FERTILITY AND STERILITY®
VOL. 77, NO. 6, JUNE 2002

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Effect of endometriosis on in vitro fertilization

Kurt Barnhart, M.D., M.S.C.E.,[a,b] *Rebecca Dunsmoor-Su, M.D., M.S.C.E.,*[a] *and Christos Coutifaris, M.D., Ph.D.*[a]

Center for Reproductive Medicine and Surgery, University of Pennsylvania Medical Center and Health System; and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Objective: To investigate the IVF outcome for patients with endometriosis.

Design: Meta-analysis.

Setting: Academic research center.

Patient(s): A MEDLINE search and review of the literature were performed. Patients were classified by level of endometriosis, and controls were classified according to the indication for IVF.

Intervention(s): Bivariate analysis and multivariate logistic regression was used to estimate overall effect and control for confounding.

Main Outcome Measure(s): Pregnancy rates, fertilization rate, implantation rates, and numbers of oocytes retrieved.

Result(s): Twenty-two published studies were included in the overall analysis. The chance of achieving pregnancy was significantly lower for endometriosis patients (odds ratio, 0.56; 95% confidence interval, 0.44–0.70) when compared with tubal factor controls. Multivariate analysis also demonstrated a decrease in fertilization and implantation rates, and a significant decrease in the number of oocytes retrieved for endometriosis patients. Pregnancy rates for women with severe endometriosis were significantly lower than for women with mild disease (odds ratio, 0.60; 95% confidence interval, 0.42–0.87).

Conclusion(s): Patients with endometriosis-associated infertility undergoing IVF respond with significantly decreased levels of all markers of reproductive process, resulting in a pregnancy rate that is almost one half that of women with other indications for IVF. These data suggest that the effect of endometriosis is not exclusively on the receptivity of the endometrium but also on the development of the oocyte and embryo. (Fertil Steril® 2002;77:1148–55. ©2002 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, infertility, fertilization in vitro, meta-analysis

Received July 27, 2001; revised and accepted February 5, 2002.

Reprint requests: Kurt Barnhart, M.D., M.S.C.E., Senior Scholar Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Medical Center, 106 Dulles, 3400 Spruce Street, Philadelphia, Pennsylvania 19104 (FAX: 215-349-5512; E-mail: kbarnhart@mail.obgyn.upenn.edu).
[a] Center for Reproductive Medicine and Surgery.
[b] Center for Clinical Epidemiology and Biostatistics.

0015-0282/02/$22.00
PII S0015-0282(02)03112-6

Endometriosis is a condition characterized by endometrial tissue located outside of the uterus, most commonly on the ovary and peritoneum. It affects approximately 10% of women in the United States and 20%–40% of women seeking infertility evaluation (1–3). Endometriosis is associated with dysmenorrhea, chronic pelvic pain, and infertility. The mechanisms by which endometriosis impairs fertility have not been completely determined but are likely varied. Severe endometriosis is associated with pelvic adhesions and a distortion of pelvic anatomy leading to a possible mechanic or anatomic disturbance of fertility. However, it is probable that endometriosis, even in a mild stage, may have a direct negative effect on oocyte development, embryogenesis, or implantation. Postulated mediating factors include local paracrine action of interleukins or other cytokines, alteration in inflammatory response, or autoimmune factors (4–8).

Although both surgical and medical management of endometriosis have been associated with a reduction in symptoms, both have resulted in only a minimal increase in fertility (9, 10). In vitro fertilization offers the highest pregnancy rates of assisted reproductive technologies and is often used to treat women with infertility associated with endometriosis. The question of whether the presence of endometriosis affects the outcome of women undergoing IVF has not been resolved, with some authors noting negative associations and others noting no association (11–14). The importance

of the investigation into this association is magnified because the evaluation of patients undergoing IVF allows the study of surrogate markers of reproductive success, such as peak E_2 levels, number of oocytes retrieved, fertilization, implantation, as well as pregnancy rates. If endometriosis is associated with poor IVF outcome, by evaluating each component, it may be possible to determine the specific effects of endometriosis on reproductive outcome.

In this manuscript, we present the results of a meta-analysis of the published literature on endometriosis and IVF outcome. Meta-analysis is a statistical overview method by which the results of many studies can be combined to increase statistical power. This is a method most often employed with the results of clinical trials but that has been and can be applied to observational studies (15, 16). Meta-analysis is best used to clarify conflicting results, as exist for this important clinical and scientific question.

METHODS

Selection of Studies

We conducted a MEDLINE search (January 1980 through May 1999) using combinations of the following keywords: *infertility, endometriosis, embryo transfer, fertilization in vitro,* and *reproduction techniques*. All pertinent peer-reviewed, English language articles were retrieved. A manual search of references was then conducted for additional articles. Articles selected included only those with original data comparing the outcome of IVF for patients with endometriosis with that of women undergoing IVF for other indications, or those comparing IVF outcome for women with different stages of endometriosis. We did not include articles evaluating other assisted reproductive techniques such as ovulation induction or GIFT.

To be included in our analysis, articles had to contain information on number of cycles and at least one of the outcomes studied. Articles could not be categorized as to whether the endometriosis was medically or surgically treated before initiation of IVF, as this information was not uniformly reported. A total of 24 articles were retrieved; 1 was excluded in favor of a later article that included the same data, and 1 was excluded because it did not include information on pregnancy rate, only live birth rate (17, 18). Institutional review board approval was not sought because only previously published data were used.

Data Abstraction

Data were abstracted by one author on two independent occasions, and any discrepancies were solved by review of the original publication. The data were then entered into a spreadsheet. The outcome reported for each study varied, with some studies reporting absolute pregnancy rate (detection of hCG); some, clinical pregnancy rate (ultrasound detection of a gestational sac); and some, live birth rate. We chose absolute pregnancy rate as the main outcome for our study because it was the only parameter comparable across all studies. Actual number of pregnancies was available or easily calculated from the raw data of each study. Miscarriage rates were not uniformly reported; therefore, they were not considered as an outcome. Exposure was defined as the presence or absence of endometriosis.

Subcoding of patients with endometriosis included the stage of endometriosis and presence or absence of other cause of infertility (tubal factor, male factor, ovulatory dysfunction). Patients without endometriosis were subcoded for the other infertility factors (male factor, ovulatory dysfunction, unexplained infertility) or for tubal factor only. Information was also collected on potential confounding factors and on other markers of IVF response, including fertilization rate (number of embryos per number of oocytes retrieved), implantation rate (number of gestational sacs visualized with ultrasound examination per number transferred), number of oocytes retrieved, and peak E_2 during stimulation.

Statistical Analysis

The main outcome measure was odds ratio for pregnancy after IVF for those with endometriosis compared with those without endometriosis. To pool information for logistic analysis, the actual number of pregnancies per cycles was retrieved from the original articles, and the data were expanded in STATA (College Park, TX). All calculations assumed two-tailed tests for statistical significance using univariate analysis, stratified analysis, logistic regression, and conditional logistic regression. All possible confounding variables were entered, and a categorical variable was constructed to reflect the changes in stimulation regime employed over time. Three categories were used to represent the following regimes: no stimulation regime, hMG only, and other (studies in which multiple stimulation regimes were used, including combinations of hMG, Clomid, and FSH).

Descriptive statistics were used to compare patients with and without endometriosis. Bivariate analysis using the Student's *t* test and χ^2 analysis was undertaken for all potential confounding variables. Stratified analysis was used to assess for confounding and effect modification (of which there was no evidence). Logistic regression model construction was completed using a manual selection of confounding variables, with the criteria for inclusion being a 10% change in the odds ratio for pregnancy (19). This resulted in a final model that included age, publication date (year), and stimulation regime as confounding variables. The above steps were then repeated for all subgroup analyses performed. Heterogeneity between studies was examined, with stratified analyses and logistic regression conditional on study.

RESULTS

We included data from 22 studies, for a total of 2,377 IVF cycles of women with endometriosis cycles and of 4,383 IVF cycles of women without endometriosis. Table 1 summarizes

TABLE 1

Characteristics of 22 studies used in meta-analysis.

Reference	Publication date	Study dates	Patient type	No. of cycles	Control type	No. of cycles
Mahadevan et al. (41)	1983	1981–1982	Endo, all stages, +/− tubal factor	14	Tubal factor	261
Chillik et al. (23)	1985	1981–1984	Endo treated, separated by stage I–II and III–IV	39	None	0
Wardle et al. (40)	1985		Endo, all stages	17	Tubal factor	47
Matson and Yovitch (10)	1986		Endo, I–IV by stage	154	Tubal factor	40
Devroey et al. (42)	1987	1986	Endo, II–III	16	None	0
Frydman and Belaisch-Allart (39)	1987	1986	Endo, all stages	53	Tubal factor	933
Tummon et al. (43)	1991	1984–1988	Endo, I–IV by stage	240	None	0
Inoue et al. (36)	1992	1988	Endo, all stages	309	All other infertility	372
Mills et al. (38)	1992	1988–1990	Endo, all stages	62	Tubal factor	122
Simón et al. (11)	1994	1990–1993	Endo, all stages	96	Tubal factor	96
Dmowski et al. (12)	1995	1991–1993	Endo, all stages + other infertility factors	119	All other infertility	118
Gerber et al. (35)	1995	1988–'91	Endo, all stages	129	Tubal factor	1,139
Olivennes et al. (13)	1995	1988–'92	Endo, all stages	236	Tubal factor	160
Tanbo et al. (37)	1995	1986–'94	Endo, I	265	Tubal factor	331
Arici et al. (22)	1996	1988–'94	Endo, I–II and Endo III–IV	89	Tubal factor	147
Cahill et al. (20)[a]	1996		Endo, all stages	22	Tubal factor	48
Padigas et al. (14)	1996	1990–1994	Endo, II–III	37	Tubal factor	414
Huang et al. (33)	1997	1993	Endo, I–II and III–IV	75	Tubal factor	60
Issacs et al. (44)	1997	1993–1997	Endo, all stages and III–IV	147	None	0
Bergendal et al. (34)	1998	1994–1997	Endo, all stages	65	Tubal factor	98
Pal et al. (21)	1998	1994–1997	Endo, I–II and III–IV	85	None	0
Yanushpolsky et al. (24)	1998	1994–1995	Endo, III–IV	37	N/A	

Endo = endometriosis; N/A = not available.

[a] Excludes medroxyprogesterone acetate study group.

Barnhart. IVF in endometriosis-associated infertility. Fertil Steril 2002.

the characteristics of the studies included in the meta-analysis. Our initial analysis was to compare all subjects with endometriosis at the indication for IVF with women with any other indication for IVF. In this analysis, cases were defined as any women diagnosed with endometriosis (at any stage), including those in one study that allowed a patient to be classified as having endometriosis coincident with other indications for IVF (12).

Table 2 presents the results of bivariate analysis of possible confounding factors, all of which were significantly different, with the exception of the use of luteal support, which was not statistically different for endometriosis vs. control, primarily because of the lack of reporting of this parameter. Although these factors were significantly different when tested in the logistic regression model as confounding variables, most did not affect the odds ratio and were therefore not included in the final model, with the exception of age, publication date, and stimulation regime. Additional data that were obtained but could not be controlled for in our analysis because of incomplete information included information on the method of embryo transfer (12, 20, 21), the use of luteal phase GnRH-a (11, 13, 14, 20, 22), and the use of a medroxyprogesterone acetate regimen (23). Baseline FSH was only noted in three studies (13, 20, 23), and information on the maturity and quality of oocytes retrieved was noted in only four (11, 20, 21, 24). These data, where noted, were similar in women with endometriosis and controls.

The forest plot (Fig. 1) presents the results of the unadjusted analysis comparing the odds for pregnancy among patients with endometriosis with the odds in tubal factor patients across 15 studies. The combination of these 15 studies results in much greater precision of our measure of association and a narrow 95% confidence interval.

The comparison of the pregnancy rate, fertilization rate, implantation rate, number of oocytes retrieved, and peak E_2 concentration for women with endometriosis undergoing IVF compared with those without endometriosis is demonstrated in Table 3. These data are derived from pooling the raw data from all included studies. The crude (unadjusted) analysis demonstrates a 19% decrease in the chance of achieving a pregnancy for women with endometriosis compared with women undergoing IVF for different indications (odds ratio [OR], 0.81; 95% confidence interval [CI], 0.79–0.91). The calculated ORs for fertilization rate, implantation rate, and peak E_2 concentrations are also significantly lower in women with endometriosis compared with in those with-

TABLE 2

Results of bivariate analysis of study variables comparing all patients with endometriosis (including other infertility factors) and all controls (including tubal and other infertility factors).

Variable	All endometriosis	All control	*P*
Age (y)	34.14	33.48	<0.001
Publication date (y)	93.45	92.27	<0.001
Study end date (y)	91.77	89.99	<0.001
Percentage of subjects using GnRH-a	27.08	49.90	
Percentage of subjects for whom GnRH-a not used	14.48	8.54	<0.001
Percentage of subjects for whom hCG was administered by follicular size criteria	40.72	41.46	<0.001
Percentage of subjects for whom hCG was administered by date criteria	10.52	4.05	<0.001
Luteal support: none, % subjects	0.87	2.13	0.468
Luteal support: progesterone or hCG, % subjects	33.16	63.84	0.468
Transvaginal retrieval, % subjects	46.17	30.24	<0.001
Laparoscopic retrieval, % subjects	9.63	13.96	<0.001
Stimulation regimen: none, % subjects	0.57	1.25	<0.001
Stimulation regimen: hMG, % subjects	21.40	51.35	<0.001
Stimulation regimen: other, % subjects	14.43	11.00	<0.001

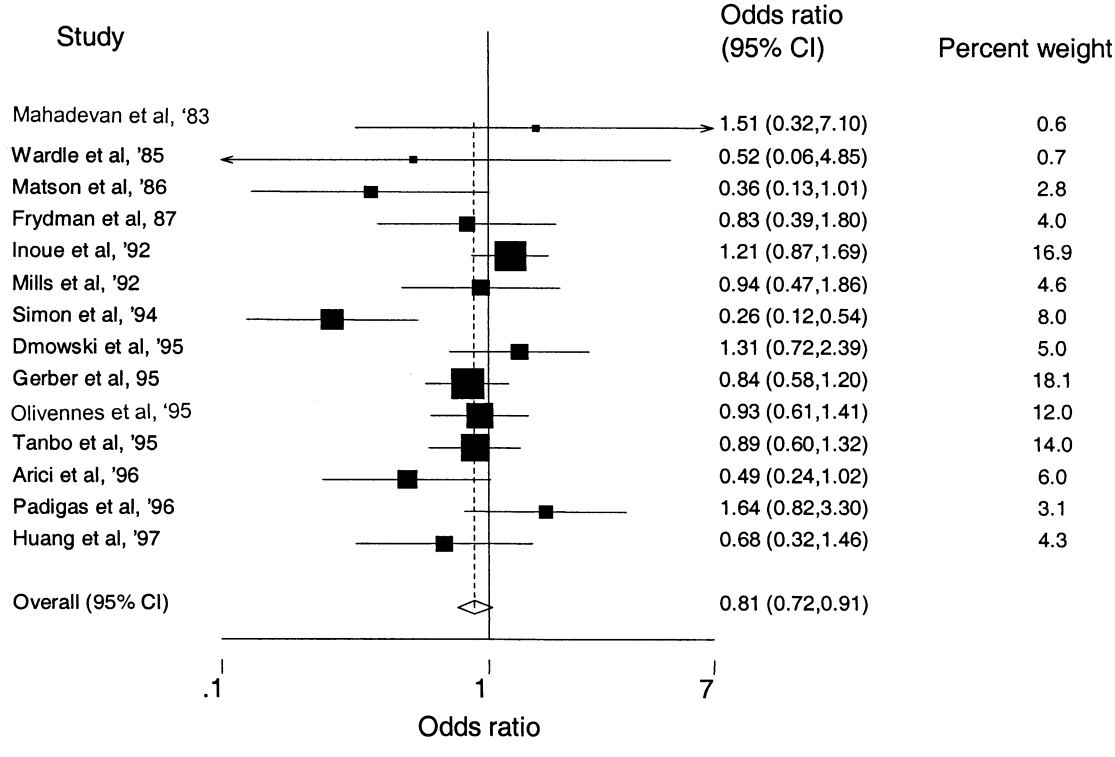
Note: Student's *t* test or χ^2 used for analysis.

Barnhart. IVF in endometriosis-associated infertility. Fertil Steril 2002.

out. This unadjusted analysis also demonstrated that a significantly greater number of oocytes is retrieved from women with endometriosis (OR 1.06 [1.04–1.08]). Stratified analysis based on study and logistic regression conditional on study did not affect results. Therefore, data was pooled for multivariate analysis.

FIGURE 1

Unadjusted meta-analysis of odds of pregnancy in endometriosis patients vs. tubal factor controls.



Barnhart. IVF in endometriosis-associated infertility. Fertil Steril 2002.

TABLE 3

Results of bivariate analysis and multiple logistic regression analyses comparing endometriosis patients with controls.

Outcome	Endometriosis	Control	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
All patients[b] (n = 2,909)				
Pregnancy rate	25.42	29.52	0.81 (0.72–0.91)	0.63 (0.51–0.77)
Fertilization rate	59.69	65.94	0.95 (0.94–0.95)	0.87 (0.85–0.88)
Implantation rate	12.72	18.08	0.86 (0.85–0.87)	0.86[c] (0.85–0.88)
Mean no. of oocytes	7.81	7.30	1.06 (1.04–1.08)	0.92 (0.85–0.99)
Peak E_2	3545.04	4399.93	N/A	N/A
Endometriosis only vs. tubal factor only[d] (n = 2,893)				
Pregnancy rate	25.38	27.71	0.88 (0.79–1.00)	0.56 (0.44–0.70)
Fertilization rate	59.50	66.09	0.95 (0.94–0.95)	0.81 (0.79–0.83)
Implantation rate	12.72	18.08	0.86 (0.85–0.88)	0.86[c] (0.85–0.88)
Mean no. of oocytes	7.79	7.30	1.06 (1.04–1.08)	0.82 (0.75–0.90)
Peak E_2	3545.04	4399.93	N/A	N/A
Stage I–II[e] (n = 2,602)				
Pregnancy rate	21.11	27.71	0.70 (0.56–0.87)	0.79 (0.60–1.03)
Fertilization rate	58.38	66.09	0.93 (0.92–0.94)	0.94 (0.93–0.96)
Implantation rate	11.31	18.08	0.80 (0.78–0.82)	0.88 (0.85–0.90)
Mean no. of oocytes	8.19	7.30	1.11 (1.06–1.14)	0.56 (0.49–0.65)
Peak E_2	5813.38	4399.93	N/A	N/A
Stage III–IV[f] (n = 2,575)				
Pregnancy rate	13.84	27.71	0.42 (0.31–0.57)	0.46 (0.28–0.74)
Fertilization rate	74.47	66.09	1.08 (1.06–1.10)	1.54 (1.39–1.70)
Implantation rate	10.23	18.08	0.75 (0.72–0.79)	not interpretable
Mean no. of oocytes	6.70	7.30	0.94 (0.91–0.98)	not interpretable
Peak E_2	1447.74	4399.93	N/A	N/A

Note: $P<.001$ comparing endometriosis with control group in every outcome category. N/A = not applicable.

[a] Adjusted for stimulation regime, publication date, and age except where noted.

[b] Includes endometriosis patients with other concurrent infertility factors; controls include all factors except endometriosis.

[c] Adjusted for publication date and age.

[d] Includes only endometriosis patients (all stages) with no other infertility factors, controls are tubal factor only.

[e] Compares stages I–II endometriosis patients with tubal factor controls.

[f] Compares stages III–IV endometriosis patients with tubal factor controls.

Barnhart. IVF in endometriosis-associated infertility. Fertil Steril 2002.

Table 3 also presents the results of the analysis after adjusting for confounding variables. We see a greater negative association with endometriosis and IVF outcomes with a 35% reduction in the change of achieving pregnancy with IVF in women with endometriosis compared with women without it (OR, 0.63; CI, 0.51–0.77). After adjustment for confounding variables, there was a reduction in the OR for all outcomes evaluated, with the exception of implantation rate, which remained unchanged. The difference in all outcomes remained statistically significant. Of note was that the adjusted analysis demonstrated that a significantly fewer number of oocytes were retrieved from women with endometriosis (OR, 0.92; CI, 0.85–0.99), a reversal of the unadjusted finding.

The results of the crude and adjusted comparisons between women with endometriosis only (no other indication for IVF) and tubal factor controls are also reported in Table 3. All outcomes (pregnancy rate, fertilization rate, implantation, mean number of oocytes retrieved, and peak E_2 concentration) are statistically significantly lower in women with endometriosis compared with women with tubal factor. The reversal of association of number of oocytes retrieved in women with endometriosis is again noted after adjustment for confounding factors.

We then separately compared women with stages I–II endometriosis and those with stages III–IV disease with women with tubal factor infertility. The crude and adjusted results of both of these comparisons are presented in Table 3. Findings regarding the comparison of mild endometriosis to patients with tubal factor included significant differences in all crude comparisons and adjusted comparisons with the exception of pregnancy rate, where the strength of association was similar to other comparisons, but results did not achieve statistical significance (OR, 0.79; CI, 0.60–1.03). The comparison of women with severe endometriosis (stage III or IV) to women with tubal infertility demonstrates a large reduction of pregnancy rate, with an OR of 0.46 (CI, 0.28–0.74). Fertilization rate was higher in women with severe endometriosis compared with women with tubal factor (adjusted OR, 1.54; CI, 1.39–1.70).

TABLE 4

Results of bivariate analysis and multiple logistic regression comparing endometriosis (Endo) patients with stage III–IV disease with patients with stage I–II disease.

Outcome	Endo III–IV	Endo I–II	*P*	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Pregnancy rate	13.84	21.12	<0.001	0.60 (.42–.87)	0.64 (.35–1.17)
Fertilization rate	74.47	58.38	<0.001	1.11 (1.09–1.13)	not interpretable
Implantation rate	10.23	11.31	0.003	0.93 (.89–.98)	0.21 (.15–.32)
Mean oocyte count	6.70	8.19	<0.001	0.83 (.78–.87)	0.31 (.24–.39)
Peak E_2	1447.74	5813.38	<0.001	N/A	N/A

Note: Total no. of observations: 669. N/A = not applicable.

[a] Adjusted for publication date and age.

Barnhart. IVF in endometriosis-associated infertility. Fertil Steril 2002.

To further investigate differential effects of IVF outcome by stage of endometriosis, we also directly compared women with mild (stage I or II) endometriosis with women with severe (stage III or IV) endometriosis. The results of this analysis are reported in Table 4. Compared with women with mild endometriosis, women with severe endometriosis have a statistically significantly lower pregnancy rate and implantation rate, have fewer oocytes obtained at retrieval, and have a lower peak E_2 concentration. There was no significant difference in fertilization rate.

DISCUSSION

Endometriosis affects a significant number of women of reproductive age and is a known cause of subfertility (9). There has been some success in overcoming the effects of endometriosis and increasing fecundity with surgical interventions and ovulation induction in conjunction with insemination (18, 25–30); however, many women opt for IVF to enhance their chance of achieving a pregnancy. When the data from previously conflicting studies are pooled in this meta-analysis, women with endometriosis have ≤54% reduction in pregnancy rate after IVF (OR, 0.46; CI, 0.28–0.74) compared with women with tubal factor infertility. The finding of a negative association of endometriosis and a lower pregnancy rate was consistent in all analyses. We noted a statistically significant negative association in the crude analysis and a stronger negative association after controlling for confounding variables. Additionally, we demonstrated a poorer success with IVF with an increase in severity of the disease. There is a 36% reduction in pregnancy rate for those with severe endometriosis compared with those with mild disease (OR, 0.64; CI, 0.35–1.17).

These data demonstrate that all aspects of IVF are affected by the presence of endometriosis including peak E_2 concentration, number of oocytes retrieved, fertilization rate, and implantation rate. These data therefore suggest that the presence of endometriosis affects multiple aspects of the reproductive cycle, including oocyte quality, embryogenesis, and/or the receptivity of the endometrium. Specifically, ovarian response is negatively affected, as noted by a decrease both in the peak E_2 concentration and in the number of oocytes retrieved. Fertilization rate and implantation rates were also statistically and clinically significantly decreased when women with endometriosis were compared with those with all other indications, or tubal-factor infertility only. Thus, it is unlikely that the effect of endometriosis is due solely to alterations of normal pelvic anatomy, and an effect on the developing follicle, oocyte, and embryo is suggested. This is consistent with results of a small study that evaluated pregnancy rates of patients undergoing IVF with donated oocytes, which showed that recipients who had endometriosis had results that were no different than those of patients with other causes of infertility. However, when the results were classified by *donor* factors, the eggs from women with endometriosis led to a statistically significant decrease in pregnancy rate regardless of recipient status (11). This is indicative of a possible detrimental effect in oocyte development even before the oocyte is released into the peritoneum, where it may come in contact with the endometriosis lesion or its secretory products.

Interestingly, the negative association between endometriosis and number of oocytes retrieved was only noted in the adjusted analysis, after controlling for confounding variables. The reversal of the association between the presence of endometriosis and the number of oocytes retrieved per patient demonstrates that women identified as having endometriosis were in aggregate more likely to have a high number of oocytes secondary to factors other than the presence of endometriosis. Controlling for confounding factors, which include age, stimulation regime, and publication date (and therefore IVF technique) allows an independent assessment of the impact of endometriosis on the number of oocytes retrieved. This negative association would have been missed without a multivariable analysis. These results differ from those reported in the analysis of the Society for Reproductive Technology (SART) registry because of the differences between the population of women undergoing IVF for endometriosis and those with tubal factor infertility. The

SART analysis is not adjusted for confounding as our analysis is. Controlling for confounding strengthened all of the negative associations noted in this study with the exception of implantation rate, which remained unchanged. One possible explanation for this is that in aggregate, women undergoing IVF for the indication of endometriosis had better prognosis for success in terms of other demographic factors known to affect IVF outcome (see Table 1). The effect of endometriosis on implantation may be independent of these known factors.

We also conducted analyses to assess the differential effect of mild and severe endometriosis compared with controls and compared IVF outcome of women with mild and severe endometriosis. There were significant negative associations in all parameters evaluated when women with either severe or mild endometriosis were compared with controls, including pregnancy rate. The stronger negative associations consistently were noted in women with severe disease. When directly compared, women with severe endometriosis were noted to have a decrease in pregnancy rate, implantation rate, a decrease in the mean number of oocytes retrieved per cycle, and a lower peak E_2 concentration than women with mild endometriosis. The only exception to this trend was fertilization rate.

The fertilization rate in women with severe endometriosis was higher than that in women with tubal factor infertility (OR, 1.54; CI, 1.39–1.70) and higher in women with severe endometriosis compared with women with mild endometriosis (OR, 1.11; CI, 1.09–1.13). One possible reason for this may be that lesions associated with severe endometriosis often do not have active endometrial glands, but instead are "burned-out" lesions resulting in pelvic adhesions. Thus, it may be the secretory components of an active lesion that are affecting oocyte quality and thus fertilization. This is consistent with results of previous work showing an increase in chemotactic activity in the peritoneal fluid of women with active endometriosis lesions (1, 8, 31).

Limitations to this study include the limitations of the studies reviewed. A meta-analysis is only as good as the data summarized. None of the studies reviewed were randomized controlled trials. Observational studies may be affected by bias and confounding. However, given the strength and consistency of the results reported, it is unlikely that unknown unbalanced factors could explain these results. One important limitation to our analysis is that the summarized studies did not consistently report which patients (if any) enrolled were treated for endometriosis before initiation of IVF. Therefore, we are unable to draw any conclusions as to whether treatment of endometriosis will improve IVF outcome. Similarly, we are unable to assess the impact of endometriosis on the chance of obtaining a multiple birth after IVF, or on the rate of miscarriage. We were also unable to determine whether there was heterogeneity among tubal factor patients in terms of presence or absence of hydrosalpinx, a possible confounding factor.

It is important to note that although we have demonstrated that the success with IVF is lower for women with endometriosis compared with women without it, the overall chance of achieving a pregnancy with IVF (25%) in these 22 studies was still very good. In addition, IVF success rates have risen dramatically in recent years, with proportional increases in success for women with endometriosis. Therefore, despite a lower success rate compared with that of women undergoing IVF for other indications, IVF is still the most successful form of assisted reproduction that can be offered to an infertile couple with endometriosis. It has already been demonstrated that the presence of endometriosis decreases pregnancy rates for couples who attempt conception without assisted reproductive technologies or with ovulation induction (14, 18, 26–30). On the basis of these findings, we recommend that patients with endometriosis should be referred for early aggressive infertility treatment, including IVF, to increase chances of conception.

References

1. Lessey BA, Castelbaum AJ, Sawin SW, Buck CA, Schinnar R, Bilker W, et al. Aberrant integrin expression in the endometrium of women with endometriosis. J Clin Endocrinol Metab 1994;79:643–9.
2. Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am 1997;24:235–8.
3. 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.
4. Ayers JWT, Birenbaum DL, Jiaram Menon KM. Luteal phase dysfunction in endometriosis: elevated progesterone levels in peripheral and ovarian veins during the follicular phase. Fertil Steril 1987;47:925–9.
5. Hahn DW, Carraher RP, Foldesy RG, McGuire JL. Experimental evidence for failure to implant as a mechanism of infertility associated with endometriosis. Am J Obstet Gynecol 1986;155:1109–13.
6. Pellicer A, Oliveira N, Ruiz A, Remohi J, Simon C. Exploring the mechanism(s) of endometriosis-related infertility: an analysis of embryo development and implantation in assisted reproduction. Hum Reprod 1995;10:91–7.
7. Yovitch JL, Matson PL, Richardson PA, Hilliard C. Hormonal profiles and embryo quality in women with severe endometriosis treated by in vitro fertilization and embryo transfer. Fertil Steril 1988;50:308–13.
8. Lucena E, Cubillos J. Immune abnormalities in endometriosis compromising fertility in IVF-ET patients. J Reprod Med 1999;44:458–64.
9. Marcoux S, Maheux R, Berube S, Canadian Collaborative Group on Endometriosis. Laparoscopic surgery in infertile women with minimal or mild endometriosis. N Engl J Med 1997;337:217–22.
10. Matson PL, Yovitch JL. The treatment of infertility associated with endometriosis by in vitro fertilization. Fertil Steril 1986;46:432–4.
11. Simón C, Gutierrez A, Vidal A, del los Santos MJ, Tarin JJ, Remohi J, et al. Outcome of patients with endometriosis in assisted reproduction: results from in-vitro fertilization and oocyte donation. Hum Reprod 1994;9:725–9.
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. Padigas 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. Hennekens CH, Buring JE. Epidemiology in medicine. Boston: Little, Brown, 1987.
16. Mulrow C, Cook D, eds. Systematic reviews: synthesis of best evidence for health care decisions. Philadelphia: American College of Physicians, 1998.
17. Jones HW, Acosta AA, Andrews MC, Garcia JE, Seegar Jones G,

Mayer J, et al. Three years of in vitro fertilization at Norfolk. Fertil Steril 1984;42:826–34.
18. Kodama H, Fukuda J, Karube H, Matsui T, Shimizu Y, Tanaka T. Benefit of in vitro fertilization treatment for endometriosis associated infertility. Fertil Steril 1996;66:974–9.
19. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125–37.
20. Pal L, Shifren JL, Isaacson KB, Chang Y, Leykin L, Toth TL. Impact of varying stages of endometriosis on the outcome of in vitro fertilization–embryo transfer. J Assist Reprod Genet 1998;15:27–31.
21. Arici A, Oral E, Bukulmez O, Duleba A, Olive DL, Jones EE. The effect of endometriosis on implantation: results from the Yale University in vitro fertilization and embryo transfer program. Fertil Steril 1996;65:603–7.
22. Yanushpolsky EH, Best CT, Jackson KT, Clarke RN, Barbieri RL, Hornstein MD. Effects of endometriomas on oocyte quality, embryo quality, and pregnancy rates in in vitro fertilization cycles: a prospective case-controlled study. J Assist Reprod Genet 1998;15:193–7.
23. Cahill DJ, Wardle PG, Harlow CR, Hull MGR. Effect of progesterone therapy on follicular development, related hormone concentrations and fertilization in-vitro in unstimulated cycles and unexplained and endometriosis-associated infertility. Hum Reprod 1996;11:647–50.
24. Chillik CF, Acosta AA, Garcia JE, Perera S, Van Uem JFHM, Rosenwaks Z, et al. The role of in-vitro fertilization in infertile patients with endometriosis. Fertil Steril 1985;44:56–61.
25. Wheeler JM, Malinak LR. Recurrent endometriosis: incidence, management, and prognosis. Am J Obstet Gynecol 1983;146:247–53.
26. Guzick DS, Yao YAS, Berga SL, Krasnow JS, Stovall DW, Kubnik CJ, et al. Endometriosis impairs the efficacy of gamete intrafallopian transfer: results of a case control study. Fertil Steril 1994;62:1186–91.
27. Adamson GD. Treatment of endometriosis-associated infertility. Semin Reprod Endocrinol 1997;15:263–71.
28. Tummon IS, Asher LJ, Martin JS, Tulandi T. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. Fertil Steril 1997;68:8–12.
29. Falcone T, Goldberg JM, Miller KF. Endometriosis: medical and surgical intervention. Curr Opin Obstet Gynecol 1996;8:178–83.
30. Lu PY, Ory SJ. Endometriosis: current management. Mayo Clinic Proc 1995;70:453–63.
31. Lessey BA. Medical management of endometriosis and infertility. Fertil Steril 2000;73:1089–96.
32. Wingfield M, Healy DL. Endometriosis: medical therapy. Baillieres Clin Obstet Gynaecol 1993;7:813–38.
33. Huang HY, Lee CL, Lai YM, Chang MY, Chang SY, Soong YK. The outcome of in vitro fertilization and embryo transfer therapy in women with endometriosis failing to conceive after laparoscopic conservative surgery. J Am Assoc Gynecol Laparoscopists 1997;4:299–303.
34. Bergendal A, Naffah S, Nagy C, Bergqvist A, Sjoblom P, Hillensjo T. Outcome of IVF in patients with endometriosis in comparison with tubal-factor infertility. J Assist Reprod Genet 1998;15:530–4.
35. Gerber S, Paraschos T, Atkinson G, Margara R, Winston RML. Results of IVF in patients with endometriosis: the severity of the disease does not affect outcome, or the incidence of miscarriage. Hum Reprod 1995;10:1507–11.
36. Inoue M, Kobayashi Y, Honda I, Awaji H, Fujii A. The impact of endometriosis on the reproductive outcome of infertile patients. Am J Obstet Gynecol 1992;167:278–82.
37. Tanbo T, Omland A, Dale PO, Abyholm T. In vitro fertilization/embryo transfer in unexplained infertility and minimal peritoneal endometriosis. Acta Obstet Gynecol Scand 1995;74:539–43.
38. Mills MS, Eddowes HA, Cahill DJ, Fahy UM, Abuzeid MIM, McDermott A, et al. A prospective controlled study of in vitro fertilization, gamete intra-fallopian transfer and intrauterine insemination combined with super ovulation. Hum Reprod 1992;7:490–4.
39. Frydman R, Belaisch-Allart JC. Results of in vitro fertilization for endometriosis. Contrib Gynecol Obstet 1987;16:328–31.
40. Wardle PG, McLaughlin EA, McDermott A, Mitchell JD, Ray BD, Hull MGR. Endometriosis and ovulatory disorder: reduced fertilization in vitro compared with tubal and unexplained infertility. Lancet 1985;3:236–9.
41. Mahadevan MM, Trounson AO, Leeton JF. The relationship of tubal blockage, infertility of unknown cause, suspected male infertility, and endometriosis to success of in vitro fertilization and embryo transfer. Fertil Steril 1983;40:755–62.
42. Devroey P, Braeckmans P, Camus M, Khan I, Smith J, Staessen C, et al. Gamete intra-fallopian transfer versus in vitro fertilization and embryo transfer in endometriosis. Contrib Gynecol Obstet 1987;16:332–6.
43. Tummon IS, Colwell KA, MacKinnon CJ, Nisker JA, Yuzpe AA. Abbreviated endometriosis-associated infertility correlates with in vitro fertilization success. J In Vitro Fert Embryo Transfer 1991;8(3):141–53.
44. Issacs ND, Hines RS, Sopelak VM, Cowan BD. Ovarian endometriomas do not adversely affect pregnancy success following treatment with in vitro fertilization. J Assist Reprod Genet 1997;14:551–3.