

ORIGINAL ARTICLES

The presence of small uterine fibroids not distorting the endometrial cavity does not adversely affect conception outcome following embryo transfer in older recipients

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Summary

Purpose: To determine if uterine fibroids have a negative impact in older patients having embryo transfer (ET).

Methods: Comparison of clinical and viable pregnancy rates, implantation rates, and spontaneous abortion rates in older (>35) oocyte or embryo recipients with uterine leiomyomata compared to comparable patients without fibroids.

Results: The clinical pregnancy rate per transfer was 56% in the fibroid group vs 64% for the controls. Implantation rates were also very similar (33 vs 32%). There were no spontaneous abortion or preterm deliveries <32 weeks in the fibroid group and the average term of pregnancies was also similar.

Conclusion: Small fibroids not distorting the uterine cavity do not seem to negatively affect conception outcome even in older women.

Key Words: Donor oocytes; Fibroids; Uterine fundus and corpus.

Introduction

It is becoming more common to treat older women for infertility. Many women have delayed childbearing for a variety of reasons. This delay can add other fertility factors not commonly seen in younger women. It is well known that fecundity decreases with age due to decreased ovarian function and number of oocytes as well as an increased incidence of aneuploidy. These factors can be corrected through the use of donor oocytes if attempts at ovulation induction fail. Pelvic pathology, such as uterine fibroids and endometriosis, also increases with age [1]. Uterine fibroids are the most common solid pelvic tumor in women [2-7].

Most physicians believe that large myomas (≥ 7 cm) should be surgically removed [8, 9]. The majority of myomas are asymptomatic and do not require any treatment in women not attempting to achieve a pregnancy [6, 10]. However, the treatment of uterine fibroids in women undergoing fertility treatment is controversial.

Many studies have been conducted to determine the effect of fibroids on the outcome of in vitro fertilization-embryo transfer (IVF-ET). Farhi *et al.*, found that decreased implantation is associated with uterine fibroids only when uterine cavity abnormalities co-exist [11]. Stovall *et al.*, found reduced implantation in women with intramural or subserosal leiomyomata; they did not, however distinguish between the two types of myomas [12]. Eldar-Geva *et al.*, reported lower pregnancy rates (PRs) and implantation rates in women with intramural and

submucosal fibroids despite the absence of uterine cavity distortion while no impact was found with respect to subserosal fibroids [7]. Ramzy *et al.*, found that uterine corporeal myomata that did not encroach upon the uterine cavity and were < 7 cm in diameter did not affect the implantation or miscarriage rates in IVF and intracytoplasmic sperm injection (ICSI) [9]. Check *et al.*, also found that intramural and subserosal leiomyomas were not related to pregnancy and implantation rates following IVF-ET in women with no other uterine abnormalities nor prior uterine surgery [13]. All of these studies were conducted on patients who had undergone controlled ovarian hyperstimulation (COH) and assisted reproductive technology (ART).

The study presented herein was conducted to determine the effect of uterine fibroids on implantation and conception outcome in donor oocyte and embryo recipients. Since this group is older than women who undergo oocyte retrievals, it was considered that these patients might have a greater number of fibroids or larger ones and that these fibroids might have a greater effect on the IVF-ET outcome. We believe this study to be the first to evaluate the impact of uterine fibroids in an IVF population who has not undergone COH.

Materials and Methods

All donor oocyte and embryo recipients at our IVF center having their first ET between January 1, 1997 and March 31, 1998 and were >35 years old were included in the study. Patients excluded were those having a prior pregnancy through our practice, or those with a history of previous myomectomy

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or other uterine surgery, or uterine cavity abnormalities, e.g. septum, endocervical polyps or endometrial compression or distortion by the known fibroids. Patients monitored outside our own institution were also excluded. All of the patients with fibroids had at least one intramural fibroid; some also had co-existing subserosal fibroids, but no patients had submucosal fibroids. Most patients were eliminated because of prior surgery and/or that the monitoring was not performed in our center. Nine recipients with fibroids were compared to 11 recipients without fibroids.

Diagnosis of uterine fibroids was made using transvaginal sonography performed with a multi-frequency endovaginal transducer on a GE Logic 400 (General Electric Medical Systems, Milwaukee, WI). Recorded was the type of fibroid (intramural, subserosal, submucosal, or pedunculated) based on the location in the uterus as well as the measurements of the dimensions of the fibroids, i.e., length, width and depth, and the mean diameter was then calculated. Also recorded was the position of the fibroid in the uterus based on height (fundus, corpus, lower uterine segment or cervical). The size of the fibroid was remeasured every three months to determine any increase or decrease in size.

In preparation for ET, all patients were treated with hormone replacement therapy. Those with some ovarian function remaining were down-regulated with leuprolide acetate (LA) until they were synchronized with their oocyte donor. Once synchronization occurred, the LA dosage was decreased for the first five days of 17 Beta estradiol (E2) therapy and then discontinued. E2 was administered orally on a daily basis in graduating dosages; 2 mg for the first five days, increasing to 4 mg for the next four days and then 6 mg for five days. On the fifth day of 6 mg of E2, sonographic evaluation was performed to evaluate the endometrial thickness and echo pattern. Women with no ovarian function commenced estrogen therapy in the same regimen on the same day that their oocyte donor started gonadotropin therapy. An endometrial thickness of at least 8 mm and a trilaminar echo pattern was considered to be acceptable for ET. If the donor was not ready for her injection of human chorionic gonadotropin (hCG) at this time, the patient remained on the same dosage of E2 for an extended period of time. Oocyte recipients whose endometrium did not reach the acceptable criteria for ET had their dosage of E2 increased and ultrasound examination repeated on the estimated day of their donor's hCG injection.

If the endometrial receptiveness remained inadequate or synchronization failed to occur, all embryos were then cryopreserved. The patient started preparation for frozen ET on day 2 of following a cycle with oral E2. Patients receiving donor embryos were treated with E2 in graduating dosages until the acceptable endometrial thickness and echo pattern were observed sonographically. Donor embryos had been cryopreserved for one to seven years.

All embryos were transferred on the fourth day of progesterone (P) supplementation. Hormone replacement therapy was continued until the patient had a negative pregnancy test, or, in the event of pregnancy, through at least the first trimester.

Factors evaluated were clinical PR, implantation rate, live birth rate and fetal age at delivery. Clinical pregnancy was determined by the presence of a gestational sac in the uterus seen by transvaginal sonography.

Statistical analysis included chi-square analysis and t-tests as indicated. A p-value of .05 was used to assess significance.

Results

There were nine oocyte recipients with fibroids who met the criteria for inclusion in the study and 11 controls without fibroids. All oocyte recipients were at least 36

years of age. The mean age in the fibroid group was 44.1±4.1 years (41-51) while the mean age of the control group was 41.5±4.5 (36-49) (Table 1). A similar number of embryos were transferred in each group: 3.3±.5 in the fibroid group and 3.4±.5 in the group with no fibroids.

A total of 25 fibroids were observed in the nine recipients. Patients had between one and six fibroids with an average of 2.8±1.4 per patient. Eighteen (72.0%) of the myomas were intramural and seven (28.0%) were subserosal; none were pedunculated. There were five (20.0%) fibroids located in the uterine fundus while 19 (76.0%) were seen in the corpus, one (4%) was in the lower uterine segment and none in the cervix. The average size of the smallest fibroid per patient was 12.4±4.5 mm, ranging from 6.0 to 19.3 mm. The average size of the largest fibroid was 19.7±10.7 mm with a range of 10.7 to 26.0 mm.

The clinical PRs per transfer were 55.6% in the fibroid group and 63.6% for the control group (p=NS) (Table 1). There was no difference in the implantation rate with respect to presence of fibroids (33.3% with fibroids vs. 32.4% without). There were three multiple gestations in women with fibroids and three in the control group. All patients in the fibroid group who had a clinical pregnancy delivered at least one baby as did six of the seven (85.7%) in the control group. The percentage of implanted sacs delivered in the two groups was 90.0% in the fibroid group and 66.7% in the control group (Table 1). The average term of pregnancies was 37.8±2.3 weeks in women with fibroids compared to 38.0±1.3 weeks in the control group. There were no preterm deliveries (<32 weeks) in either group (Table 1).

Discussion

We have previously demonstrated that small intramural intrauterine myomas (<5 cm) in the absence of other uterine abnormalities or uterine surgery do not affect pregnancy and implantation rates in women undergoing oocyte retrieval [13]. The data we now present also confirm the same findings in oocyte and embryo recipients. While these studies agree with the findings of Farhi *et al.*, [11], Ramzy *et al.*, [9], and Seoud *et al.*, [14] they disagree with those of Stovall *et al.*, [12] and Eldar-Geva *et al.* [7].

A possible explanation for the discrepancies is the amount of heterogeneity in the diagnosis of myomas.

Table 1. — Comparison of conception outcome in older oocyte recipients according to the presence or not of intramural uterine fibroids.

	Intramural uterine fibroids (n=9)	Controls (n=11)
Age	44.1±4.1 (41-51)	41.5±4.5 (36-49)
Clinical pregnancy rate	55.6% (5 of 9)	63.6% (7 of 11)
Implantation rate	33.3% (10 of 30)	32.4% (12 of 37)
Multiple pregnancies	3	3
% Implanted sacs that delivered	90.0% (9 of 10)	66.7% (8 of 12)
Week of delivery	37.8±2.3	38.1±1.3
Number preterm deliveries	0	0

When evaluating patients, it is important to consider the number, size and location of fibroids as well as other uterine abnormalities and whether or not endometrial compression is involved. In the Stovall study, 93.3% of the fibroids were located in the uterine fundus [12], whereas we saw only 20.0%. The PRs in our study according to location of the fibroid were 40.0% (2 of 5) in women who had fundal fibroids and 75.0% (3 of 4) in women whose fibroids were not in the uterine fundus ($p=NS$). Eldar-Geva *et al.*, did not provide this information [7].

The average number of fibroids per patient and their sizes were comparable in the Stovall [12], Eldar-Geva [7] and current study. Eldar-Geva *et al.* reported no multiple gestations [7], whereas we had three; Stovall also reported multiple gestations [12]. This finding could possibly represent a difference in the type of patients enrolled in each study.

None of the studies have found an adverse effect of myomas on spontaneous abortion rate. In our previous study, we found a 33.3% spontaneous abortion rate in women with fibroids compared to 16.7% in the controls [13]. However, the differences were not significant. The fact that the present study demonstrated not only no difference in abortion rates in the two groups but a trend toward fewer abortions in those with fibroids suggest that fibroids as a cause of spontaneous abortion is less likely.

In this small series, there was no increased incidence of preterm deliveries. The same was found in a study by Roberts *et al.*, [15] who found no increased risk for preterm labor or delivery as well as other untoward pregnancy outcomes. They did report a higher rate of Caesarean delivery; this data was not available in the current study.

Thus, these data suggest that the presence of small to moderate sized fibroids do not impair conception outcome following ET in women over the age of 40. Before one can conclude that smaller fibroids <7 cm do not adversely impact conception outcome it will be necessary to study a larger group of women with fibroids involving the uterine fundus. To find the small number that we reported we evaluated all 171 transfers in egg or embryo recipients performed over a 15-month time period. A larger series may require a cooperative study among several IVF centers.

Even if a larger series confirms these data that smaller (<7 cm) intramural fibroids which do not compress the uterine cavity do not adversely affect outcome following ET in the majority of patients, each case must be considered on an individual basis since myomectomies have been found to improve IVF-ET outcome [14], as well as PRs for unexplained infertility without IVF-ET [16-18].

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