (150 IU to 300 IU/ daily) is started after confirmation of pituitary inhibition. HCG (5,000 or 10,000 IU) is administered to induce final oocyte maturation and ovum pick-up performed 34-36 h afterwards. The short protocol with GnRH analogue was an alternative in some cases of poor responders.

Statistical analysis. The Student's t-test (with the Welch correction for unequal variances) was used to compare normally distributed continuous variables, while non-parametric data were examined with the Mann-Whitney rank sum test. Comparison of categorical variables was performed with the Fisher's exact test. Two-sided p values < 0.05 were considered statistically significant.

Results

Endometriosis was found in 44.6% of the 783 patients. The disorder was classified as minimal or mild in 263 patients (group A), and moderate or severe in 86 patients (group B); 434 women did not show endometriosis (group C). Demographic data are shown in Table 1. In short, age was similar in the three groups and mean duration of infertility was significantly lower in group B than A ($p = 0.022$) and C ($p = 0.012$). Overall pregnancy rates of 57.0% for group A, 48.8% for group B and 55.8% for couples in group C were not statistically different. When pregnancies resulting from IVF were excluded, couples with moderate/severe endometriosis showed a significantly lower conception rate than those in group A (the difference was not statistically significant versus group C). Time of follow-up and time to conception also did not differ among the groups. The same was found when duration of waiting list for IVF (± 18 months) was taken into consideration. Fourteen percent of couples in group A suffered a lost pregnancy (spontaneous abortion or stillbirth). Corresponding numbers were 14.3% for group B and 11.2% for group C (not statistically significant).

Of couples in groups A, B, C, respectively, 39.2%, 51.1% and 39.2% needed to undergo IVF (group B significantly higher than group C – $p = 0.042$, and marginally higher than group A – $p = 0.059$). Out of the 103 couples in group A that underwent IVF, 45.6% achieved a pregnancy by this technique after one to four initiated treatment cycles; corresponding numbers were 43.2% for group B and 46.5% for group C (differences not significant) (Table 2).

Table 1. — Patient demographics and overall pregnancy rates.

	Group A (n = 263)	Group B (n = 86)	Group C (n = 434)	p value
Age of female (years)	30.9 ± 3.9	30.3 ± 4.1	30.9 ± 4.0	NS
Duration of infertility (months)	52.7 ± 31.1	47.0 ± 29.5 ^{a, b}	55.6 ± 33.0	^a 0.022; ^b 0.012
Duration of follow-up (months)	20.5 ± 17.0	20.5 ± 15.0	18.9 ± 14.4	NS
No. of couples with pregnancies (%)	150 (57.0%)	42 (48.8%)	242 (55.8%)	NS
No. of couples with pregnancies other than by IVF (%)	103 (39.2%)	23 (26.7%) ^d	163 (37.6%)	^d 0.039
Time to conception excluding IVF (months)	8.6 ± 10.5	8.2 ± 5.4	9.2 ± 9.2	NS
No. of couples included in IVF program (%)	103 (39.2%)	44 (51.1%) ^c	170 (39.2%)	^c 0.042

Values are given as mean ± SD; ^a When compared with group A; ^b When compared with group C; ^c When compared with group C (and p = 0.059 when compared with group A); ^d When compared with group A (and NS when compared with group C).

Table 2. — Results of IVT-ET.

	Group A (n = 103)	Group B (n = 44)	Group C (n = 170)	p value
Age of female (years)	31.2 ± 3.3	30.1 ± 3.6	31.1 ± 3.6	NS
Duration of infertility (months)	56.4 ± 33.8	47.1 ± 24.3 ^a	59.3 ± 32.7	^a 0.028
Duration of follow-up (months)	30.4 ± 16.1	28.5 ± 15.1	28.5 ± 15.2	NS
No. of couples with pregnancies by IVF(%)	47 (45.6%)	19 (43.2%)	79 (46.5%)	NS
Time to conception (months)	24.6 ± 15.7	23.9 ± 14.6	23.6 ± 12.7	NS

Values are given as mean ± SD; ^a When compared with group C.

Table 3. — Characteristics and pregnancy rates in couples with unexplained infertility.

	Group A (n = 116)	Group B (n = 110)	p value
Age of female (years)	31.4 ± 4.0	31.4 ± 3.6	NS
Duration of infertility (months)	55.5 ± 31.5	51.7 ± 27.1	NS
Duration of follow-up (months)	20.9 ± 16.3	18.4 ± 14.2	NS
No. of couples with pregnancies (%)	68 (58.6%)	62 (56.4%)	NS
No. of couples with pregnancies other than by IVF (%)	49 (42.2%)	45 (40.9%)	NS
Time to conception (months)	12.7 ± 11.3	14.0 ± 13.6	NS
No. of couples included in IVF program (%)	47 (40.5%)	36 (32.7%)	NS
No. of couples with pregnancies by IVF(%)	19 (40.4%)	17 (47.2%)	NS

Values are given as mean ± SD.

In couples with unexplained infertility in groups A (n = 116) and C (n = 110), overall pregnancy rates were respectively 58.6% and 56.4% (or 42.2% and 40.9% if pregnancies resulting from IVF are excluded); the proportion of couples that needed IVF was 40.5% and 32.7%, and the cumulative pregnancy rates resulting from IVF after a maximum of four initiated cycles were 40.4% and 47.2% (p = 0.66; NS) (Table 3). Time of follow-up and time until pregnancy were similar in the two subgroups. In these couples, 16.2% and 19.4% of the pregnancies ended in embryo/fetal losses (difference not significant).

Red peritoneal lesions were seen in 68 patients of couples with no abnormality besides endometriosis I or II. Forty-eight patients had other types of lesions only. Pregnancy rates in these two subsets were similar (57.4% and 60.4%, respectively) and also were not different from the 56.4% found in the group of 110 couples with unexplained infertility. The same was true if pregnancies using

IVF were not considered – 42.6% and 41.7% for couples with and without red lesions, respectively. These figures are not different from the 40.9% for the unexplained infertility subgroup.

Intrauterine insemination with ovarian hyperstimulation was performed in 24 couples with unexplained infertility in group A and 23 couples in group C. Pregnancy occurred in seven and four couples, respectively.

Discussion

In the present study, we analyzed data from almost 800 infertile couples to evaluate the possible consequences of the diagnosis of endometriosis in the success of clinical management of the infertility. Despite being an observational retrospective study, it is based on systematic registered data of patients submitted to laparoscopy and to standardized clinical management in the same Unit.

Endometriosis was diagnosed in 44.6% of patients, a prevalence that is similar to that reported in the literature by many others. Characteristics of patients did not differ among groups with the exception of a shorter duration of infertility in couples with moderate/severe endometriosis. The presence of pelvic complaints (namely pelvic pain) may be the explanation for a relatively faster diagnosis in those patients.

As a whole, we found no significant differences in the overall pregnancy rates comparing the group of couples in which minimal/mild endometriosis was present, the group of those with moderate/severe endometriosis, and the group of couples without endometriosis. A previous study [21] reported conception rates of 30.7% in 1,263 infertile couples with endometriosis and of 30.0% in 817 infertile couples without endometriosis and found no differences among patients with endometriosis in different stages (except between Stage I and IV). It is not possible

to directly compare those values with our results because the duration of follow-up was not disclosed and we aggregated patients with minimal and mild forms of the disorder in one group and patients with moderate and severe endometriosis in another, following the "endometriotic disease theory" [4]. A clinical finding traditionally associated with endometriosis is a higher frequency of pregnancy losses, but we found no different proportion of spontaneous abortions and/or stillbirths among our three study groups.

The number and characteristics of couples that were included in the IVF program using the criteria previously defined were also evaluated and the sole difference found was the more frequent need of the couples with endometriosis III-IV to undergo IVF. This can be understood from the severity of the anatomical distortion of the pelvis in most such patients resulting in a significant reduction of the conception rate using other approaches.

The cumulative pregnancy rates after IVF were similar in our three groups. The implications of endometriosis in IVF efficacy are not clear despite numerous reports on the subject. A recent meta-analysis [22] highlighted the enormous heterogeneity of the populations evaluated and concluded that patients with endometriosis undergoing IVF respond with significantly decreased levels of all markers of the reproductive process. To be more precise, patients with minimal or mild endometriosis demonstrated a reduction in crude and adjusted comparisons of several parameters but a similar pregnancy rate versus patients with tubal factor. Women with moderate or severe endometriosis had a significant reduction in pregnancy rates compared to patients with either tubal factor or with minimal/mild endometriosis. In cases of endometriosis III or IV some impairment of ovarian response to hyperstimulation and/or decreased oocyte quality, a consequence of the disease itself and/or of the surgery, have been suggested [23] as possible explanations for the unfavorable outcome of IVF in these patients. Although more than 90% of our patients in group B had been operated on, the pregnancy rate was not significantly reduced. The effect (if any) of endometriosis I or II on IVF results was evaluated by our group in a previous study [24]. We performed an analysis of IVF cycles in couples with either tubal factor, male factor or unexplained infertility and within each group the results of the cycles were compared between two subgroups – with or without a diagnosis of endometriosis I or II. No relevant differences were found in the characteristics of cycles or pregnancy rates.

Our total 263 couples with endometriosis I or II had similar overall pregnancy rates, proportion of couples included in the IVF program, and pregnancy rates after IVF when compared to the 434 couples without endometriosis. Infertility being, most of the time, a multifactorial situation with countless nuances in the relative importance of multiple disturbances of the mechanisms involved in reproduction, these groups are of course far from homogeneous. In fact, in the present series, couples

without endometriosis had significantly more frequent tubal and hormonal infertility factors while in the group with minimal or mild endometriosis, couples with absence of identifiable major infertility factors were significantly more numerous (data not shown). Thus, our raw results must be seen as strongly supporting the possibility that the identification of a few spots of peritoneal endometriosis does not adversely affect the final outcome in a general population with infertility.

We have studied indepth the subgroups of couples with endometriosis I or II, as a unique abnormality, and with unexplained infertility. The expectation is that in these groups the importance of the diagnosis and the consequences of the management of minimal or mild endometriosis may be more clearly seen. However, important doubts have been raised concerning the real distinction between the two populations. In fact, besides methodological difficulties (different diagnostic accuracy among surgeons, for example), microscopic evidence of endometriosis was found in 6% of biopsies of normal looking peritoneum of infertile patients without visible endometriosis [25] and macroscopic endometriotic lesions were found in 20% of women with so-called unexplained infertility and a previously normal pelvis when a second laparoscopy was performed two or more years later [26].

Our 116 couples with endometriosis I or II and 110 couples with unexplained infertility did not differ in their characteristics. The overall pregnancy rate was 58.6% and 56.4%, respectively, and 42.2% and 40.9% of the couples achieved pregnancy outside the IVF environment. These results do not support a lower conception rate in women with minimal or mild endometriosis when compared to women with unexplained infertility as suggested in some studies with either donor insemination [27] as a control for male and coital factors or with artificial insemination by the husband [28]. This concept is also called into question by another study with donor insemination [29] and by an important paper that showed no difference in the fecundity of 169 women with endometriosis I or II and 263 with unexplained infertility managed expectantly for 36 weeks (18.2% and 23.7%, respectively) [30]. The fecundity of our couples with endometriosis I or II was not different from that of the couples with unexplained infertility. The numbers now presented are substantially higher than those reported by the Canadian group [30] but our couples were not always managed expectantly and the follow-up period was longer.

Almost 30% of the 24 couples with endometriosis I or II alone that performed IUI achieved a pregnancy with this technique and the same occurred in 17.4% out of the 23 with unexplained infertility. Pregnancy rates were similar but absolute numbers are too small to call into question the reported lower pregnancy rates after IUI in patients with minimal/mild endometriosis than in those with unexplained infertility [28].

After the publication of the results of the ENDOCAN study [14] there was a general movement in favor of surgical destruction of the peritoneal lesions of infertile patients with mild or minimal endometriosis. In this

study, the cumulative pregnancy rate at 36 weeks was significantly higher in patients in whom ablative surgery for peritoneal endometriosis was performed, compared with the no treatment group. Different conclusions were reached by a smaller but also well-designed study [15] in which no differences between the resection/ablation and the control groups were found after one year of follow-up. Based on the results of the ENDOCAN study, it was calculated that eight women with minimal or mild endometriosis need to undergo laparoscopic ablation to achieve an additional advanced pregnancy, which is considered a quite limited efficacy in practical terms [31]. We did not perform destruction of peritoneal lesions in our patients and cannot participate directly in this discussion.

Couples with minimal or mild endometriosis and no other abnormal findings and couples with unexplained infertility behave clinically in the same way in terms of the need to be included in an IVF program and in terms of the cumulative pregnancy rate after this technique (40.7 vs 47.2%, respectively). In our Unit we cannot offer more than a limited number of IVF cycles because of financial constraints, so the cumulative pregnancy rates refer to a maximum of four initiated cycles.

A possible clinical meaning of the presence of red lesions, recognized as the most biochemically and morphologically active type of peritoneal lesions [18-20], has not been reported. As it has been suggested that peritoneal factors are relevant to the subfertility associated with mild/moderate endometriosis we evaluated this subject. No significant difference was found when comparing couples with endometriosis I or II and no other disturbance where red lesions were found, couples in the same subgroup but without red lesions and couples with "pure" unexplained infertility. It is possible that the so-called activity of red lesions has a real importance in the implantation process but a limited life span. This would be in accordance with the possible intermittent character of the subtle lesions [1-3].

Conclusion

We can answer the initial questions saying that in our clinical setting 1) the chance of achieving a pregnancy was not significantly different for couples in which endometriosis was diagnosed during their etiologic evaluation; moderate or severe endometriosis, although related to a higher need for IVF, did not impair the overall success of infertility treatment, and 2) couples with minimal or mild endometriosis as a unique abnormality did not differentiate from couples with unexplained infertility in their outcome; the presence of red peritoneal lesions in these couples had no influence on the final outcome of infertility.

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