background: The effect of fibroids that do not distort the endometrial cavity on pregnancy rate (PR) and implantation rate (IR) is controversial. Use of oocyte donor-derived embryos offers an ideal patient population to study the effect of fibroids in patients utilizing assisted reproductive technologies (ARTs). METHODS: We conducted a retrospective cohort study of patients undergoing oocyte donor recipient (ODR) IVF cycles at two tertiary care fertility centres. We examined medical records for the presence of non-cavity-distorting fibroids and evaluated subsequent PR and IR. RESULTS: Three hundred and sixty-nine patients, 94 with fibroids, underwent oocyte donor recipient transfer cycles with fresh embryos. There was no statistical difference in IR (36 versus 38%) or clinical PR (47 versus 54%) between patients with or without fibroids. Neither the location (subserosal versus intramural) and the presence of multiple myomas nor the size of the myomas affected outcomes. Fibroids were more likely to be present in patients with increasing recipient age. CONCLUSIONS: Clinical PR and IR are not affected by the presence of multiple myomas nor the size of the myomas affected outcomes. Fibroids were more likely to be present in patients with increasing recipient age. CONCLUSIONS: Clinical PR and IR are not affected by the presence of non-cavity-distorting leiomyomata. This evidence does not support myomectomy before ART in patients with asymptomatic fibroids that do not significantly distort the endometrial cavity or cause abnormal uterine bleeding.

Key words: ART/fibroid/myoma/oocyte donor

Introduction

Uterine leiomyomas are present in 20–40% of reproductive-age women. Only 5% of fibroids are believed to be located in the submucosa where they can distort the endometrial cavity or cause abnormal bleeding patterns (Novak and Woodruff, 1979). Submucosal and intramural fibroids that protrude into the endometrial cavity have been associated with decreased pregnancy rate (PR) and implantation rate (IR) in patients undergoing IVF (Narayan et al., 1994; Farhi et al., 1995; Varasteh et al., 1999; Bernard et al., 2000). The accepted standard of care for patients with cavity-distorting submucosal fibroids is myomectomy before IVF. The influence of fibroids that do not distort the endometrial cavity on assisted reproductive technology (ART) outcomes remains controversial.

Over the past decade, several retrospective cohort and case-control studies have suggested that intramural and subserosal fibroids have an adverse effect on clinical PR and IR in women undergoing IVF (Elder-Geva et al., 1998; Stovall et al., 1998; Buletti et al., 1999; Oliveira et al., 2004; Gianaroli et al., 2005; Feinberg et al., 2006). An increased incidence of miscarriage has been inconsistently identified in similarly designed studies (Buttram and Reiter, 1981; Li et al., 1999; Vercellini et al., 1999; Campo et al., 2003; Wang and Check, 2004; Gianaroli et al., 2005). Despite the small numbers and retrospective nature of these studies, recent review articles have validated their findings by recommending myomectomy before IVF attempts in patients with large myomas close to the endometrium or in patients with fibroids and multiple failed IVF cycles (Benecke et al., 2005; Rackow and Arici, 2005). Retrospective studies are subject to both publication and ascertainment biases, and subsequent review articles and meta-analyses reproduce these biases.

The strongest evidence supporting a role for fibroids in infertility is reported in a prospective study by Hart et al. demonstrating a marked decrease in PR and IR among patients undergoing IVF with fibroids (Hart et al., 2001). Unfortunately, patients in the cohort with fibroids were an average of 2 years older, which introduces significant selection bias as embryo viability is likely to be different between the two cohorts.

A subsequent study compared 245 patients with fibroids with 245 age-matched patients without fibroids (Oliveira et al., 2004). The results showed no statistically significant difference in IVF PRs between groups; however, a subgroup analysis using patients in the same study found a statistically significant difference when they compared 41 patients with 4- to 7-cm fibroids with 201 patients whose fibroids were <4 cm. These findings suggest that fibroids may affect IVF outcomes, but
only when they are >4 cm in size. By contrast, the study by Hart et al. had an average fibroid size of 2.3 cm and patients were excluded if their fibroids were >5 cm in diameter. The Oliveira et al. group found that patients with fibroids of <4 cm had a statistically insignificant trend towards better PRs than patients in the cohort without fibroids.

Over the last 5 years, several negative studies have been reported, but none have been adequately powered to detect a clinically significant difference (Dietterich et al., 2000; Jun et al., 2001; Surrey et al., 2001; Yarali and Bukulmez, 2002; Wang and Check, 2004). We sought to examine the null hypothesis in a setting where we could control for the effect of recipient age on embryo viability. The uniformly high viability of donor oocyte-derived embryos from fertile young women controls for many of the confounding factors in earlier studies. Oocyte donor recipients (ODRs) have a PR of ~50% per cycle in our institutions, which further improves our probability to detect a statistically significant difference if one exists. This is the first adequately powered study to examine the effect of fibroids on ART outcomes exclusively in fresh ODR cycles.

Materials and methods

Study population

We conducted a retrospective chart review of patients undergoing ODR IVF cycles between January 2003 and July 2005 at one of two tertiary care fertility centres. A total of 431 charts were reviewed, of which 369 met criteria for inclusion in our primary analysis. We included only patients undergoing their first recipient cycle using fresh oocyte donor-derived embryos. Exclusion criteria were defined before initiating our study. We excluded patients who lacked precise information on donor age (n = 18) or number of embryos transferred (n = 8), as well as patients with adenomyosis (n = 13) or Mullerian abnormalities (n = 3). Adenomyosis was diagnosed by either magnetic resonance imaging (MRI) or sonographic findings demonstrating a diffusely enlarged uterus without a focal lesion. In order to further standardize our populations, we also excluded patients whose fresh transfer cycles were cancelled because of poor endometrial thickness, illness or social reasons.

A single researcher who was blinded to outcome until after cohort assignment reviewed all of the charts. Charts were collected and interrogated for the presence of fibroids in patients undergoing recipient transfer cycles using donor oocyte-derived embryos. Information on cycle outcome was recorded on a separate electronic database, and the reviewer did not access this information until after cohort assignment was completed. The proportion of patients with fibroids was evenly distributed between the two clinics.

Before initiating ODR cycles, all patients had a normal evaluation of their uterine cavity to rule out intracavitary lesions. Uterine cavity assessment was performed in accordance with the standard of care at each centre. At one institution, all patients underwent routine saline sonohysteroscopy, whereas the other institution performed screening transvaginal ultrasounds and hysterosalpingograms, with sonohysterograms reserved for abnormal or ambiguous findings. Both centres routinely stored images from any ultrasound in each chart. All printed images from both routine screening and treatment ultrasounds were reviewed for fibroids. All cycle and pre-cycle notes were inspected for any written indication of fibroids that were not identified in accompanying ultrasound images.

In keeping with the standard of care at both institutions, patients with submucosal fibroids or endometrial polyps underwent hysteroscopic removal of these lesions before proceeding with ART cycles. Similarly, patients with cavity-distorting intramural fibroids underwent myomectomy before initiation of any ODR cycles. Repeat transvaginal ultrasounds are performed after surgery, in order to rule out persistent endometrial lesions or cavity-distorting fibroids. Patients who were successfully treated, with appropriate documentation that there was no evidence of persistent polyps or fibroids, were then included for analysis in the ‘no fibroid’ cohort. The study was approved by the Committee on Human Research (the institutional review board at the University of California, San Francisco).

Intervention

All oocyte donors underwent similar gonadotrophin stimulation protocols at the two institutions using down-regulation with either midluteal lupron or late follicular GnRH antagonist treatment. Standard doses of gonadotrophins were used for donor stimulation. hCG injection was administered when the lead follicle was ≥18 mm in diameter. Follicular aspiration was performed 36 h after the administration of the hCG trigger. Insemination of all oocytes was performed using either standard insemination or ICSI.

Recipient preparatory cycles were similar for all patients. A standard protocol was used for all oocyte recipients that included either estradiol (E2) transdermal patches or E2 valerate i.m. injections in incremental doses with the addition of progesterone in oil i.m. injections initiated the day after the oocyte donor was triggered with hCG injection. Fresh embryo transfers were routinely performed on day 3. No day 5 transfers were included in this analysis. There were no significant differences in treatment protocols between patients with or without fibroids.

Outcome variables

The primary outcome measure was clinical pregnancy. IR was a secondary outcome measure. Routine ultrasound was performed between the 6th and 7th weeks and between the 8th and 9th weeks of gestation in order to confirm the presence of gestational sacs and fetal cardiac motion. Clinical pregnancy was defined as the presence of fetal cardiac motion at 9 weeks with no clinical evidence of threatened abortion. IR was calculated as the total number of gestational sacs divided by the number of embryos transferred.

Subgroup analysis was planned to assess differences in fibroid location (subserosal versus intramural), diameter of the largest myoma and number of fibroids. Pregnancy outcomes including miscarriages and ectopic pregnancies were also collected. Additionally, we collected outcome data on patients undergoing multiple recipient transfer cycles to see if there was a higher prevalence of fibroids in patients with repeat cycle failures.

Statistical analysis

The primary aim of this study was to determine the impact of the presence of fibroids as an independent predictor of clinical pregnancy using multipredictor logistic models. The analysis focused on a small set of dependent variables hypothesized on the basis of previous studies to affect the likelihood of success. These variables included fibroids, their location, mean fibroid diameter, number of fibroids, donor age, recipient age, number of embryos transferred and a history of a prior hysteroscopic or abdominal myomectomy. Ethnicity was included in initial models but was dropped from the final analysis due to the lack of its impact on the model. The same logistic regression model was applied to secondary outcomes of spontaneous miscarriage and ectopic pregnancy.

Clinical pregnancy, spontaneous miscarriage and ectopic pregnancy are dichotomous outcomes so logistic regression analysis was
performed. IR was analysed as a continuous outcome, and linear regression analysis was performed using the same predictors as those used in clinical pregnancies.

Power calculations were performed to ensure that we had the ability to detect the 47% decrease in ongoing PR previously reported in the study by Hart and colleagues. After completing a review of the data at the University of California San Francisco (UCSF) Center for Reproductive Health, we added a second centre (Pacific Fertility Center) to increase the power of our study to detect a decrease in PR of 33%. We found that with our study population of 369 cycles, we have a 98% power, with an α error of 0.05 to detect the previously demonstrated difference of 47% in ongoing PR between subjects undergoing IVF with and without fibroids. Additionally, we achieved our goal of 80% power to detect a reduction in PR of 33%, or an absolute reduction of 16.5%.

Results
We identified 369 oocyte donor cycles that met criteria for inclusion in our study. Ninety-four patients had fibroids; 275 did not. Clinical parameters for each population are summarized in Table I. Overall, 10% of patients had previously undergone a myomectomy. These included 21 (22%) patients who presented with recurrent or persistent fibroids and 17 (6%) patients who were free of fibroids. PRs were 53% in both groups of patients, with and without a history of myomectomy. Ten patients had undergone a prior hysteroscopic resection of submucosal fibroids, whereas 29 had previously been treated by an abdominal approach. Our findings relating to myomectomy are consistent with the published literature in that a history of prior myomectomy by either abdominal or transvaginal approach was not predictive of pregnancy (Surrey et al., 2005). Patients with fibroids were significantly older than those without fibroids ($P < 0.001$), and the risk of having fibroids increased by 9% per year of life. There were no other differences in the demographics between the populations with and without fibroids, including the age of the ovum donor.

The clinical PR was not statistically different between the two groups (Table II). PRs were 47% for women with fibroids and 54% in women without (OR = 0.74, 95% CI = 0.45–1.22). IRs were also similar between the groups, 36% in the fibroid group and 38% among patients with no fibroids (OR = 0.92, 95% CI = 0.55–1.53). Miscarriage rates were similar in each group, 15% in women with fibroids and 9% in the no fibroid group (OR = 1.79, 95% CI = 0.80–4.03). Ectopic pregnancy is a rare outcome that occurred in a higher proportion of ODR with fibroids than those without, 4% with fibroids versus 1% in the no fibroid group, but statistical significance was not reached (OR = 4.03, 95% CI = 0.67–27.90).

The average diameter of fibroids in our study was 28 mm. Characteristics of fibroids and outcomes by fibroid type are listed in Table III. Fifteen patients had fibroids of >4 cm in diameter. Among the patients with fibroids, 53% of patients had intramural fibroids only, 20% of patients had both intramural and subserosal fibroids and the remaining 27% of patients had subserosal fibroids. More than one fibroid was reported in 36% of patients, the fibroid cohort.

We attempted to identify any trends or significant differences in our subgroup analysis evaluating factors that have been associated with altered PRs in the past (Table III). More patients had intramural fibroids than subserosal. Both intramural and subserosal fibroids had similar PRs, 45 versus 54%, respectively. Patients with fibroids of >4 cm had similar PRs as patients without fibroids, 67 versus 54%, respectively. Size, number and location of fibroids also failed to predict the chance of pregnancy with each cycle. Logistic regression analysis revealed that none of the other variables including recipient or donor age, presence or absence of endometriosis, recipient BMI, ethnicity or any fibroid characteristics independently predicted clinical PR or IR.

Patients who experienced a miscarriage or failed to get pregnant were followed in subsequent cycles. A similar percentage of patients with and without fibroids failed to conceive with ongoing clinical pregnancies in two consecutive cycles, 24 versus 21%, respectively.

Discussion
When treatment or screening ultrasounds identify fibroids, ‘treatment’ of these lesions is tempting for both providers and patients, especially in cases of unexplained infertility. Initial studies reporting an adverse effect of fibroids on fertility rates arose from small, uncontrolled case reports and case series.
These reports only demonstrated that myomectomy is a viable therapeutic alternative to hysterectomy in women with symptomatic fibroids who desire fertility preservation. Most subsequent studies are limited by sample size and multiple methodological flaws.

Our data suggest that there is inadequate evidence to conclude that fibroids that do not distort the endometrial cavity have a significant effect on clinical PRs in patients undergoing IVF. Thus, there is inadequate evidence to support myomectomy for patients with non-cavity-distorting myomas, before treatment with ART. Myomectomy may unnecessarily place the patient at risk of delayed treatment as well as exposing them to associated surgical morbidity. Furthermore, it is unknown whether surgery itself may have a negative impact on pregnancy outcomes. Even among patients who failed to achieve a clinical pregnancy in two consecutive donor embryo transfers and would appear to exhibit some diminished uterine receptivity, we saw no increased incidence of fibroids. Our data suggest that if there are patients with poor endometrial function and decreased receptivity, then factors other than fibroids are more likely to be responsible (Sharkey and Smith, 2003; Cicinelli et al., 2005).

If we apply the Bradford Hill criteria to help differentiate an association from a causal relationship, we cannot conclude that intramural fibroids without cavity penetration adversely affect PRs (Hill, 1965). Results of multiple clinical studies with different outcomes lack consistency. The hypothesis also lacks specificity, as infertility is not found specifically in patients with fibroids, nor is the incidence of fibroids higher in age-matched patients with infertility than it is in the general population. A biologic gradient has not been reliably demonstrated in our study as the number of fibroids has not been reported to be an independent risk factor and the size of fibroids has only been implicated in a small subgroup analysis of one study. We found comparable outcomes in patients with very large (4–8 cm) or multiple fibroids, and we did not see a difference in pregnancy outcomes when comparing subserosal and intramural location. Furthermore, we did not observe any strong trends in different IRs or PRs among patients with multiple fibroids or larger fibroids. Admittedly, our study was not powered to detect a difference in pregnancy outcome based on fibroid size or location. Finally, the biological plausibility that these fibroids influence outcomes is ambiguous as demonstrated by the ambiguity of the multiple unproven and untested theories that explain how fibroids cause infertility. Using donor embryos of healthy young women thus controlling for ovarian age, our study was the closest approximation of a controlled assay for uterine receptivity, and we failed to appreciate a detrimental effect.

While the issue of prior myomectomy was not specifically addressed here, a history of prior myomectomy in our patients was not predictive of pregnancy in our ODR cycles. Nevertheless, if intramural fibroids did affect outcomes, a randomized-controlled intention-to-treat analysis comparing myomectomy with conservative management would be necessary before recommending routine surgical removal of intramural fibroids in patients undergoing IVF. However, given the inadequacy of the evidence to support a causal relationship between intramural fibroids and ART outcomes, we cannot ethically encourage such a study at this time. Myomectomy has proved to be a safe and effective treatment for submucous fibroids and intramural fibroids that distort the endometrial cavity (Surrey et al., 2005). Nevertheless, if fibroids do not significantly affect ART outcomes, surgery delays time to treatment and may expose patients to unnecessary related morbidity, including the need for future Cesarean sections, if patients achieve a pregnancy.

Our study population had a higher incidence of fibroids than previously reported in patients undergoing infertility treatment. Our data suggest that particularly for women with age-related infertility or otherwise diminished ovarian reserve, the prevalence of fibroids approaches 25.5%. We attribute this higher incidence to the older age of our population. The average age of our patients was 41.4. As ARTs improve, fibroids will be increasingly identified as older women are able to receive infertility treatment. This high incidence highlights the importance of determining appropriate, evidence-based approaches for treating infertility patients with fibroids.

We found an increase in ectopic rate among women with fibroids, but this was not statistically significant. Given the rarity of this outcome and the relative small size of our population to examine this outcome, we do not believe this association to be significant enough to warrant prophylactic myomectomy. Most prior studies have not listed ectopic rates; however, one controlled retrospective review of 212 IVF pregnancies reported a 3.0% rate of ectopic pregnancy in women without fibroids, compared with 2.3% among patients with fibroids (Jun et al., 2001). In the absence of much larger studies, a meta-analysis or a systematic review of the literature would more appropriately address this association.

The primary limitation of our study is that it is retrospective and subject to the associated methodological biases. We tried to reduce recall and ascertainment bias by using one reviewer for all charts who was blinded to outcomes until cohort assignment had been completed. Most patients had multiple ultrasounds with repeated images documented in the charts; however, most of the images were midline. It is conceivable that small, laterally situated myomas were not imaged in the chart nor commented on in the clinician’s notes as they were not expected to significantly affect outcomes. However, the high incidence of fibroids in our study reassures us that we identified most of the patients with fibroids.

More detailed information about fibroid volume, number and exact distance from the endometrium was not readily available as the data were collected retrospectively and these details were usually not recorded. When many fibroids were present, they were often documented as ‘multiple’ without providing the exact number. Additionally, two different types of screening ultrasounds were performed at the two different centres, sonohysterograms and transvaginal sonograms. Although these were treated as identical, we cannot be sure that they similarly detect intracavitary effects of intramural fibroids. We are currently initiating a multicentre, prospective study that will prospectively document fibroid size, location from endometrium and the ability of vaginal sonography and sonohysterography to identify fibroid distance from the endometrium. We invite any interested colleagues to join our work group.
Recipient age was statistically different between the two cohorts. We do not believe that this significantly affected our findings as the mean oocyte donor age was similar in both groups. Recipient age was not an independent predictor of pregnancy, and the age of the donor has a much greater influence on IR and PR (Lydic et al., 1996). Although each centre reports a different background PR in ODR cycles (60 versus 47%), each centre has a similar proportion of patients with fibroids (23 versus 27%); thus, heterogeneity between laboratories is unlikely to have affected our findings.

Another limitation is that subserosal and intramural fibroids were grouped together in the primary analysis, and this may have diminished the effect that intramural fibroids situated closer to the endometrium had on IR and PR. Recent unpublished data in IVF patients suggest that intramural fibroids within 0.5 cm of the endometrial junction may negatively affect ART outcomes (Shastri et al., 2005). Subgroup analysis of our data does not show a significant difference in outcomes between patients with intramural or subserosal fibroids; however, our data are not powered to detect a difference in outcome based on location, and the distance of the fibroids from the endometrium was not routinely measured.

The main strength of our study is that by exclusively using an ODR population to control for embryo viability, we eliminated oocyte age as a confounding variable in the assessment of uterine fibroid impact on clinical pregnancy outcome. The high clinical PR, coupled with the larger number of patients, also improved the power of our study to examine fibroid exposure as a clinically important predictor of ART outcomes. Future prospective studies are needed to confirm our observation and more specifically address the role of larger intramural fibroids within close proximity to the endometrial stripe. This subset of patients could be identified in a multicentred prospective trial in order to adequately power a study within a reasonable time frame.

Our study was powered to detect a 33% difference in PRs. We felt that this was a clinically significant threshold that would be required before recommending myectomy, particularly through an abdominal approach. Future prospective studies should be powered to define and detect a clinically important difference in PR that would justify delaying treatment and performing surgery on patients with fibroids. The data from the current trial do not support performance of a myectomy for non-cavity-distorting fibroids.

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