Uterine Leiomyomas and Their Effect on In Vitro Fertilization Outcome: A Retrospective Study

SUNNY H. JUN,[1] ELIZABETH S. GINSBURG,[1] CATHERINE RACOWSKY,[1] LAUREN A. WISE,[1] and MARK D. HORNSTEIN[1,2]

Purpose: *The effect of uterine leiomyomas on the outcome of in vitro fertilization (IVF) treatment has been controversial. This study was undertaken to clarify influence of fibroids on IVF success, in a large population with age and other potential confounding variables controlled for in the analysis.*

Methods: *A population of 141 patients with and 406 without leiomyomata undergoing their first IVF cycle was studied.*

Results: *The association between uterine leiomyomas and assisted reproduction treatment outcome was not statistically significant (OR = 0.73, 95% CI: 0.49–1.19, p = 0.21) after controlling for age and other risk factors. Also, fibroids neither affected the risk of spontaneous abortion (OR = 1.06, 95% CI: 0.44–2.60) nor the risk of ectopic pregnancy (OR = 0.78, 95% CI: 0.08–8.02). Location of fibroids (intramural vs. submucosal/subserosal) and their size had no significant effect on pregnancy outcome.*

Conclusions: *Results from our analyses indicated that in vitro fertilization outcome was not affected by the presence of uterine leiomyomas. Therefore, in patients with normal uterine cavities and fibroids less than a certain size (i.e., <7 cm), undergoing myomectomies as a prerequisite for assisted reproduction treatment is seriously questionable.*

KEY WORDS: Assisted reproduction cycle; effect on in vitro fertilization outcome; fibroids; myomectomy; uterine leiomyomas.

INTRODUCTION

The association between infertility and uterine leiomyomas (fibroids), the most common benign pelvic tumors in women of reproductive age, has yet to be clearly defined (1). There is an increased prevalence of infertility and miscarriages in women having fibroids, with size and location being the two most important factors (2). Reduced sperm transport efficiency for fertilization because of distortion of the uterine cavity, vascular changes, and irritation of the endometrium, resulting in poor implantation and mechanical obstruction of the uterine tubes are some of the possible mechanisms by which fibroids may cause infertility (2–5). Higher pregnancy rates and lower rates of spontaneous abortions have been reported after myomectomy (4) which further supports this idea.

The incidence of fibroids increases with age (1). Because of a growing patient population of older women undergoing in vitro fertilization (IVF), uterine fibroids and their effect on the outcome of assisted reproduction is of great interest. However, this issue still remains controversial. Implantation rates with leiomyomas may be reduced only in those with uterine cavity deformation (6). This study found no significant effect on IVF outcome as long as there was no change in uterine contour. Ramzy *et al.* (7) found fibroids to have no effect on implantation and miscarriage rates in IVF and intracytoplasmic sperm injection (ICSI) procedures unless the leiomyomas were >7 cm in size and caused distortion of the endometrial cavity (7). However, others found that intramural and submucosal fibroids considerably reduce the pregnancy and implantation rates even with a normal endometrial cavity (8). Consistent results of impaired pregnancy and delivery rates in patients with

[1] Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.
[2] To whom correspondence should be addressed at Department of Obstetrics and Gynecology, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. e-mail: mhornstein@partners.org.

leiomyomas undergoing their assisted reproduction cycles were presented by Stovall *et al.* (9).

The purpose of our study was to help clarify this controversy by examining a much larger patient population than those previously reported for the effect of uterine leiomyomas on in vitro fertilization outcome, with age and other potential confounding variables accurately controlled for in the analyses.

MATERIALS AND METHODS

Medical records from Brigham and Women's Hospital (BWH), of IVF patients diagnosed with uterine leiomyomas and who were undergoing their first assisted reproduction cycle between January 1997 and December 1998 were analysed retrospectively. Baseline pelvic ultra-sonography results were used to determine presence, size, and location of fibroids. All ultrasounds and laboratory studies were performed at BWH. As part of the standard fertility evaluation, a hysterosalpingogram, hysteroscopy, or sonohysterogram was performed on each patient.

Of the 587 patients initially reviewed, 40 patients were excluded from the study because their outcomes were associated with donor eggs, gestational carriers, frozen embryos, GIFT and ZIFT procedures. The remaining 547 IVF patients were divided into two groups: 141 patients with fibroids (exposed) and 406 without (unexposed). Patients with prior myomectomies, whose ultrasound showed no fibroids were considered unexposed at the time of the study. This study was approved by the Partner's Healthcare System Human Research Committee for medical records review.

Stimulation Protocols

Controlled ovarian hyperstimulation was performed with luteal down-regulation. The standard IVF protocol was as follows: Leuprolide acetate (Lupron, TAP Pharmaceuticals, Deerfield, IL; 1.0 or 0.5 mg depending on prior gonadotropin response), was begun either a week after documentation of urinary LH surge, or on the day after a midluteal progesterone determination, and was continued until at least Day 2 of menses. Following appropriate downregulation gonadotropin therapy was begun with ether purified FSH (Fertinex, Serono Laboratories, Norwell, MA), recombinant FSH (Follistim, Organon, West Orange, NJ; Gonal-F, Serono Laboratories, Norwell, MA) or human menopausal gonadotropins (Humegon, Organon, West Orange, NJ).

Follicle growth monitoring, achieved with use of ultrasonography and measurement of serum estradiol, was begun on stimulation Day 6, and then performed every 1–3 days, as indicated. A dose of 10,000 IU of hCG (Profasi, Serono, Norwell, MA) was administered intramuscularly when two follicles reached a maximal diameter of >20 mm (mean 16.5 mm) with estradiol ≥500 pg/mL.

Transvaginal oocyte retrieval was performed 36 hours after hCG administration. Luteal progesterone supplementation was initiated the day after oocyte retrieval and achieved by one of three regimens: 1) daily intramuscular progesterone (50 mg); 2) daily vaginal gel (8% progesterone; Crinone, Wyeth-Ayerst, Philadelphia, PA); or 3) twice daily vaginal progesterone suppositories (50–100 mg). Embryo transfer was performed 3 or 5 days after retrieval.

Statistical Analyses

Unconditional multiple logistic regression was used to derive odds ratios (ORs) of IVF outcome associated with uterine leiomyoma and to calculate 95% confidence intervals (CIs), while controlling for age (continuous) and eight other risk factors: number of days stimulated, number of eggs retrieved, number of follicles stimulated, number of fertilized eggs, number of cells per embryo, number of cells in embryos transferred, year of treatment (1997 vs. 1998), and physician's diagnosis of the primary cause of infertility (using indicator terms for adhesions/tubal factor/pelvic inflammatory disease (PID), anovulatory/oligoovulation/polycystic ovarian syndrome (PCOS), cervical factor/DES/immunological/ovarian cancer, endometriosis, male factor, unexplained, uterine factor, and not indicated).

Three separate analyses were run using a modified dichotomous outcome variable for "no pregnancy" (reference category) versus "pregnancy ending in either 1) livebirth, 2) spontaneous abortion, or 3) ectopic pregnancy." The same set of risk factors was controlled for in each of the three analyses.

In a separate analysis, consisting of the subset of women with fibroids (*n* = 141), we added indicator terms for uterine leiomyoma locations (intramural vs. submucosal/subserosal) and sizes to determine whether these factors had any independent effect on IVF outcome, after controlling for the same set of potential confounders. To maximize the number of women in each of the exposure groups, sizes were divided into quartiles (<1.05 cm, 1.05–1.5 cm, 1.6–2.3 cm, >2.3 cm). In all logistic regression models,

Table I. Descriptive Statistics of Women With and Without Fibroids

Variable	Fibroids (Mean ± SD)	No Fibroids (Mean ± SD)	95% CI	p
Age (y)	36.9 ± 4.0	34.8 ± 4.2	(1.29, −2.87)	<.0001
Number of days stimulated	11.4 ± 2.0	11.2 ± 1.8	(−0.10, 0.62)	.16
Number of eggs retrieved	14.1 ± 8.3	16.4 ± 9.4	(−4.07, −0.47)	.01
Number of fertilized eggs	7.7 ± 5.6	8.8 ± 6.7	(−2.34, 0.18)	.09
Average number of cells in embryo within the cohort	5.1 ± 1.5	4.9 ± 1.4	(−0.13, −0.45)	.27
Number of cells transferred	5.7 ± 1.8	5.6 ± 1.7	(−0.27, 0.41)	.67
Number of follicles stimulated	12.2 ± 7.4	13.3 ± 6.9	(−2.44, 0.24)	.11

we considered a characteristic to be independently associated with uterine leiomyoma if deleting that variable from the model resulted in a statistically significant likelihood ratio test (10). We considered a characteristic to confound the association between fibroids and IVF success if deleting that variable from the model containing all other independent predictors resulted in a change of 2% or more in the OR for the association between leiomyoma and pregnancy success. We used a lower cutoff than the conventionally used 10% change in point estimate because we wanted to minimize possible confounding (11). Prior studies on IVF outcome consistently demonstrate that age is an important predictor of pregnancy success.

To assess the presence of effect modification between age and fibroids, we inserted an interaction term into a logistic regression model with main effects. If the inclusion of the interaction term resulted in a statistically significant Wald test statistic (10), age would be considered an effect modifier of the relationship between fibroids and IVF outcome. Then, age-stratified ORs would be presented.

Two-sample t-test for independent samples with unequal variances (Satterthwaire's Method) (11) was applied to assess any mean differences between women with and without fibroids with respect to age, number of days stimulated, number of eggs retrieved, number of fertilized eggs, number of cells in embryo, number of cells transferred, and number of follicles stimulated. Results were reported as mean (SD) with a two-tailed p-value <.05 as statistically significant.

RESULTS

Mean values for number of days stimulated, number of follicles, number of fertilized eggs, number of cells in all embryos within the cohort, and number of cells in embryos transferred were not significantly different between women with and without fibroids (Table I). Statistically significant differences were found between women with and without fibroids for mean age (36.9 vs. 34.8 years, respectively; 95% CI: 1.29–2.87) and mean number of eggs retrieved (14.1 vs. 16.4 eggs, respectively; 95% CI: −4.07–0.47). Women without fibroids were on average over 2 years younger than women with fibroids, and similarly, women without fibroids retrieved on average two eggs per cycle more than women with fibroids did.

Of the 141 patients with fibroids, 43 (30.5%) became pregnant after one IVF cycle compared to 169 (41.6%) of 406 patients without fibroids ($p = .23$) (Table II). Among women with fibroids, 8/43 (18.6%) pregnancies resulted in spontaneous abortion and 1/43 (2.3%) in an ectopic pregnancy. Women without fibroids had 22/169 (13.0%) spontaneous abortions and 5/169 (2.9%) ectopic pregnancies. An analysis of the crude data revealed that women with fibroids

Table II. Association Between Fibroids and Pregnancy Outcome in IVF Patients

Pregnancy outcome	Fibroids, N (%)	No Fibroids, N (%)	Crude OR	Adjusted OR[a]	95% CI[a]	p[a]
No positive pregnancies	98 (69.5)	237 (58.4)	1.00	1.00	—	—
All pregnancies	43 (30.5)	169 (41.6)	0.62	0.76	0.48–1.19	0.23
Live Birth	34 (79.1)	142 (84.0)	0.58	0.73	0.49–1.19	0.21
Spontaneous Abortions	8 (18.6)	22 (13.0)	0.88	1.06	0.44–2.6	0.89
Ectopic Pregnancies	1 (2.3)	5 (2.9)	0.48	0.78	0.075–8.02	0.83

[a] Adjusted for (continuous) age, (continuous) number of days stimulated, (continuous) number of follicles stimulated, (continuous) average number of cells in embryo within cohort, (continuous) number of cells in embryos transferred, year of treatment and diagnosis of the primary cause of infertility.

Table III. Association Between Size of Fibroid (in Quartiles) and IVF Outcome (Live Birth vs. No Pregnancy)

Fibroid size (n)	Live births	No pregnancy	OR crude	OR adjusted (95% CI)[a]	p^a
<1.05 cm (37)	9	28	1.00	1.00	—
1.05–1.50 cm (36)	12	24	1.56	1.41 (0.40–5.01)	0.59
1.60–2.30 cm (33)	12	21	1.78	1.65 (0.47–5.77)	0.43
>2.30 cm (35)	10	25	1.24	1.97 (0.49–7.97)	0.34

[a] Adjusted for (continuous) age, (continuous) number of days stimulated, (continuous) number of follicles stimulated, (continuous) average number of cells in embryo within cohort, (continuous) number of cells in embryos transferred, year of treatment and diagnosis of the primary cause of infertility.

were less likely than women without fibroids to have a livebirth (OR = 0.58, 95% CI: 0.37–0.90, p = .015). However, after adjusting for age and other potential confounders, the association was much weaker and no longer statistically significant (OR = 0.73, 95% CI: 0.49–1.19, p = .21). Fibroids were also not associated with risk of spontaneous abortion (OR = 1.06, 95% CI: 0.44–2.6) or risk of ectopic pregnancy (OR = 0.78, 95% CI: 0.08–8.02), although the numbers for these outcomes were small (Table II).

In a separate analysis among women with fibroids, there was no association between the size of the fibroid and pregnancy outcome (livebirth vs. no pregnancy), after adjusting for age, number of eggs retrieved, number of fertilized eggs, number of follicles stimulated, number of days ovaries were stimulated, or within cohort number of cells in embryos transferred, year of treatment, primary cause of infertility, and fibroid location (Table III). There was a modest trend of increasing likelihood of livebirth with increasing size of fibroid after controlling for potential confounders, but this trend was not statistically significant. Location of fibroid (intramural vs. submucosal/subserosal) had no significant effect on pregnancy outcome (OR = 0.49, 95% CI: 0.09–3.12).

DISCUSSION

The objective of this study was to test our hypothesis that there is no association between fibroids and IVF pregnancy rates. Age was the strongest independent predictor of pregnancy outcome and was determined to be a strong confounder of the relationship between uterine leiomyoma and pregnancy outcome. For each 1-year increase in a woman's age, the likelihood of pregnancy decreases by almost 10%, after controlling for fibroids and other risk factors (OR = 0.91, 95% CI: 0.86–0.96). After removing age from a logistic regression model consisting of fibroids and all other potential confounders, the likelihood ratio test was highly statistically significant; its deletion resulted

in a 24% change in the exposure effect estimate. The Wald test for heterogeneity of OR did not reveal any effect modification by age on the association between fibroids and IVF outcome. In women undergoing their first assisted reproduction cycle, results from our analyses indicated that uterine leiomyomas do not have an independent effect on IVF success.

Myomectomies have been shown to improve fertility with a 44.4% pregnancy rate postoperatively in a prospective clinical study (12). Surgical removal of fibroids >5 cm in diameter greatly improved pregnancy success by 67% (13). In several other uncontrolled studies, women having no other infertility factor associated with fibroids improved in fertility performance by a 54% pregnancy rate postmyomectomy (14–16). However, when Seoud *et al.* (17) specifically examined the effect of prior myomectomy on IVF success, he found no significant association.

Although myomectomies have been shown to decrease the rate of spontaneous abortions (4), our results were not consistent with a correlation between fibroids and increased pregnancy wastage; however, the accuracy of this observation is limited by the sample size. In our patient population, for women with and without fibroids, the spontaneous abortion rates were 18.6% and 13.0%, respectively. Also, the ectopic pregnancy rates among patients with and without a leiomyoma were 2.3% and 2.9%, respectively. Differences in both spontaneous abortion and ectopic pregnancy rates were not statistically significant. Because the majority of fibroids in our study population were intramural (87.9%) and <4 cm in size, there is a possibility that an increased rate of miscarriages is seen mostly with submucosal fibroids distorting the uterine cavity or ones larger than our mean size (1). Earlier studies (9, 18) have been consistent with our results in finding no significant relationship between fibroids and increased pregnancy loss.

A fibroid size of <7 cm in patients with a normal uterine cavity size were found not to have a significant effect on IVF outcome (7). The differences in clinical pregnancy rates among women with and without

fibroids were also not statistically significant. The mean size of all fibroids reported in (7) was 3.5 ± 0.9 cm, which was considerably larger than the mean size, in our study, of 1.93 ± 1.26 cm. In the present study, the majority of our patients had an average leiomyoma size <4 cm with all tumors <7 cm except for one 7.1-cm fibroid. Therefore, in both studies, fibroid size was not a factor in IVF outcome.

Unlike prior studies, the present study includes an adjustment for age in our analyses. In a study in which women with fibroids had an older age distribution ($p < .05$), the authors did not control for age in their analyses (7). In other studies, patients were matched by age; however, the process of matching by age using two broad categories (<35 and ≥35 years) is not precise (9). Thus far, our sample size was one of the largest ever studied and possessed reasonably sufficient power (64%) to detect a difference between the groups. Power calculations were not reported in most studies. Despite these strengths, however, as a retrospective analysis, there possibly could have been some unknown biases entered into our study. For example, it is likely that physicians performed myomectomies on patients whose fibroids were thought to be problematic, such as submucous or large intramural fibroids. Thus this study cannot exclude the possibility that more clinically significant fibroids might have an adverse impact on IVF outcome.

In conclusion, fibroids are shown not to have a significant effect on IVF outcome after controlling for age and other variables. Further studies are essential in order to confirm our conclusions and to determine the size limit and other potential characteristics of fibroids justifying the need for a myomectomy before undergoing an assisted reproduction cycle.

REFERENCES

1. Wallach EE, Zacur HA (eds): Reproductive Medicine and Surgery. St. Louis, Plenum Medical, 1995

2. Hunt JE, Wallach EE: Uterine factor in infertility: An overview. Clin Obstet Gynecol 1974;17:44–64

3. Jacobson FN, Enzer N: Uterine myomas and endometrium. Obstet Gynecol 1956;7:206–210

4. Buttram VC, Reiter RC: Uterine leiomyomata: Etiology, symptomatology and management. Fertil Steril 1981;36:433–435

5. Vollenhoven BJ, Lawrence AS, Healy DL: Uterine fibroids: a clinical review. Br J Obstet Gynaecol 1990;97:285–298

6. Farhi J, Ashkenazi J, Feldberg D, Dicker D, Ovieto R, Ben Rafael Z: Effect of uterine leiomyomata on the results of in-vitro fertilization treatment. Hum Reprod 1995;10:2576–2578

7. Ramzy AM, Sattar M, Amin Y, Mansoor RT, Seroor GI, Aboulghar MA: Uterine myomata and outcome of assisted reproduction. Hum Reprod 1998;13:198–202

8. Eldar-Geva T, Meagher S, Healy DL, MacLachlan V, Breheny S, Wood C: Effect of intramural, subserosal, and submucosal uterine fibroids on the outcome of assisted reproductive technology treatment. Fertil Steril 1998;70:687–691

9. Stovall DW, Parrish SB, Van Voorhis BJ, Hahn SJ, Sparks AET, Syrop CH: Uterine leiomyomata reduce the efficacy of assisted reproduction cycles: Results of a matched follow-up study. Hum Reprod 1998;13:192–197

10. Hosmer DW, Lemeshow S: Applied Logistic Regression. New York, John Wiley & Sons, 1989

11. Rosner B: Fundamentals of Biostatistics. 4th Ed. Belmont, Wadsworth, 1995

12. Dubuisson JB, Chapron C, Chavet X, Gregorakis SS: Fertility after laparoscopic myomectomy of large intramural myomas: Preliminary results. Hum Reprod 1996;11:518–522

13. Rosenfeld DL: Abdominal myomectomy for otherwise unexplained infertility. Fertil Steril 1986;46:328–330

14. Brown AB, Chamberlain R, Telinde RW: Myomectomy. Am J Obstet Gynecol 1956;71:759–763

15. Babaknia A, Rock JA, Jones HW: Pregnancy success following abdominal myomectomy for infertility. Fertil Steril 1978;30:644–647

16. Ranney B, Frederick I: The occasional need for myomectomy. Obstet Gynecol 1979;53:437–441

17. Seoud MA, Patterson R, Muasher SJ, Coddington CC: Effect of myomas or prior myomectomy on in vitro fertilization (IVF) performance. J Assist Reprod Genet 1992;9:655–658

18. Muram D, Gillieson M, Walters JH: Myomas of the uterus in pregnancy: Ultrasonographic follow-up. Am J Obstet Gynecol 1980;138:16–19